

Treatment Of Snoring And Mild And Moderate Obstructive Sleep Apnea (Osa) Using Oral Appliances - An Update And Overview



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Abstract: Obstructive Sleep Apnea (OSA) is a condition characterized by apnoic pauses during sleep, decrease of the oxygen pressure in the blood, frequent arousals and other symptoms which are stressful and can lead to heart, metabolic, neurologic diseases, etc. It is due to collapse of the soft tissues of the upper airway during sleep and obstructing the airway patency. The diagnosis is set by using thorough examination of the upper airways by endoscopy, sleep endoscopy, Muller's maneuver, polysomnography, questionnaires. Continuous Positive Airway Pressure (CPAP) is considered as a golden standard for the treatment of OSA, but the

low compliance and intolerance of the patients to the machine call for alternative treatment. Oral appliances are highly effective in the treatment of selected patients with OSA, mainly mild and moderate cases according to the Apnea-Hypopnea Index (AHI). The precise pretreatment workout is of uppermost importance in assessment the grade of OSA and the site of obstruction, the exact measurement of the protrusion and fitting of the oral appliance play certain role for the success of the treatment. If there is a multilevel obstruction, combined treatment with surgery and oral appliances could be a viable option for such patients.

Introduction

OSA is a condition characterized by apnoic pauses during sleep, decrease of the oxygen pressure in the blood, frequent arousals and other symptoms which are stressful and can lead to heart, metabolic diseases, etc. (1)

The prevalence of OSA is about 2-4% of the population (2). The symptoms are due to upper airway collapse and obstruction during sleep. The main symptoms and the consequences of OSA are outside the boundaries of just one medical specialty. That is why, the diagnostic and treatment of OSA is multidisciplinary.

Polysomnography (PSG) is considered as a gold standard for diagnostic of OSA. The AHI is an objective, sensitive and specific measure of the severity of OSA. It allows useful disease categorization, although differing hypopnea definitions introduce variability. The American Academy of Sleep Medicine defines mild OSA as an AHI of 5-14 events per hour; moderate OSA as 15-30 events per hour; and severe OSA as an AHI of greater than 30 events per hour (3).

Treatment of OSA with CPAP is recommended as a method of choice in the standards of the American (3, 4) and European societies of sleep medicine (5), which leads to prescription of CPAP almost to every patient with OSA. The other methods of treatment like surgery and oral appliances are considered as "alternative therapies", although they could solve the patient's problems better in selected cases. On the other hand, CPAP effectiveness is limited by intolerance and poor compliance, with failure rates of 46-83% (6), especially in young people, which indicates that different methods of treatment should be offered to the patients when indications for them exist.

The custom indications for the alternative methods are mild and moderate OSA, but in patients who do not tolerate CPAP, they should be used as a first choice of treatment as well, even in cases with severe OSA. In our opinion the diagnostic protocol should be based on questionnaires, PSG or polygraphy, done in specialized laboratories by a specialist of sleep medicine, endoscopy of the upper airways, Muller's test, rhinomanometry and/or acoustic rhinometry, sleep endoscopy, anatomic

screening, done by the ENT specialists and dental status, occlusion and TNJ assessment, done by the dentist. Surgery and oral appliances are good alternatives which could be helpful in selected patients with OSA (7).

The aim of this study is to review and discuss the current concepts for using oral appliances and setting the correct diagnosis, indications for treatment and treatment of patients with oral appliances based on literature review and our experience with series of 37 patients mainly with mild and moderate OSA (7).

Oral appliances – how they work and main indications for their use.

An oral appliance was considered as treatment for mandibular deficiency and upper airway obstruction as early as 1934 (8). In 1934 Pierre Robin described a monoblock functional appliance that was used to pull the jaw and, therefore, tongue forward. Robin's appliance was utilized for cases of micrognathia in both children and adults. One limitation of the intraoral appliance approach that Robin noted was that it was not usable in the newborn without any teeth (8).

Since then, due to the advances of dentistry and the improvement of the materials, many types of oral appliances were created. They are called with different names like oral (dental) appliances (OA), mandibular advancement device (MAD), mandibular advancement splints (MAS), mandibular repositioning appliances (MRA), etc.

