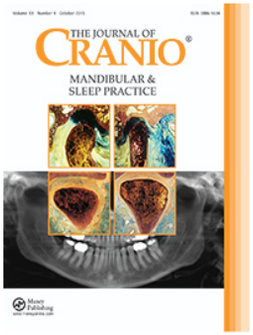

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SLEEP APPLIANCES

Oral appliance therapy in obstructive sleep apnea and snoring - systematic review and new directions of development

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ABSTRACT

Objective: Oral appliance therapy is a non-invasive treatment that offers a wide variety of oral devices for the treatment of obstructive sleep apnea (OSA). The present review focuses on the effectiveness of mandibular advancement devices for the treatment of OSA.

Methods: A systematic review based on the PRISMA checklist was carried out. A detailed electronic database search was conducted using "Obstructive sleep apnea" AND "Oral appliance" AND "Dentistry" as keywords.

Results: The initial search in the electronic databases resulted in a total of 262 papers. After the title and abstract analysis and full-text review, the number of eligible papers was reduced to 15.

Conclusion: The mandibular advancement device is an effective treatment, improving the Apnea Hypopnea Index and the symptoms of patients with OSA in 92% of the subjects from all the investigated studies. The future may include the integration of a biosensor for the diagnosis and follow-up.

Abbreviations: OSA: Obstructive sleep apnea; MADs: Mandibular advancement devices; CPAP: Continuous positive airway pressure; OAT: Oral appliance therapy; MRD: Mandibular repositioning devices; MAS: Mandibular advancement splints; MAA: Mandibular advancement appliances; OA: Oral appliances; AASM: American Academy of Sleep Medicine; AHI: Apnea-hypopnea index; EEG: Sleep-related breathing disorder SRBD; Electroencephalogram; EOG: Electrooculogram; ECG: Electrocardiogram; QOL: Quality of life; TMJ: Temporomandibular joint.

KEYWORDS
Obstructive sleep apnea; oral appliance; mandibular advancement device; mandibular repositioning device; mandibular advancement splint; dentistry

Introduction

Verse & Homann [1] define sleep-related breathing disorder (SRBD) as consisting of simple snoring and obstructive sleep apnea (OSA). OSA is viewed as the repetitive, partial or complete obstruction of the upper airways during sleep. This is the result of a narrowing or collapse of the pharyngeal walls, and it may occur several times during sleeping; it is accompanied by micro-arousals and episodes of oxyhemoglobin desaturation, which result in sleep fragmentation and loud snoring [2,3]. The degree of OSA is commonly classified using the apnea-hypopnea index (AHI) by measuring the mean number of apneas and hypopneas within the hours of sleep. According to the AHI system, OSA can be classified as mild (AHI 5–15), moderate (AHI 16–30), or severe (AHI >30) [4].

On the other hand, snoring is defined as the sounds produced by the vibrations of the soft palate and uvula during inspiratory breathing while sleeping [1]. It can occur alone (primary snoring) or in association with OSA. Besides the potential disputes with the partner of the affected person, simple snoring has been proven to have several pathological consequences. An article published by Bhattacharyya [5] reveals that snoring has

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been linked to an increased hazard ratio, increased cardiovascular events in women, and an association with all-cause mortality. Another study, published by Brockmann et al. [6], investigated the possible correlation between snoring and metabolic syndrome. After investigating 934 patients presenting self-diagnosed snoring, the results revealed a higher risk for dyslipidemia and metabolic syndrome, with a higher percentage of metabolic consequences in men than in women. Another population-based study was published by Lindberg et al. [7], investigating snoring and excessive daytime sleepiness as possible risk factors for hypertension and diabetes in women. The authors questioned 6779 patients and determined that snoring, in combination with excessive daytime sleepiness, is a risk factor for both diabetes and hypertension. The differentiation between harmless snoring and snoring as a sign in OSA has to be determined by a sleep physician [1].

Potential risk factors for developing OSA include age, male gender, ethnicity, genetic susceptibility, craniofacial anatomical structure variations (e.g. retrognathism, micrognathism, macroglossia, a more inferior and anterior position of the hyoid bone, hypoplasia of the middle third of face), trauma, tumors, and tonsillar hypertrophy. In addition, cerebrovascular disease and hormonal factors during menopause, as well as in acromegaly, Down syndrome and hypothyroidism are risk factors for developing OSA [8,9]. Moreover, obesity has been identified as the most important predisposing factor for OSA, due to the increased neck circumference and parapharyngeal fat deposition, which could compress the upper airways [9].

The consequences of untreated OSA include cardiovascular complications, such as systemic hypertension, coronary artery disease, atrial fibrillation, and congestive heart failure [10]. Furthermore, metabolic and pulmonary manifestations, daytime sleepiness, decreased quality of life for the affected person and their partners, as well as increased risk of traffic accidents can be negative outcomes of OSA [11]. Taking these consequences into consideration, OSA can be associated with a high morbidity and mortality [3,11,12]. The mortality caused by OSA is significantly increased in patients with AHI > 20 [13].

It is estimated that more than 20–25% of the general population suffers from OSA, of whom 2–8% are found to have moderate or severe forms of the disease, while the rest have the mild form [14]. Furthermore, only 10% of all cases are actually diagnosed and receive treatment [14]. Moreover, there are differences between the ethnic groups. The main risk factor for Caucasians is obesity, while for Asians, the craniofacial anatomy plays a major role in developing OSA [12].

OSA has a dramatic effect on the anatomy and morphology of patients. A systematic review and meta-analysis of 25 studies published in 2017 by Neelapu et al. [15] determined that there is a strong correlation between certain craniofacial modifications and OSA. Thus, in patients presenting this pathology, the size and position of the maxilla and mandible is modified, associated with an increased size of the tongue and soft palate. Furthermore, the airway space of the pharynx is reduced, and the anterior facial height is increased in OSA patients.

