REDELVE INTERNATIONAL PUBLICATIONS

Dentistry: Advanced Research
Volume 2019, Issue 01
Review Article: RD-DEN-10003

The Future Perspectives in Multidisciplinary Approaches of Oral Appliance Therapy in Obstructive Sleep Apnea

Aranka Ilea[1], Daniela Timuș[2], Julian Höpken[3], Vlad Andrei[4], Anida-Maria Băbțan[1], Nausica Bianca Petrescu[1], Radu Septimiu Câmpian[1], Bianca Adina Boșca[5], Alina Simona Șovrea[5], Marius Negucioiu[6], Anca Ștefania Mesaros[7]*

[1]"Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Department of Oral Rehabilitation, Oral Health and Dental Office Management, Faculty of Dentistry, Romania
[2]Student in the 6th year of "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Faculty of Dentistry, Romania
[3]Postgraduate student of "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Faculty of Dentistry, Romania
[4]Rezident doctor in Periodontology, Clinical County Hospital of Târgu Mureș, Romania
[*5]"Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Department of Histology, Faculty of Medicine, Romania
[6]"Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Department of Prosthodontics, Romania
[7]"Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Department of Dental Propedeutics and Esthetics, Faculty of Dentistry, Romania

***Corresponding author:** Boșca Adina Bianca, Department of Histology, Faculty of Medicine, "Iuliu Haţieganu", University of Medicine and Pharmacy, Cluj-Napoca, Romania. Postcode : 400349 ; Tel: +40740248923 ; Email : biancabosca@yahoo.com*

***Citation:** Ilea A, Timuș D, Höpken J, Andrei V, Băbțan AM, et al. (2019) The Future Perspectives in Multidisciplinary Approaches of Oral Appliance Therapy in Obstructive Sleep Apnea. Dentistry: Advanced Research. Review| ReDelve: RD-DEN-10003.*

***Received Date:** 14 January 2019; **Acceptance Date:** 11 February 2019; **Published Date:** 12 February 2019*

Abstract

Obstructive Sleep Apnea (OSA) is a respiratory sleep disorder characterized by recurrent obstruction of the upper airways during sleep which results into sleep fragmentation and loud snoring and are accompanied with multiple biochemical disturbances. Non-invasive and continuous assessment using a biosensor attached to an Oral Appliance (OA), can be a future solution for assessing and treating patients with OSA. This device would be not only a therapeutic tool, but also a diagnostic and monitorization device for the specialist.

Keywords: Dentistry; Mandibular Repositioning Device; Mandibular Advancement Splint; Mandibular Advancement Device; Oral Appliance; Obstructive Sleep Apnea; Salivary Biosensors

Abbreviations

AASM	:	American Academy of Sleep Medicine
AHI	:	Apnea-Hypopnea Index
CPAP	:	Continuous Positive Airway Pressure
MAD	:	Mandibular Advancement Device
MAS	:	Mandibular Advancement Splints

OA : Oral Appliances
OAT : Oral Appliance Therapy
OSA : Obstructive Sleep Apnea

Introduction

Obstructive Sleep Apnea (OSA) is a respiratory sleep disorder characterized by recurrent obstruction of the upper airways during sleep which results into sleep fragmentation and loud snoring. The degree of OSA is commonly classified using the Apnea-Hypopnea Index (AHI). This index quantifie 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 15-30), or severe (AHI >30) [1].

The study of Aarab G. et al. 2010 investigates the effects of an Oral Appliance (OA) with different mandibular protrusion positions on OSA. This was a randomized clinical trial conducted on 17 participants for 39 weeks. All participants met the inclusion criteria of having an AHI of 5-45/hour and presenting 2 or more OSA symptoms. The methods for assessing the effects of the oral appliance were polysomnography, for the determination of AHI, and questionnaires for evaluating subjective symptoms changes. The design of the mandibular repositioning device was not specified, but a mean maximal mandibular protrusion of 9.6 mm was described. As an outcome, the study revealed that the AHI decreased to normal values (AHI < 5/ hour) in 12 out of 17 participants using the oral appliance, giving a success rate of 70% for oral appliance therapy (OAT). The study also reported a compliance rate of 97% and a decrease in snoring intensity along the participants [2].