The main principle of their action is to protrude the mandible in a forward position and therefore enlarge the upper airway (9). When such an appliance is inserted into the mouth, it works directly by enlarging the pharyngeal airway primarily in the velopharyngeal and oropharyngeal areas due to stretching of the pharyngeal soft tissues attached to the mandible (9).

The tongue is affected by all the appliances, either directly by forward movement of the tongue, or indirectly by advancing the mandible. The airway space is mostly enlarged laterally, thought to be due to traction on soft tissue connection between the pharynx and mandibular ramus (10).

This reduces the upper airway collapsibility by altering the upper airway morphology, structure, and function. In addition, oral appliances treatment may influence the neuromuscular function in the upper airway (9).

Although questionnaires, scales, for example Epworth sleepiness scale (ESS), polysomnography and polygraphy are standards for the correct assessment of OSA and its grade, clinical examinations are of greater value for the prediction of the success of the oral appliances in the treatment of OSA. The anatomical relationships between the structures in the upper airways are of uppermost significance in setting the indications for their use.

Successful results of application of oral appliances could be expected when the main reason for the obstruction of the upper airway is the tongue. If endoscopy or sleep endoscopy is done, it could show quite precisely the place of the obstruction.

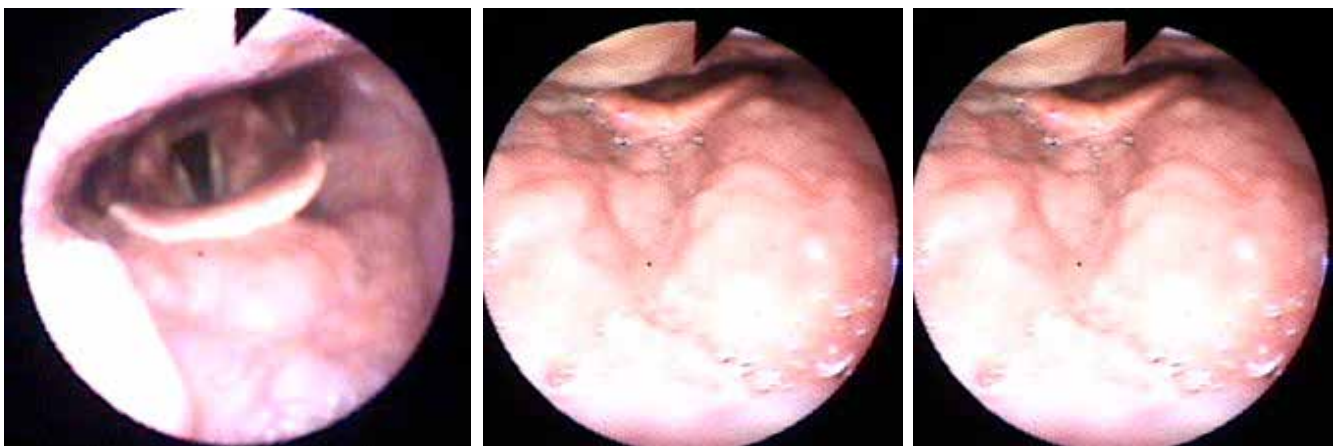


Figure 1. Endoscopy in patients with mild, moderate and severe OSA due mostly to tongue enlargement or posterior position.



Figure 2. Multilevel obstruction

Müller's maneuver could be a good prognostic factor for predicting the effect of oral appliances. The technique is designed to look for collapsed sections of the upper airways. In this maneuver, the patient attempts to inhale with his mouth closed and his nostrils plugged, which leads to a collapse of the airway. After a forced expiration, an attempt of inspiration is made with closed mouth and nose, whereby the negative pressure in the chest and lungs is made very subatmospheric; the reverse of Valsalva maneuver. Introducing a flexible fiberoptic through the nose in the pharynx to obtain a view, the examiner may notice the collapse and identify weakened sections of the airway. Müller's maneuver is used to help determine the cause of sleep apnea. A positive test result means that the site of upper airway obstruction is likely below the level of the soft palate, and the patient will probably not benefit from surgery alone (11).