Simple snoring is more common among the general population, affecting 60% of men aged 60 years or older and 50% of postmenopausal women [1]. Moreover, snoring in adults appears more often occasionally than habitually [16].

The diagnosis of OSA can only be established by a trained specialist in sleep medicine. It is diagnosed during a clinical examination based on the information about the history and progression of the disease and is confirmed by nocturnal polysomnography [16,17]. Polysomnography is the gold standard diagnostic procedure for detecting OSA. It involves the monitoring and recording of sleep stages with an electroencephalogram (EEG) and electrooculogram (EOG) and recording the heart rate, using an electrocardiogram (ECG). Furthermore, the oronasal thermistor and nasal pressure sensors for recording breathing, as well as chest and waist bands for respiratory effort and arterial oxygen saturation of the patient who stays overnight in a sleep laboratory, supplement the data recorded [16,17].

The treatment goal in OSA is to restore an adequate respiratory function and oxygen saturation during sleep. Treatment options depend on the degree of severity of the OSA and can be divided into four categories [16,18,19]: (1) lifestyle modification; (2) continuous positive airway pressure (CPAP); (3) mandibular advancement devices (MADs); and (4) surgical procedures.

Oral appliance therapy is defined as a non-invasive treatment, using intraorally applied devices in patients suffering from OSA and snoring. These appliances are worn during sleep. The aim of this therapy is to achieve a stabilization of the mandible and the pharyngeal structures to prevent pharyngeal collapsibility and to keep the upper airway's patency at night [20]. Using oral appliances, the consequences of OSA, such as daytime sleepiness, high AHI, and hypertension or other cardiovascular diseases can be improved [8].

There are numerous designs and types of oral appliances available on the market, and the number is still increasing. In general, they can be divided into three major categories: soft palate lifters, tongue retaining devices, and devices that work by mandibular advancement [9]. The soft palate

lifters are no longer used in clinical practice, while the tongue retaining devices are used only rarely [9]. The most often-used terms for appliances that work by mandibular advancement are MADs, mandibular repositioning devices (MRD), mandibular advancement splints (MAS), and mandibular advancement appliances (MAA) [8]. These types of oral appliances can be prefabricated and bought over the counter, known as "boil and bite devices" or can be custom-made [1,21–23].

The dental practitioner's main role in the treatment of sleep-related breathing disorders is to recognize the disturbance and to refer the patient to a physician who is trained in sleep medicine for further investigations and for establishing the diagnosis [16,17].

To monitor treatment adherence, oral appliance (OA) deterioration, and oral health, practitioners recommend that patients who wear OAs should be followed-up by a qualified dental practitioner regularly during the first year, and afterwards, on an annual basis [18].

In the past decade, an increasing number of studies investigated the efficiency or effectiveness of oral appliance therapy in the management of sleep apnea. The present systematic review explores the outcomes of these studies and illustrates them using descriptive statistics, in order to establish a clear answer to the question of whether oral appliances should be used for the treatment of sleep-related breathing disorder.

Materials and methods

A systematic review based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist was carried out.

A detailed electronic database search was conducted using PubMed and EBSCO. The keywords for the search were "Obstructive sleep apnea" AND "Oral appliance" AND "Dentistry."

Only full text articles written in the English language and with the publication date within the last 10 years (2008–2018) were included. Another filter used for the database search was selecting articles concerning only human patients. In the next step, the titles and abstracts of all articles were assessed for their importance regarding the effectiveness and efficacy of oral appliances. In case an abstract did not provide sufficient information to make a decision of whether to include or exclude it, the full text of the article was obtained for a more detailed review.

For the inclusion of an article, the accepted studies for this review included randomized clinical trials, case reports, randomized crossover trials, retrospective analysis of clinical trials, retrospective and prospective case-control studies, cohort studies, and interventional studies. For this review, studies of patients with OSA with an AHI higher than 5 were included. The treatment approach in these studies had to be any kind of custom-made or prefabricated MAD. Another inclusion criterion was the use of polysomnography with or without questionnaires as a method for measuring the efficacy or effectiveness of the oral appliance.

The success criteria, according to the American Academy of Sleep Medicine (AASM), for a treatment with MADs are defined as one of the following:

- a complete success – the AHI is reduced to less than 5
- a partial success – AHI is reduced to less than 50% of the value at baseline but is still higher than 5 [21,22].

Results

The initial search in the electronic database PubMed, using the keywords "Obstructive sleep apnea" AND "Oral appliance" AND "Dentistry," resulted in a number of 217 articles; whereas, the same search in the EBSCO database returned a number of 45 articles. Thus, the total number of papers identified by the electronic database search was 262.

Based on the title and abstract review, 190 articles were excluded, bringing the number of eligible articles to 72.

The remaining 72 articles were subjected to the full text review, and 57 articles were excluded. Thus, 15 papers were included in the present systematic review.

The search strategy, with numerical values of included and excluded studies, is illustrated as a flow chart in Figure 1.

The following variables of the selected studies were recorded and summarized in Tables 1 and 2: author, year of publication, study design, duration of the study, number of participants and the inclusion criteria for participants, methods of measurement, MAD types, and degree of maximum mandibular protrusion. The results of each study, showing importance to this review, were the outcome for AHI, based on polysomnography, and the outcomes regarding the compliance, the improvement of quality of life, and the sleep quality, based on subjective measurements, such as questionnaires.

The study types included in this review ranged from randomized clinical trials (60%) to several other types (Figure 2).

The sample size within the studies varies between 1 and 425 participants and represents the total number of 851 participants (Figure 3).