Benoist L. et al. conducted a multicenter prospective randomized controlled trial of OAT for position-related sleep apnea. The trial of a 3-month period included 36 participants with mild to moderate OSA (AHI >5/hour). Beside other measuring methods which were not relevant for the present review, polysomnography and a questionnaire were used for assessing the effectiveness of a custom-made tritrable OA (SomnoDent flex from SomnoMed, Sydney, Australia), set at a maximal protrusion of 75% or 90%. The outcome of the investigation was the reduction of the AHI mean from 11.7 [9.0-16.2] to 9.1 [4.9-11.7], $p < 0.001$, demonstrating that AHI dropped by 46.5%. The questionnaire revealed a compliance rate for the OAT of 88.8%, but no relevant change in quality of life [3].

Another randomized clinical trial included in this review was performed by Cilil V.R. et al. in 2015 [4]. It investigated the efficiency of custom-made OA for treatment of OSA on several 15 participants with an AHI value of > 5-15/hour and was followed up for 1 month. Polysomnography was used to establish the outcome with and without oral appliance. The results showed that the mean AHI decreased from 23.8 ± 18.12 to 10.87 ± 11.56 while 8 out of 15 patients showed a decrease with 50% of the initial AHI value. The study did not provide data about subjective measurements because a questionnaire was not used.

Filiz K. et al. conducted a case report of an edentulous, 63-year old woman, who was diagnosed with intrusive snoring and an AHI of 13.3/hour (mild OSA) [5]. The patient was followed up for a 5-month period and was investigated using polysomnography and a questionnaire. The device used in this study was a modified mandibular repositioning appliance shaped as a complete denture. The polysomnographic measurements before and after the 5-month interval demonstrated an AHI reduction from 13.3 events/hour to 3.0 events/hour and a decrease of apneic duration from 31.5 seconds to 16.5 seconds. The questionnaire revealed that the OA

also reduced snoring, wake gasping and choking, as well as diminished daytime sleepiness and headache.

A comparison between the efficacy of continuous positive airway pressure treatment and OAT was performed by Hoekema A. et al. in 2008 [6]. The parallel randomized clinical trial investigated 47 patients who received Continuous Positive Airway Pressure (CPAP) treatment and 47 patients with OAT. The participants were investigated after 8-12 weeks. Inclusion criteria for the patients was the presence of OSA with an AHI > 5 events/hour. The measurements for the baseline and follow-up evaluations were conducted by polysomnography while the participants slept at home and a questionnaire was used to evaluate compliance. The oral appliance used in the study group of 47 patients was the Thornton Adjustable Positioner type-1 (from Airway Management Inc., Dallas, Texas, USA). The trial demonstrated that the oral appliance therapy was effective in reducing the AHI according to the success criteria of the American Academy of Sleep Medicine (AASM) in 39 patients, while 8 patients were non-responsive to the therapy. Furthermore, the questionnaire showed that 42 patients wore the Mandibular Advancement Device (MAD) 7 nights/week, while 46 wore it more than 5 hours/night. The study revealed an OA effectiveness of 76.5%.

Johal A. et al. performed a randomized crossover trial for a 3-month period [7]. The study investigated the effectiveness of ready-made and custom-made mandibular repositioning devices in the treatment of sleep apnea. Several 25 participants with an AHI > 10/hour, considered as mild OSA, wore both types of oral appliances during various follow-up periods. Polysomnography and questionnaires were used for obtaining the results. The oral appliances used in this study were a custom-made mandibular repositioning device (Medical Dental Sleep Appliance) and a ready-made mandibular repositioning device (Snore shield). Based on the results of the polysomnographic evaluation, the trial with the custom-made mandibular repositioning device demonstrated that 24 out of the 25 participants (96%) showed a total treatment success while in the trial with the ready-made mandibular repositioning device, 16 out of 25 participants (64%) had a successful treatment outcome. Furthermore, the questionnaires revealed that both types of oral appliances showed a statistically significant improvement in quality of life. Also, the custom-made mandibular repositioning device showed effectiveness in terms of compliance (MAD was worn in average 7 nights per week and 5 hours/night in 25 patients).

Kaur A. et al. conducted a pre- and post-trial comparison study for the evaluation of the effect of a MAD on oropharyngeal dimension and parameters for severity in patients with OSA [8]. Several 20 patients with mild to moderate OSA were evaluated at baseline and after 4-6 weeks of using a MAD. Besides a computer tomographic investigation to determine the oropharyngeal dimension, polysomnography and a questionnaire were used. The 20 participants received a Twin Block appliance which was set to 75% of maximum mandibular protrusion or to at least 7 mm of mandibular advancement. The polysomnographic measurements before and after the trial showed that the AHI score decreased from 43.83 ± 30.00 to 20.31 ± 14.58. The reduction of the AHI score had a mean of 53.39% in all participants. The answers to the questionnaires showed a significant decrease in snoring volume, frequency and duration.