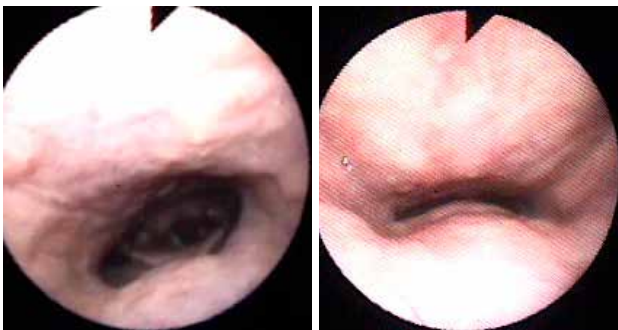


Figure 2. Müller's maneuver

According to our experience, the indications for using oral appliances could be: mild to moderate OSA or severe OSA in patients who do not tolerate or adhere to CPAP or are not suitable for surgical treatment. Patients with 20 or more teeth, with bone loss of less than 50% and evenly disturbed occlusal tooth contact. Patients with tongue hypertrophy III or IV grade according to Friedman and retrolingual collapse. Patients with retrognathia.

Contraindications for using oral appliances

Loose teeth, periodontal disease, insufficient dentition, regular use of sedatives or narcotics, lung or psychiatric diseases (7).

Diagnostic approach

The diagnostic workout is very important and is multidisciplinary. The diagnostic plan should include interdisciplinary consultation and examination by an otorhinolaryngologist, dentist and specialist of sleep medicine. It should consist of anamnesis, Body Mass Index (BMI), Epworth Sleepiness Scale (ESS), otorhinolaryngological status assessed by endoscopy, Müller's maneuver, rhinomanometry, sleep endoscopy, done by ENT specialist; dental status, done by a qualified dentist with experience in oral appliances for OSA; polysomnography or polygraphy done by specialists of sleep medicine. If comorbidities are found, a consultation with other specialists like cardiologists, neurologists, endocrinologists, pulmonologist, etc. are performed.

The anamnesis should be directed to the sleep disturbances, comorbidities, upper airways and dental problems of the patient. Epworth sleepiness scale (ESS) should be filled by all patients. Polysomnography and polygraphy are performed by specialists of sleep medicine in different certified laboratories or at the home by the patient. AHI, O₂ desaturation, snoring events are evaluated. Based on the AHI OSA is graded as mild, moderate or severe - mild OSA as an AHI of 5–14 events per hour; moderate OSA as 15–30 events per hour; and severe OSA as an AHI of greater than 30 events per hour. Polysomnography and ESS are used for the initial diagnoses, but also to measure the results of the treatment.

The otorhinolaryngological examination is performed by fiberoptic nasopharyngoscopy or nasal endoscopy or laryngeal endoscopy in cases with specific pathology. Special attention should be directed to the nasal patency and pathological conditions like deviation of the nasal septum, hypertrophy of the inferior turbinates, nasal polyps etc.; the volume of the tonsils and the tongue are measured according to Friedman's scale (from 0 to 4); the position of the hard and the soft palate, the length of the uvula and lateral pharyngeal narrowing are assessed and taken into considerations.

The dental examination includes the assessment of a full dental status, occlusion check and screening for temporomandibular joint disorders (TMD). Condition for the treatment with oral appliance was the presence of at least 20 teeth, showing no dental or periodontal pathologies, sufficient prosthodontics restorations and no TMD symptoms, such as pain by palpation of the lateral and dorsal area to the TMD, articular sounds, pathology of the masticatory muscles, deviation and limitation of the mandibular mobility.

Types of oral appliance

There are several types of MAD including: thermo-plastic 'boil and bite' devices, which are available from pharmacies and online, semi-tailored devices, also available from pharmacies or online, where the patient creates their own dental impression mould (using something similar to a boil and bite device) and sends it away to have an MAD made. Patients may benefit from assistance by a sleep specialist or a dentist to create the mould. The third type are the tailored MADs, which are custom-made by sleep specialists or dentists specialized in the use of oral appliances to treat OSA, after taking an impressions of the teeth and determining the proper position of the lower jaw and the amount of protrusion. (12).