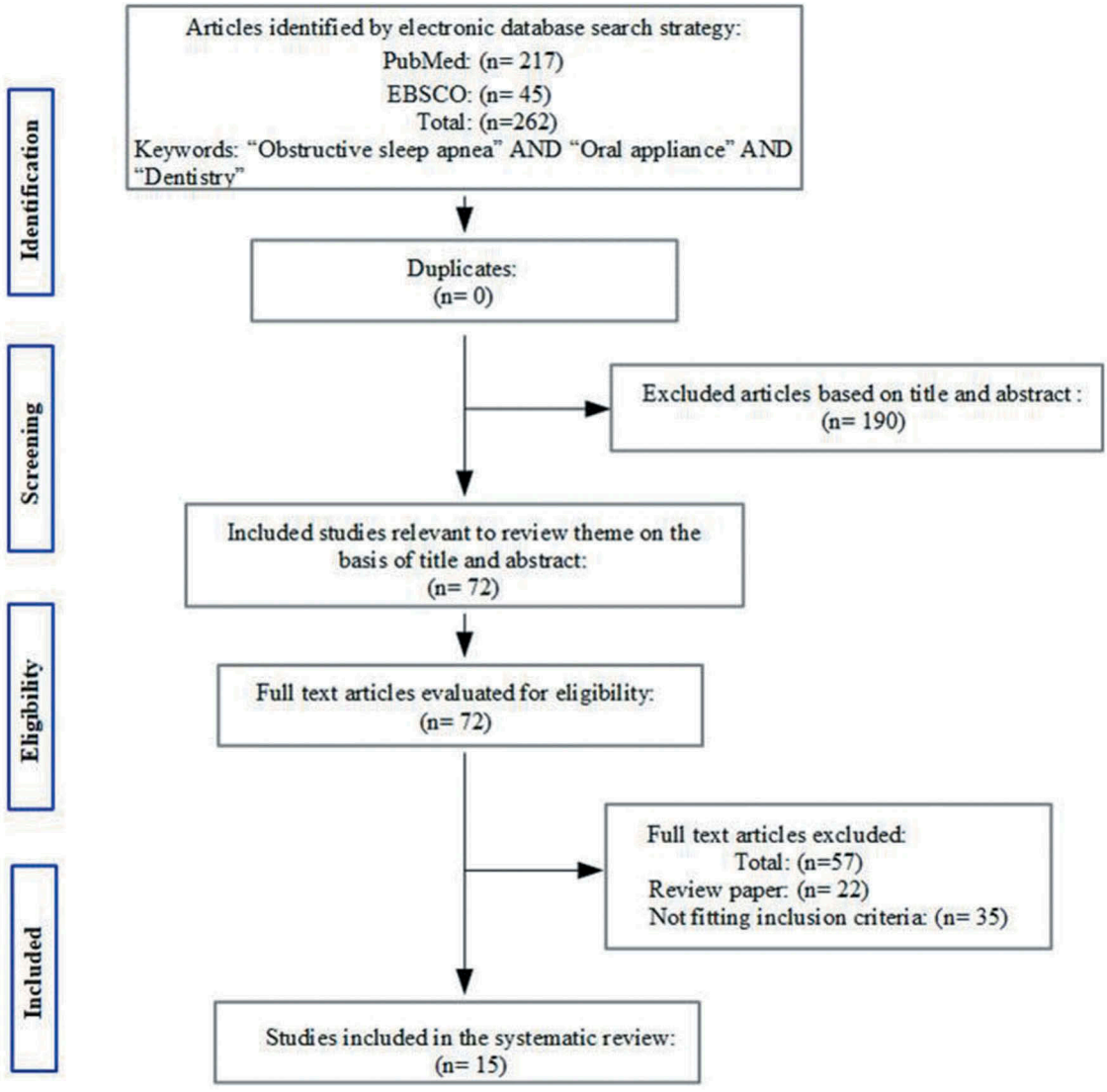

Figure 1. Algorithm of study selection procedure – flow chart.

The type of oral appliance used in the studies differs significantly. Ten studies used custom-made MADs, two studies used the Twin Bloc, another two used prefabricated MADs, and one study used a modified complete denture (Figure 4).

Discussion

The studies included in this review were mostly randomized controlled trials, which represent the "Gold Standard" in clinical research. Nonetheless, various other types of studies were included, in order to provide as much evidence related to the hypothesis as possible.

The follow-up period of the studies varied widely, but none of them exceeded 12 months of duration. This fact could raise the question of whether OAT is also effective on a long-term basis. Furthermore, MADs need to be worn during every night of sleep and for an undefined period of time in order to combat the symptoms and consequences of OSA. Based on this, another question that could arise is whether long-term use of an oral appliance would induce anatomical changes in the oropharyngeal area, in favor of superior airway patency, which would actually reduce the sleep-related breathing disorder and eliminate the necessity of any kind of therapy for OSA. This could be demonstrated by quantitative measurements of morphological changes at the level of the superior airways.

While the number of participants in the individual studies was relatively small, with the exception of studies conducted by Phillips et al. [32] and Sutherland et al. [35], the summed-up sample size of all studies can

Table 1. Extracted data from each study.