A randomized clinical trial performed by Miljus D et al. in 2014, with a 6-month duration, included 15 participants diagnosed with mild to moderate OSA (AHI >10/hour) [9]. The participants received a custom-made mandibular repositioning appliance, which was designed at a position of 50% of maximum mandibular advancement. The results of the therapy with the oral appliance were evaluated using polysomnographic measurements and questionnaires. The

study revealed that the AHI values of the patients were significantly lower ($p < 0.05$) at the end of the 6-month follow-up period in comparison to the values at the beginning of the treatment. The mean AHI decreased from 15-28 events/hour to 6.1 ± 3.5, while 7 out of 15 patients showed a complete success and another 7 participants showed a partial success of the treatment. Treatment failure was mentioned in 1 patient. Additionally, the results from the questionnaires showed an overall increase in sleep quality, a decrease in snoring and a reduced daytime sleepiness.

Nerfeldt P. et al. also investigated the effectiveness of OA in the treatment of OSA by using a prospective intervention study [10]. Several 36 patients with mild to moderate OSA and an AHI score > 5 events/hour agreed to a follow-up period of 12 months. The follow-up involved polysomnographic evaluations and questionnaires. The subjects received different types of oral devices: 58% received a hard monobloc, 8% a soft monobloc and 34% a two-piece or split device. The oral appliances were set to 75% of maximal protrusion. At the end of the follow-up period, the study reported that 27 patients (75%) had a successful OAT according to the AHI criteria. Among the successfully treated patients, an AHI reduction of 74% for arousers and 68% for desaturaters was observed. In terms of subjective outcomes, the questionnaires showed a compliance rate of 85% (28 out of 33 patients), improved sleep in 59%, improved daytime sleepiness in 52%, improved general health in 33% and improved quality of life in 41% of the study group.

Phillips C.L. et al. performed a randomized crossover trial of one-month duration in which several 108 study subjects with mild to moderate OSA (AHI > 10 events/hour) participated [11]. In this study, polysomnography as well as questionnaires were used for assessing the health outcome for OAT in comparison to CPAP. The device used on all participants was the SomnoDent custom fitted two-piece and tritrable MAD (from SomnoMed Ltd., Sydney, Australia). The set mean mandibular advancement was 8.09 ± 2.6 mm or a range from 1.1-15 mm. The result measured with polysomnography after the follow-up period was a reduction of the mean AHI from 25.6 ± 12.3 to 11.1 ± 12.1/hour ($p = 0.01$). The decrease of AHI score was more significant in the treatment with CPAP. On the other hand, patients treated with MAD reported in the questionnaires a longer sleep and higher compliance compared with CPAP treatment. Furthermore, 55 patients out of the 108 (51%) preferred a MAD for the treatment of their condition.

Next, Sari E. et al. conducted a randomized clinical trial of one-month duration [12]. Out of the 24 participants, half had mild OSA, while the other half had moderate OSA. Moreover, in this study the polysomnographic evaluation and questionnaires were used to assess objective and subjective treatment outcome. The group of 24 patients was split into half and each half (12 patients) received either a Mandibular Advancement Splint (MAS) or the oral appliance "Klearway". The MAS was set to 75% of maximal protrusion and for the Klearway appliance, the dentist advanced the appliance by 0.5mm per week. After the follow-up period, the Klearway group showed a decrease in AHI from the baseline mean value of 18.8 ± 7.3 to the final mean value of 7.3 ± 3. The MAS group showed an AHI score reduction from 17.9 ±6.8 to 9.1 ± 4.9. Regarding the success rate of both treatment modalities, 10 out of 12 patients in the Klearway group were successfully treated, while 8 out of 12 in the MAS group had a successful response. Based on the questionnaire's results, all patients reported an improved sleep and the reduction of snoring.

Another randomized clinical trial, performed by Schütz T.C. et al. in 2013, lasted 2 months [13]. In this trial, several 9 patients with mild to moderate OSA and an AHI of > 10/hour were

included. The study used polysomnography for determination of the AHI score and did not include a questionnaire. An individually constructed and installed MAD (Brazilian Dental Appliance, Sao Paulo, SP, Brazil) was used for all patients. At the beginning of the trial, the baseline mean AHI was 30.8 ± 19.0 and dropped to 9.6 ± 10.3 ($p < 0.001$) by the end. The author of the study stated that the AHI was significantly reduced in all subjects. There was no subjective outcome determined due to the absence of a questionnaire.