Among the many kinds of dental appliances our experience is limited to only 2 types of them and they are tailored oral appliances.

The patients could choose between two types of oral appliances: Silenor- sl[®] (Erkodent Erich Kopp GmbH) and Torton-Adjustable-Repositioner - TAP[®] (Scheu Dental GmbH).

On the first visit, for manufacturing of the oral appliances, we took impressions of the the upper and lower jaw with a vinyl polysiloxane (VPS) impression material with a prefabricated standard

impression trays are taken and the position of the mandibula, using the George-GaugeTM (Fig. 5) bite registration set (Scheu Dental GmbH) is registered. For the registration we measured the distance between the centric relation and the maximal protrusion with the integrated millimeter scale. The needed protrusion for the patient was calculated as 75% of the measured distance. The upper screw is used to fix the determined position of the mandibula and after that the bite with a silicon registration material is registered.

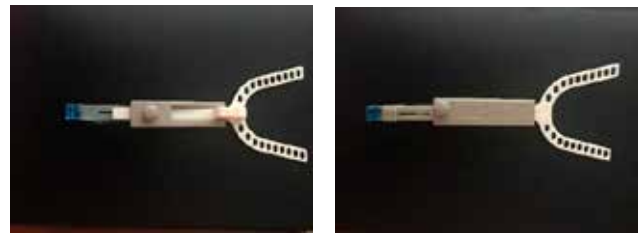


Figure 3. George-Gauge bite registration fork

The integration of the oral appliance is conducted on the second visit in the dental office after the manufacturing by the dental technician. We controlled the sufficient fitting of the upper and lower splint, as well as the right position of the mandibula and instructed the patients how to use and take care of their oral appliance. One week after the intergration of the splints the patients are recalled for a check up.



Figure 4. Silenor- sl[®]
(Erkodent Erich Kopp GmbH)



Figure 5. Torton-Adjustable-Repositioner - TAP[®] (Scheu Dental GmbH)

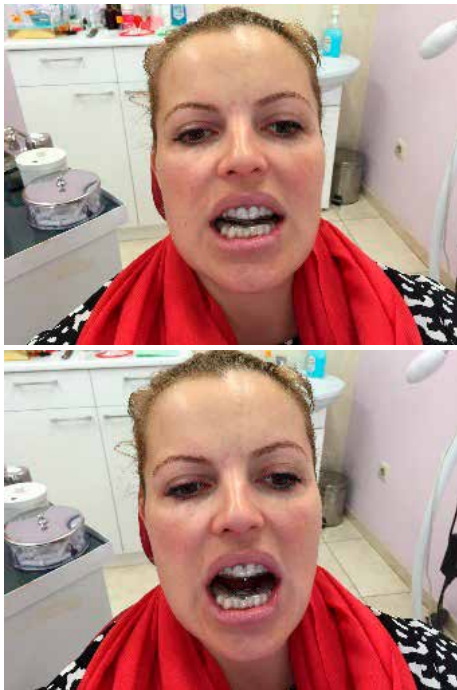


Figure 6. TAP appliance in place

In both cases the basic function of the oral appliance was to hold the jaw forward, so the tongue and soft tissues of the throat do not collapse, causing snoring and sleep apnea. The preference of the patients was based on the price difference of the appliances.

Both Silenor-sl® and TAP® devices consist of one splint for the upper jaw and one for the lower jaw, that are connected by different mechanisms. In the Silenor-sl® appliance the lower jaw is held in the predetermined position by two connectors, that are fixed laterally to the splint. The jaw movements are possible, but no falling back of the lower jaw. In the TAP® device the mandibular and maxillary splints are joined with a fixed mechanical hinge and inseparable pivot point during sleep. The TAP® is titratable with a single point of central adjustment, which prevents uneven bilateral adjustment that may create an irregular bite and jaw discomfort.