Author, Year, Reference	Study Design and Duration	Number of Participants and Inclusion Criteria	Measurement Method
Aarab et al. 2010 [24]	Randomized clinical trial; 39 weeks	N = 17, (AHI 5–45/h), 2 or more OSA symptoms	PSG, Questionnaire
Benoist et al. 2017 [25]	Multicenter prospective randomized controlled trial; 3 months	N = 36, (AHI >5/hour sleep), mild-moderate OSA	PSG, Questionnaire
Cilil et al. 2015 [26]	Randomized clinical trial; 1 month	N = 15, (AHI >5–15)	PSG
Keyf et al. 2013 [27]	Clinical report; 5 months	N = 1, 63-year-old woman, intrusive snoring & mild OSA	PSG, Questionnaire
Hoekema et al. 2008 [28]	Randomized parallel trial; 8–12 weeks	N = 47, (AHI >5), presence of OSA	PSG, Questionnaire
Johal et al. 2017 [20]	Randomized crossover trial; 3 months	N = 25, (AHI >10/h), mild OSA	PSG, Questionnaire
Kaur et al. 2012 [29]	Pre- and post-trial comparison pilot study; 4–6 weeks	N = 20, mild-to-moderate OSA	PSG, Questionnaire
Miljus et al. 2014 [30]	Randomized clinical trial; 6 months	N = 15, (AHI >10)	PSG, Questionnaire
Nerfeldt et al. 2016 [31]	Prospective intervention study; 12 months	N = 36 (AHI > 5), mild-moderate OSA	PSG, Questionnaire
Phillips et al. 2013 [32]	Randomized crossover trial; 1 month	N = 108, (AHI >10 events per h), mild-moderate OSA	PSG, Questionnaire
Sari et al. 2011 [33]	Randomized clinical trial; 1 month	N = 24, (AHI >10), 1/2 patients mild OSA, 1/2 patients moderate OSA	PSG, Questionnaire
Schütz et al. 2013 [34]	Randomized clinical trial; 2 months	N = 9, (AHI >10/h), mild-moderate OSA	PSG
Sutherland et al. 2015 [35]	Retrospective analysis of clinical trials; 13 years	N = 425, (AHI >10/h)	PSG
De Britto Teixeira et al. 2013 [36]	Controlled, prospective longitudinal crossover study; 10.5 months	N = 19, (AHI >5), mild-to-moderate OSA	PSG
Tihacek-Sojic et al. 2012 [37]	Pilot study (non-randomized clinical trial); 12 months	N = 20, (AHI >10/h), mild to moderate OSA	PSG, Questionnaire

be considered large enough to give a significant overall estimate of the outcomes.

One of the present review's limitations is the wide variability in the number of patients each study included. For example, while the study published by Sutherland et al. [35] evaluated a number of 425 patients, and the study published by Phillips et al. [32] evaluated 108 patients, all the remaining studies had fewer than 50 patients. In order to have a more precise evaluation of the effectiveness of OA therapy, future studies should focus on large samples of the population.

The presence of mild or mild to moderate OSA, diagnosed based on the AHI score > 5/h or > 10/h, was the inclusion criteria for the participants in each study. Participants with severe OSA, which is defined by an AHI > 30/h [4], were not included because the literature states limited indications of OAT in patients with this severe degree of the condition [17,21]. On the other hand, consideration of the application of a MAD for cases with severe OSA, who are intolerant to alternative treatment methods, such as CPAP or surgery, should not be excluded because a reduction of the severity in OSA is still better than no improvement at all. The opinion that severe OSA patients should not be excluded is also stated by Gotsopoulos et al. [38] and Flemons et al. [39]. Nevertheless, for demonstrating that OAT is effective in resolving the symptoms and consequences of OSA, the studied samples had to be limited to mild and moderate OSA cases.

For assessing the outcome of the efficiency of OAT, all studies included in this review used polysomnography. This provided the same quality and nature of outcome data within all studies and made the synthesis of the results possible, with the aim of obtaining an overall estimate about the efficiency of OAT. The strength of evidence regarding the overall subjective outcome is inferior compared to the objective outcome obtained by polysomnography because only 11 studies out of 15 used questionnaires for obtaining a subjective outcome. In addition, among these 11 studies, not all of them included questions for obtaining a subjective outcome about the quality of life, daytime sleepiness, and compliance.

The MADs used for the investigations were custom-made or ready-made. Some authors, such as Johal et al. [20] state that custom-made oral appliances are more efficient and, hence, a higher compliance is achieved compared to ready-made MADs. Taking this into consideration, the main outcomes could have been influenced by the heterogeneity of appliances used in the studies. Moreover, due to the large variety of oral appliances available on the market and the lack of studies investigating each of them, the question of which type of custom-made and ready-made appliances can be considered the most effective remains unanswered. Additionally, the impact of the materials used for the fabrication of the appliances on the treatment outcome cannot be made since there are no studies specifically investigating this aspect. This highlights the role of the dentist to choose a MAD on an individual basis and to investigate the outcome of the OAT regularly in order to achieve the best efficacy.

The degree of mandibular advancement was set individually for each patient in all studies that used a tritratable appliance. This ensured the maximum

Table 2. Extracted data from each study.