Results of the treatment with oral appliances

The success rate of the treatment typically is expressed as a reduction in AHI with more than 50% from the base line, or treatment outcome with AHN of less than 10 events/hour (13, 14). According to these criteria the success rate of the oral appliances ranges from 30% to 85% and for CPAP treatment from 62% to 100% (13). These

results show that the mean AHI reduction rate is higher in the patients using CPAP (13). However, adherence to oral appliances has been reported to be 76%-95%, which is superior compared to CPAP adherence ranging from 30% to 80% (14). Studies since 2005 that looked at therapy with bespoke MADs (custom made from dental impressions) have reported mean AHI reductions of between 30% and 72%. Reviewing the data of these studies revealed a complete response (AHI <5) or partial response (50% reduction in AHI from baseline, but AHI >5) of between 45% and 100% (14, 16-21). Studies with higher response rates recruited patients with lower AHI at baseline. Blanco et al. (15) reported a 100% response rate, however the study had limitations due to small sample size and a high proportion of subjects withdrawing from the trial.

Epworth Sleepiness Scale in all recent studies of patients with oral appliances show a significant improvement of daytime sleepiness, compared to inactive appliances (16, 17, 22, 23). Phillips CI et al (24) reported that oral appliances and CPAP have similar improvement in sleepiness based on Epworth Sleepiness Scale.

According to our study, the success rate of the treatment of our patients measured as AHI reduction less than 10 events/hour is very high (95%). The mean AHI reduction is 9.5 events/h. compared to 19.45 before the treatment, which is in accordance with the cited results.

The mean Epworth Sleepiness Scale result after the treatment was 8.6 compared to 12.7 before the treatment.

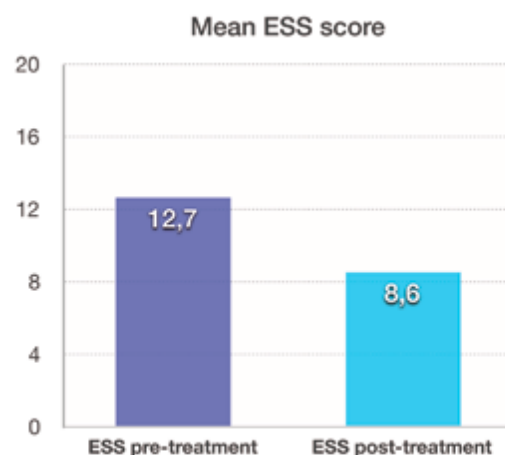


Table 6: Mean ESS score before and after the treatment.



The compliance of using oral appliances was very high too. Only one of the patients was using his appliances from time to time because of salivation during sleep.

Discussion

CPAP intolerance is one of the problems that has to be discussed. In our opinion, there are several main reasons for the low compliance to CPAP. The first one, especially in young patients, is the use of the machine itself. Most of them are willing to try all other methods, including surgery and oral appliances, but not to sleep with CPAP in the presence of their partners. The constant use of CPAP is something that frightens them and they are trying to avoid it. So, they are looking most of all for surgery in order to resolve the problem instantly and may be forever. The second reason is nasal obstruction which raises the pressure and thus awakes the patients. The problem could be solved with surgical repair of the nasal breathing and then the use of CPAP could be more comfortable. The full face mask is not a good option for most of the patients. On the other hand, the use of CPAP itself can cause hypertrophy of the nasal mucosa due to the constant positive pressure during the night. In such cases some of the patients stop using the machine and seek for medical or surgical treatment of the difficult nasal breathing. In most of the cases with CPAP intolerance, combined treatment with surgery and oral appliances could be beneficial even in patients with severe OSA.

After the decision of changing the CPAP treatment is taken, the patient should be reevaluated in order to determine if he or she is suitable for use of oral appliances. In most of the cases the diagnosis of OSA has been set by specialists of sleep medicine, neurologist or pulmonologist on the base of EES and PSG without otorhinolaryngologist to assess the exact place of obstruction. A thorough diagnostic workout should be performed by physicians of different specialties – sleep medicine, otorhinolaryngologist, dentist-specialized in oral appliances and cardiologist, neurologist, pulmonologist etc., if comorbidities exist. The decision for the use of oral appliance is taken in collaboration mainly between the otorhinolaryngologist, the dentist and the patient. As the mechanism of action of the oral appliances is to protrude the mandibula, thus increasing the space in the oral cavity and the

pharynx, the good candidates for oral appliance are patients with 20 or more teeth, with bone loss of less than 50% and evenly disturbed occlusal tooth contact, with no problems with temporomandibular joint and paraodontitis, patients with tongue hypertrophy III or IV grade according to Friedman and retrolingual collapse, patients with retrognathia. In specific cases described in the literature it is also possible to retain the MAD on dentures, but they have to be tooth or implant supported in order to have a stable position of the jaw/teeth. (25)

Good nasal patency is essential because some of the appliances limit the opening of the mouth and the oral breathing.

If the patient is considered suitable for the use of oral appliance, the question that should be answered is what kind of appliance to be offered to the patient. Peter A Cistulli (26) in an update of the oral appliances in 2023 stated that several factors need to be considered when selecting a device:

Two-piece MAS allow more mandibular movement and have a greater range of settings than a one-piece MAS. As a result, they tend to be more comfortable and more effective.

MAS that maintain mandibular advancement while permitting lateral jaw movement, jaw opening, or jaw closing may reduce the risk of complications and achieve better patient acceptance, although limited data suggest that the amount of vertical opening should be minimized.

Custom-fitted MAS are preferable to self-administered over-the-counter prefabricated varieties because they appear to be more effective and comfortable, and are more likely to be retained by both the upper and lower teeth, ensuring that the lower jaw does not fall out of the appliance during sleep.

Full occlusal coverage may be desirable to distribute the dental forces associated with mandibular advancement, thereby reducing the risk of tooth movements.

In a review of the success rate of the different kinds of devices J. Venema et al (27) find that monoblock appliances performed more favorable, compared to bilateral thrust. midline traction appliances performed more favorable, compared to other designs. Custom appliances performed more favorable, compared to thermoplastic appli-

ances. Furthermore, there were no clinically relevant differences between MAD designs in reduction of ESS, compliance, preference, side effects, and cost effectiveness. They concluded that with respect to the included trials, presently there is not one superior custom MAD design in OSA treatment regarding the effect on AHI reduction, ESS improvement, compliance, preference, side effects, cost effectiveness, and other disease-related outcomes. While many experts recommend the use of a tailored device to achieve efficacy and comfort (which affects factors such as the patient removing the device during the night or the device falling out), the TOMADO trial found that many participants preferred the semi-tailored MADs (28). The trial concluded that semi-tailored devices were the most cost-effective in the short term and should be the first-choice device. Tailored MADs may be reserved for patients who have difficulty producing their own mould for a semi-tailored device or whose dental eligibility is more marginal (12).

Our experience shows that some patients who came to us has already had boil and bite devices which they find effective but uncomfortable and they like to change them with a custom (tailor) made devices. Such patients are very good candidates for manufactured oral device. Some of them wanted sleep endoscopy with their boil and bite devices just to be sure that they will have much benefit from the new oral device.

The successive rate of the use of oral appliances is a function of several consecutive decisions, choices and actions: to find the proper patient, to offer the proper oral appliance, to manufacture it with most comfort and effectiveness to the patient to titrate the device and follow the patient. Polysomnography with the oral devices is of great value to assess the effectiveness of the appliance. The high successive rate of our patients treated with oral appliances is due, in our opinion, to the precise pretreatment assessment of the patients. The oral appliances were used mainly in patients with mild or moderate grade of OSA. The patients with severe OSA were only 3. The exact determination of the site of obstruction is very essential for the correct treatment. Most of our patients had multilevel obstruction. The nasal patency had to be surgically corrected before the treatment with oral appliances in 9 patients. The good nasal patency is of great importance of the high adherence of the

patients using the TAP appliances, in which the mouth is closed and fixed by the splint.