Author, Year, Reference	Mandibular Advancement Device and Protrusion Degree	Outcome (AHI)	Adherence/Subjective Outcome
Aarab et al. 2010 [24]	Mandibular repositioning appliance set at a constant vertical dimension; Mean maximal mandibular protrusion = 9.6 mm	MAD effectiveness: 25%; AHI decreased to NV in 12 out of 17 patients = 70% success rate	Compliance rates of up to 97% (16 patients); Decrease in snoring intensity with MAD at 50% and 75%
Benoist et al. 2017 [25]	Custom-made titratable device (SomnoDent flex, SomnoMed™, Sydney, Australia); 75%, or 90% of maximal protrusion	11.7 [9.0–16.2] to 9.1 [4.9–11.7], $p < .001$; AHI dropped by 46.5%	Compliance for OAT 88.8% (32 patients), no relevant change in quality of life
Cilil et al. 2015 [26]	Mandibular repositioning appliance, custom-made	AHI decreased from 23.8 ± 18.12 to 10.87 ± 11.56; 8 patients showed a decrease of 50% from the initial value (AHI)	N/A†
Keyf]et al. 2013 [27]	Modified mandibular repositioning appliance as a complete denture	AHI reduced from 13.3 to 3.0, duration of sleep apnea decreased (31.5 sec ≥ 16.5 sec)	Snoring, wake gasping and choking were reduced; diminished headache and drowsiness during the day.
Hoekema et al. 2008 [28]	Mandibular repositioning appliance (Thornton Adjustable Positioner type-1, Airway Management, Inc., Dallas, TX, USA)	Oral appliance effectiveness = 76.5%; Effective for 39, non-responsive in 8 cases	42 people wore it 7 nights/week, and 46 wore it >5h/night
Johal et al. 2017 [20]	Custom-made MRDc ("Medical Dental Sleep Appliance") and Ready-made MRDr ("Snoreshield")	MRDc total treatment success: 96% (n = 24); MRDr total treatment success: 64% (n = 16)	Quality of life scales showed statistically significant improvement in relation to both MRD; significant clinical effectiveness of a custom-made mandibular device in terms of compliance (MAD worn an average 7 nights per week and 5 h/night (25 patients)
Kaur et al. 2012 [29]	Twin Block appliance; advanced position: 75% of maximum protrusion or at least 7 mm of advancement	AHI score (43.83 ± 30.00 to 20.31 ± 14.58); Mean reduction of 53.39%	Significant decrease in snoring volume, frequency and duration
Miljus et al. 2014 [30]	Mandibular repositioning appliance, custom-made; Protrusive position at 50% of maximum mandibular advancement	AHI decreased from 15–28 episodes/h to 6.1 ± 3.5; Complete success in 7 out of 15; 7 patients with partial success. Treatment failure in 1 patient	Increase in sleep quality, decrease in snoring, increased efficiency during the day
Nerfeldt et al. 2016 [31]	Hard monobloc (58%), soft monobloc (8%) and split (34%) devices; 75% of maximal protrusion	27 patients (75%) were successfully treated with OAT according to AHI criteria; Reduction of AHI was 74% for arousers and 68% for desaturaters	Compliance rate (28 out of 33 = 85%); 59% reported OA improved their sleep, 52% reported improved daytime sleepiness, 33% improved general health, and 41% improved quality of life
Phillips et al. 2013 [32]	Somnodent (SomnoMed Ltd., Sydney, Australia), custom-fitted and titratable two-piece device; Mean mandibular advancement: 8.09 ± 2.6 mm (range, 1.1–15 mm)	MAD: Mean AHI dropped from 25.6 ± 12.3 to 11.1 ± 12.1/h; $p = .01$	MAD treatment patients reported longer sleep and higher compliance than with CPAP; 55 patients (51%) preferred MAD
Sari et al. 2011 [33]	Mandibular advancement splint, Klearway	Klearway group: AHI decreased from 18.8 ± 7.3 to 7.3 ± 3.3; MAS group: AHI decreased 17.9 ± 6.8 to 9.1 ± 4.9. AHI reduction in 10 out of 12 for Klearway group and 8 out of 12 in MAS group.	All patients subjectively reported more restful sleep with a reduction of snoring
Schütz et al. 2013 [34]	Mandibular repositioning appliance (Brazilian Dental Appliance, Sao Paulo, SP, Brazil) individually constructed and installed	AHI decreased from 30.8 ± 19.0 at baseline to 9.6 ± 10.3 ($p < .001$); Significant reductions in the apnea-hypopnea index	N/A
Sutherland et al. 2015 [35]	SomnoDent MAS, SomnoMed Ltd, Australia; customized two-piece appliance	Reduction of AHI by 50.3% ± 50.7% across the group	N/A
De Britto Teixeira et al. 2013 [36]	Modified twin block; mandibular advancement device; 75% of maximal mandibular advancement	AHI reduced from 16.3 to 11.7; 47% of patients showed improvement, and 26% had a normal AHI	N/A
Tihacek-Sojic et al. 2012 [37]	Custom-made MAD; 50–70% of maximum mandibular advancement (average 62%)	75% (15 patients) had complete or partial therapy success; Average AHI: 6.70 ± 4.43	80% snored less, 94% experienced better sleep quality, while 100% of patients experienced a decrease in daytime sleepiness

† N/A – Non-available/non-applicable information.

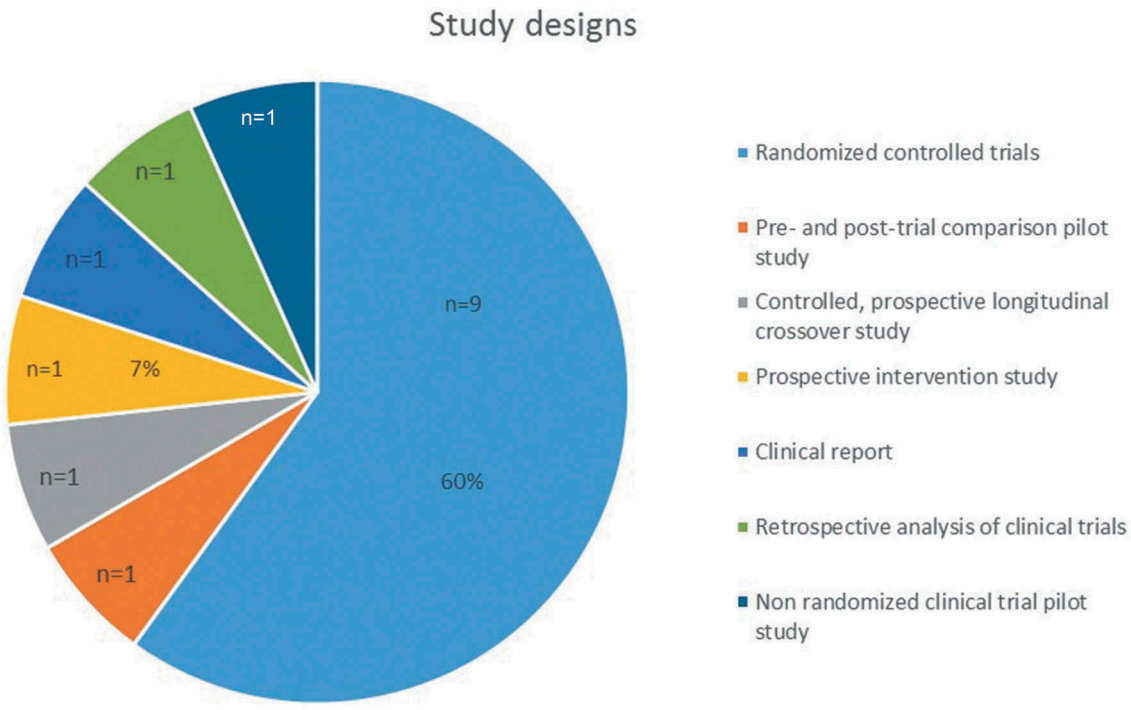

Figure 2. Synthesis of types of studies used in the review.

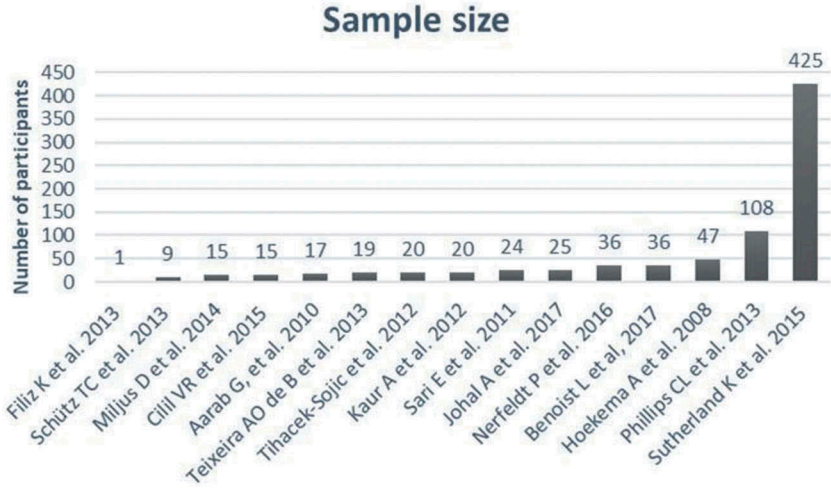

Figure 3. Number of participants in each study.

efficacy of the appliances and facilitated the highest comfort for the patients. This could have an impact on the effectiveness of the OAT. Therefore, it is important for the dentist to take into consideration that the ideal degree of mandibular advancement may not necessarily be the maximal possible protrusion, but rather the protrusion with the highest response of the patient.

The main result of this review states that 92% of all the investigated subjects were successfully treated with OAT. Even though the definition of treatment success or failure may be different from study to study, in this review, the definition of a successful treatment was taken from the American Academy of Sleep Medicine (AASM) and consists of the reduction of AHI to ≤ 5 or the reduction of AHI by more than 50% of the value at baseline, but with an AHI still ≥ 5 [35]. Therefore, for the purpose of comparing studies using MADs as a treatment method for OSA, a uniform definition of treatment success had to be established. Furthermore, the reliability of the main result could be questioned due to the fact that six studies (Benoist et al. [25], Keyf et al. [27], Kaur et al. [29], Phillips et al. [32], Schütz et al. [34], and Sutherland et al. [35]) reported a successful treatment outcome for

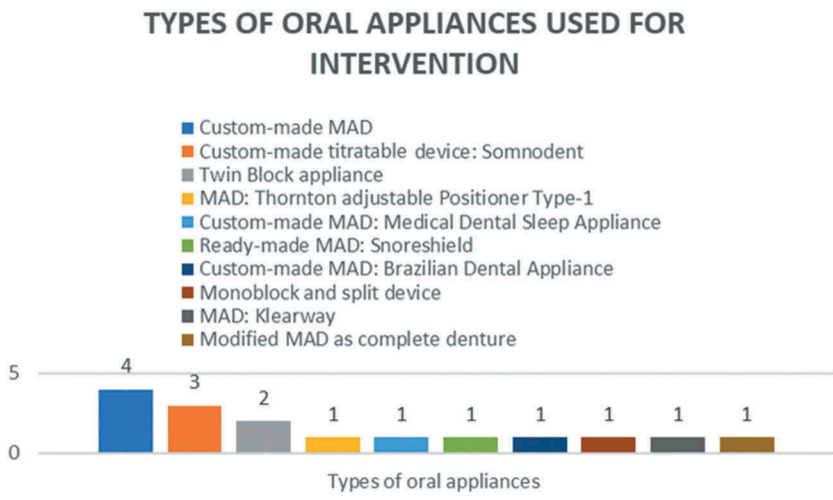

Figure 4. Synthesis of oral appliance types used in the studies.

all participants. Nevertheless, this could be explained by the small number of participants in three of the studies (Keyf et al. [27], Kaur et al. [29], and Schütz et al. [34]) or because of the use of the same MAD (SomnoDent) in the other three studies (Benoist et al. [25], Phillips. et al. [32], and Sutherland et al. [35]).

The results regarding the compliance rate demonstrated that 206 patients (77%) were compliant with the use of MADs, and 62 patients (23%) were not compliant. The smaller number of cases used for obtaining this result is due to the lack of use of questionnaires in all reviewed studies, as mentioned above. Despite the small amount of evidence, the results showed clearly that MADs had a high compliance rate. This confirms the statement from literature that OAT is a reliable alternative to CPAP therapy, due to its higher compliance [17].

Among the reviewed studies, only one (Johal et al. [20]) out of three reported an improved QOL in the cases treated with MADs. Therefore, the evidence about the impact on the improvement of QOL by MADs is not sufficient. Nonetheless, further research that examines the effects of OAT in terms of QOL has to be done for providing a more accurate statement.