Adverse effects are usually minor and infrequently require discontinuation of the oral appliance. The decision to discontinue the appliance should balance the magnitude of the adverse effect, the severity of OSA, the response to therapy, and the desirability of treatment alternatives (26). They could be early side effects (first few weeks) and late side effects. Most patients experience early side effects, particularly dental discomfort (usually of the upper and lower incisors). Other early side effects include temporomandibular joint pain, dry mouth or excessive salivation, gum irritation, and bruxism. These side effects are generally mild to moderate in severity, usually last a few weeks or less, and tend to subside over time. (26). Late side effects (occlusal changes; months to years) – occlusal (bite) changes are the major long-term adverse effect of oral appliances. Other rare late side effects include tooth loosening and device fracture, which have the potential to cause airway obstruction. Reduced efficacy due to device deterioration can also occur over time. (26).

The treatment of our patients did not show significant side effects of the oral appliances with exception of some morning stiffness of the jaws, which was seen in 5 patients and salivation during sleep in one. Most of the complications of the oral appliances are mild and temporary and are associated with the greater level of protrusion (28). Our patients were evaluated precisely and the planned protrusion was measured by George gouge. The long term side effects involving dentofacial changes leading to decrease in overbite and overjet which are noted as early as 6 months after the use of the oral appliance (30). None of our patients had such side effects. Probably the relatively short period of follow up – 2 or 3 years did not allow us to find such complications, but on the other hand the precise measurement and fitting of the appliance could prevent their appearance. A recent study from the Netherlands examined the dental side effects of OSA therapy with MAD Device and CPAP for a period of 10 years. Both treatment options (MAD and CPAP) showed significant dental changes (decrease of overate and overbite) which were progressing with the duration of the treatment (31).



Conclusions

Oral appliances are high effective in the treatment of selected patients with OSA, mainly mild and moderate cases according to the AHI.

The precise pretreatment workout is of uppermost importance in assessment of the grade of OSA and the site of obstruction.

If there is a multilevel obstruction, combined treatment with surgery and oral appliances could be a viable option for such patients.

The precise measurement and fitting of the oral appliance probably plays certain role in prevention of such complications as dentofacial changes.

References:

1. Flemons WW. Obstructive sleep apnea. *N Engl J Med.* 2002 Aug 15;347(7):49
2. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoe. *Lancet.* 2014;383(9918): 737-7478-504.
3. American Academy of Sleep Medicine Task Force Report. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep.* 1999; 22:667-89. AASM. [PubMed: 10450601]
4. Epstein LJ, Kristo D, Strollo PJ Jr, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med.*
5. National Institute for Health and Clinical Excellence. Continuous positive airway pressure for obstructive sleep apnea/hypopnea syndrome. 2008. Available online: <https://www.nice.org.uk/guidance/ta139/resources/continuous-positive-airway-pressure-for-obstructive-sleep-apnoeahypopnoea-syndrome-pdf-374791501>
6. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008; 5:173-8.
7. Bencheva M, Benchev R, Stoilov M. Oral appliances for the treatment of mild and moderate Obstructive Sleep Apnea. *International Bulletin of Otorhinolaryngology* 2019; 4: 5-13.
8. Robin P. Glossoptosis due to atresia and hypotrophy of the mandible. *Am J Dis Child* 1934; 48: 541-7.
9. Sutherland K, Cistulli P. Mandibular advancement splints for the treatment of sleep apnea syndrome. *Swiss Med Wkly.* 2011;141: w13276.
10. Brown EC, Cheng S, McKenzie DK, et al. Respiratory Movement of Upper Airway Tissue in Obstructive Sleep Apnea. *Sleep* 2013; 36:1069-76.
11. Василева С. Съвременни методи за оперативно лечение на разстройствата на дишане по време на сън. Дисертационен труд за присъждане на образователна и научна степен „Доктор“, 2014 г.
12. The Royal Australian College of General Practitioners. Mandibular advancement devices: obstructive sleep apnoea. www.racgp.org.au/handi 2016.
13. Sutherland K, Vanderveken OM, Tsuda H, et al. Oral appliance treatment for obstructive sleep apnea: an update. *J Clin Sleep Med.* 2014; 10(2):215-227.
14. Basyuni S, Barabas M, Quinell T. An update on mandibular advancement devices for the treatment of obstructive apnea hypopnea syndrome. *Journal of Thoracic Diseases* 2018; 10 (Suppl 1): S48-56.
15. Gjerde K, Lehmann S, Berge ME, Johansson AK, Johansson A. Oral appliance treatment in moderate and severe obstructive sleep apnoea patients non-adherent to CPAP. *J Oral Rehabil.* 2016;43(4):249-258.
16. Blanco J, Zamarron C, Abeleira Pazos MT, et al. Prospective evaluation of an oral appliance in the treatment of obstructive sleep apnea syndrome. *Sleep Breath* 2005; 9: 20-5.
17. Petri N, Svanholt P, Solow B, et al. Mandibular advancement appliance for obstructive sleep apnoea: results of a randomized placebo controlled trial using parallel group design. *J Sleep Res* 2008;17: 221-9.
18. Vanderveken OM, Devolder A, Marklund M, et al. Comparison of a custom-made and a thermoplastic oral appliance for the treatment of mild sleep apnea. *Am J Respir Crit Care Med* 2008;178:197-202.
19. Quinell TG, Bennett M, Jordan J, et al. A crossover randomised controlled trial of oral mandibular advancement devices for obstructive sleep apnoea- hypopnoea (TOMADO). *Thorax* 2014; 69: 938-45.
20. Aarab G, Lobbezoo F, Heymans MW, et al. Long- term follow-up of a randomized controlled trial of oral
21. appliance therapy in obstructive sleep apnea. *Respiration* 2011;82:162-8
22. Gotsopoulos H, Chen C, Qian J, et al. Oral appliance therapy improves symptoms in obstructive sleep apnea: A randomized, controlled trial. *Am J Respir Crit Care Med* 2002;166: 743-8.
23. Johnston CD, Gleadhill IC, Cinnamond MJ, et al. Mandibular advancement appliances and obstructive sleep apnoea: A randomized clinical trial. *Eur J Orthod* 2002; 24: 251-62.
24. Mehta A, Qian J, Petocz P, et al. A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. *Am J Respir Crit Care Med* 2001; 163: 1457-61.
25. Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med.* 2013;187: 879-887.
26. Pokpong Amornvit, Dinesh Rokaya, Sahana Bajracharya, Konrawee Keawcharoen, Walop Supavanich. Management of Obstructive Sleep Apnea with Implant Retained Mandibular Advancement Device, *World Journal of Dentistry*, July-September 2014;5(3):184-189 .
27. Cistulli P. Oral appliances in the treatment of obstructive sleep apnea in adults Official reprint from UpToDate® www.uptodate.com © 2023
28. Venema J, Rosenmuller B. de Vries N, et al. Mandibular advancement device design: A systematic review on outcomes in obstructive sleep apnea treatment. *Sleep Medicine Reviews* 60 (2021) 101557, www.elsevier.com/locate/smr
29. Sharples L, Glover M, Clutterbuck-James A et al. Clinical effectiveness and cost-effectiveness results from the randomised controlled trial of oral mandibular advancement devices for obstructive sleep apnoea-hypopnoea (TOMADO) and longterm economic analysis of oral devices and continuous positive airway pressure. *Health Technol Assess.* 2014;18(67):1-296.
30. Aarab G, Lobbezoo F, Hamburger HL, et al. Effects of an oral appliance with different mandibular protrusion positions at a constant vertical dimension on obstructive sleep apnea. *Clin Oral Investig* 2010; 14: 339-45
31. Robertson C, Herbison P, Harkness M. Dental and occlusal changes during mandibular advancement splint therapy in sleep disordered patients. *Eur J Orthod* 200 3;25: 371-6
32. Venema J., Doff M., Joffe-Sokolova Det al. Dental side effects of long-term obstructive sleep apnea therapy: a 10-year follow-up study. *Clinical Oral Investigations* 9/2020