Moreover, five studies that used questionnaires for evaluating the presence and characteristics of snoring (Aarab et al. [24], Keyf et al. [27], Kaur et al. [29], Miljus et al. [30], and Tihacek-Sojic et al. [37]), reported a decrease in snoring or a complete resolution of it. This might have a positive impact on the QOL of the sleep partner and improves the sleep quality of both the affected person and the sleep partner. Additionally, this outcome demonstrates that MADs are appropriate not only for persons suffering from OSA but also for people with simple snoring who want to address this issue for personal reasons.

The decrease in daytime sleepiness by using oral appliances is also a result derived from the outcomes of questionnaires conducted by six studies (Keyf et al. [27], Miljus et al. [29], Nerfeldt et al. [31], Phillips et al. [32], Sari et al. [33], and Tihacek-Sojic et al. [37]). A decrease in daytime sleepiness could contribute to a reduction in the mortality rate of OSA by traffic accidents, which are a risk of this symptom [8]. Due to this risk, the improvement of daytime sleepiness with OAT should be highly valued, even though this improvement could also be achieved with other treatment modalities for OSA.

A limitation of this systematic review might be the inclusion of studies other than randomized controlled trials. For this reason, there was an important heterogeneity among the studies, in order to perform a meta-analysis. Instead, a descriptive analysis was performed, which poses a higher risk of bias in representing the qualitative and quantitative data of the analysis of the studies. Additionally, observational studies or types of studies other than randomized controlled trials are characterized by a lower reliability. This could reflect on the quality and reliability of the outcome of these studies, as well as on the outcome of this review. On the other hand, the number of available randomized clinical trials is too small at the present time to provide a large amount of high-quality evidence. Next, for the collection of studies related to the subject of interest, only the PubMed and EBSCO databases were used, which resulted in the relatively small number of 15 articles that met the inclusion criteria for this review. The search in several databases would have given

a higher number of articles suitable for this review and a larger amount of evidence on which to draw a conclusion about the effectiveness of OAT.

The value of this study is the demonstration that oral appliances are not only effective, but also efficient, in treating mild to moderate OSA. This is based on the favorable outcome of OAT by reducing the AHI score and improving subjective symptoms, such as compliance and snoring. Therefore, OAT can be considered as a more affordable alternative for CPAP therapy. Moreover, the use of oral appliances as a primary or alternative treatment modality for OSA would give the patient a higher degree of mobility during traveling compared to the machine used for CPAP. In addition, oral appliances are very discrete in usage and might have less impact on the self-esteem and social life of the patient.

The results of this study were similar to other systematic reviews, such as the Cochrane review of Lim et al. [40] in 2006 or the Ontario systematic review in 2009 [41]. This increases the reliability of the outcome obtained in this research.

An important aspect related to this review's topic is the prevention of OSA. Unfortunately, none of the major health organizations, such as the World Health Organization (WHO) or the American Academy of Sleep Medicine (AASM), provide any information about prevention measures for this condition. The fact that OSA is not directly life- threatening, but rather, it has long-term consequences, could be the reason why these organizations did not focus on the prevention of the condition. Moreover, there are no specific studies addressing this issue. Therefore, further research should be conducted, in order to investigate potential prevention measures. Prevention could be represented by measures of weight loss or decreasing the obesity rate in the population since this is one of the main risk factors for OSA [9]. Additionally, measures of increasing awareness about the sleep position, the introduction of screening programs, or providing information to the population for a presumptive self-diagnosis are other examples that could contribute to the prevention of at least the more severe consequences of OSA. Dentists now need to undergo special training for providing an adequate therapy for OSA patients. In the future, dental faculties should train all their students to recognize the condition, to provide information for the prevention and successful treatment of OSA with oral appliances, with the aim of solving this global health issue.

The accessibility of oral appliances is vastly due to the large number of different types available on the market. On the contrary, a drawback of OAT is the price range for MADs. The American Sleep Association (ASA) states on its website (www.sleepassociation.org) that a ready-made oral appliance (e.g. Boil & Bite) is available starting from $40, while the average price for a custom-made MAD, which is fitted by the dentist, is estimated at $1800 – $2000. The latter price range would not only include the MAD, but also the costs of the dentist visits, follow-ups, and eventual modifications to the device. Comparing this with the price of a CPAP machine ($1500 – $3800), offered by different manufacturers, the treatment with oral appliances can be considered as a more accessible treatment option. On the other hand, it should be kept in mind that a low-cost MAD will also provide a lower grade of effectiveness compared with the more expensive custom-made MADs [19]. Some health insurance companies address this issue by including in their coverage contract a variable number of FDA-approved oral appliances and the health services related to them.

The long-term effects that these appliances have on the upper airways and cranial skeletal structure of the patients must be taken into consideration. A study conducted by Cossellu et al. [42] evaluated the effects of OA on 10 patients, using a three-dimensional radiographic investigation (cone-beam computed tomography). The study found an improvement of the upper airways total volume in 9 out of 10 patients following the treatment with OA.

Regarding the changes on the cranial structures determined by OA, Doff et al. [43] conducted a study on 31 patients diagnosed with OSA using polysomnography. The authors used two lateral cephalograms to conduct cephalometric analyses, one taken before the OAs were instated, and the other at a two-year follow-up. The biggest modifications were observed at a dental level, as the upper incisors suffered a retroclination, and the lower incisors were proclinated. Furthermore, the ANB angle, quantifying the angle formed by the maxilla and mandible planes, suffered an increase. Lastly, there was an increase in the lower anterior facial height, as well as in the total anterior facial height.

Another study on the side effects of OA therapy was published by Pliska et al. [8], focusing on the occlusal effects that these devices might have. Out of the total of 77 patients evaluated for over 8 years, 51% developed a posterior open bite, whereas 62% developed an anterior crossbite of at least one tooth.

Lastly, the American Academy of Craniofacial Pain has published a position paper with recommendations for dentists engaged in mandibular advancement OA therapy. The paper states not only the fact that oral appliances may cause temporomandibular joint (TMJ) disorders, but also that a complete TMJ examination should be conducted in all candidate patients for OA therapy [44].

In recent years, saliva has emerged as a potential biofluid for assessing oral and general pathologies, due, in part, to the development of biosensors [45]. Biosensors

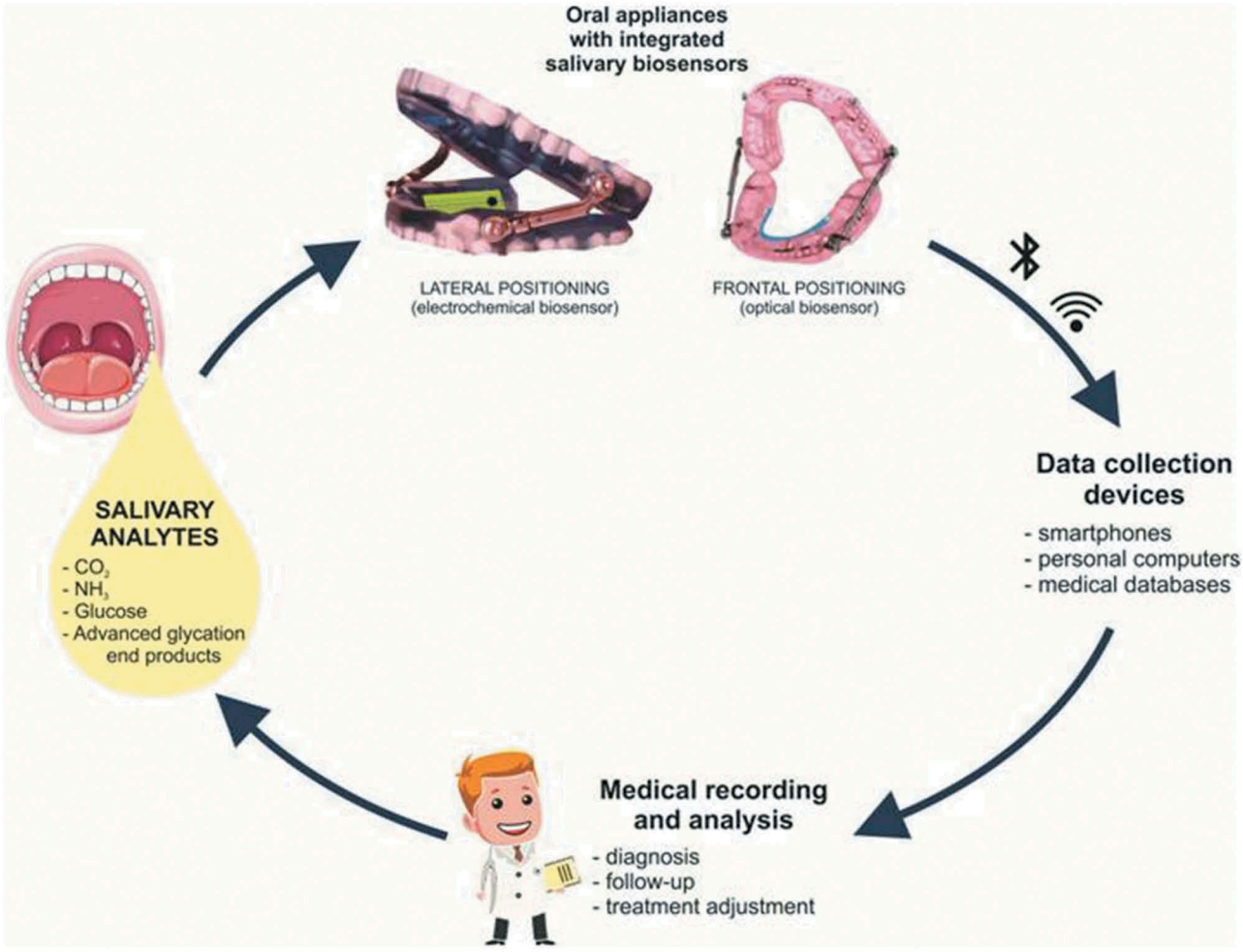

Figure 5. The use of biosensors in oral appliance (OA).

have already been used in the determination of several compounds, such as advanced end glycation products [46]. These biomarkers have been linked to both oral and general pathologies [47,48]. Another example is the use of a graphene/graphite-modified screen-printed electrode, covered with gold nanoparticles, for the detection of pyoverdine, whose existence in water was linked to the presence of *Pseudomonas aeruginosa* [49]. This bacteria can also be found in medical devices used in the treatment with CPAP. The main advantage of these salivary biosensors is the easy contact to the biofluid, and the small size of electrochemical or optical biosensors. This allows for the easy incorporation in the OA, helping in the monitorization of the patient, using a wireless transmitter and data collection equipment (Figure 5). As proof of concept, an electrochemical sensor for the detection of N-epsilon (carboxymethyl) lysine (CML) has already been developed and included in a mouth-guard, allowing for the non-invasive monitoring of CML in saliva [46].

Conclusion

As shown in the present systematic review, the mandibular advancement device is effective in providing a successful treatment by improving the Apnea Hypopnea Index and the subjective symptoms of patients with obstructive sleep apnea and snoring. In the future, the dentist should play a more active role in identifying patients with obstructive sleep apnea and in suggesting oral appliance therapy as an effective alternative to other treatment possibilities. Moreover, particular importance should be given to the collaboration between dentists and specialists in sleep disorders, in order to ensure patients' compliance and monitoring. The two specialists should be able to provide sequential or simultaneous care. Additionally, the most effective type of oral appliances and the impact of an oral appliance's material on the treatment outcome, have to be investigated in future studies.

Furthermore, 92% of all the investigated subjects were successfully treated with OAT, proving the efficacy of the treatment.

Conflict of Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work that could have influenced its outcome.

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