In 2015, a retrospective analysis of clinical trials from the past 13 years was done by Sutherland K. et al [14]. The patients of the analyzed trials were summed up to a total number of 425 patients with an AHI score of > 10/hour. The analysis focused on polysomnographic results. The oral appliance used in the trials was a custom-made two-piece MAD known as SomnoDent device (SomnoMed Ltd., Sydney, Australia). The mean result across the patient group was a reduction of the AHI score by 50.3% ± 50.7%.

The controlled, prospective longitudinal crossover study by Teixeira AO de B. et al. in 2013 lasted over a 10.5-month period and included 19 cases with mild to moderate OSA [15]. An AHI of > 5 events/hour was set as inclusion criteria for the study. Moreover, only polysomnography was used for assessment of the efficacy of the treatment. The participants received a modified Twin Bloc as MAD, which was set to 75% of each patient's maximal mandibular protrusion. The outcome of the study revealed an AHI reduction from 16.3 events/hour to 11.7 events/hour. Additionally, 47% of the patients showed an improvement (partial response) in the AHI score and 26% had a reduction until a normal AHI (complete response).

A non-randomized clinical trial pilot study was conducted by Tihacek-Sojic et al. in 2012 [16]. The study lasted over a 12 months period and included 20 participants with mild to moderate OSA and an AHI of > 10/hour. The participants were investigated using polysomnography and a questionnaire assessing the subjective symptoms during the therapy. The intervention involved a custom-made MAD, which advanced the mandible by 50%-70% (62% in average) of its maximal protrusion. After the trial period, an average AHI of 6.70/h ± 4.43 was determined with polysomnography. Furthermore, 75% (15 patients out of 20) showed a complete or partial treatment success. The questionnaire used in this study revealed that 80% of the patients had a decrease in snoring, their quality of life was improved in 94% and all subjects of the trial group experienced a decrease in daytime sleepiness.

Future Perspectives

Non-invasive and continuous assessment using a biosensor attached to an OA, can be a future solution for assessing and treating patients with OSA.

In recent years, saliva has been characterized as an alternative to the invasive collection of body fluids, such as plasma or urine. This owns to the fact that a multitude of compounds can be determined from saliva, such as glucose, cortisol, salivary proteins, ammonia, carbon dioxide, pathogens and tumoral markers, among others, with a strong correlation between plasmatic and salivary concentrations [17].

The challenge, however, has proven to be the continuous data collection and wireless transmission of this acquired information to collection devices. Furthermore, given the large amount of data that is collected, a decision should be taken regarding the continuous collection of information versus a pre-determined sequential timed collection, which would allow an easier handling of the information. A proof of concept in this regard has first been published

by Arakawa et al. in 2016, when the authors integrated a platinum and silver/ silver chloride electrode in a mouth guard for the continuous measurement of salivary glucose [18].

There are several biological parameters and compounds that can be detected in saliva, relevant to the diagnosis of OSA, with biosensors already developed for their detection [19]. Zilberman Y et al. have developed a portable optoelectronic microfluidic sensor for the salivary detection of ammonia and carbon dioxide [20]. Another biosensor has been developed by Ciui B et al. for the detection of N-epsilon (carboxymethyl) lysine in saliva, a major advanced glycated end product [21]. Advanced glycation end products have been proved to be reliable tools for the evaluation and monitorization of the metabolic syndrome [22].

The constant development and miniaturization of these sensors could mean that, in the future, one or more of these devices could be integrated in OA, allowing for the assessment of relevant parameters for the accurate diagnosis of OSA. This could widen the spectrum of information available not only for the accurate diagnosis of OSA, but also for the monitorization and follow-up of the treatment effectiveness. Furthermore, it would allow for the OA to be not only a therapeutic device, but also a diagnostic and monitorization tool for the specialist.

Conclusions

The treatment of obstructive sleep apnea should be considered a multidisciplinary undertaking. The specialist in sleep disorders should collaborate with the dental practitioner and orthodontist for the development of OAs. Furthermore, with the development of biosensors and the advantages that these medical devices could have, with their integration in OAs, chemists and engineers should be consulted in order to determine the correct applicability and limitation of these systems. Only using a multidisciplinary approach can the interception, treatment and monitorization of OSA to be fully achieved.

Acknowledgements

Aranka Ilea, Daniela Timuș, Julian Höpken and Vlad Andrei have equal contribution as first authors of this article.

This research was supported partially by the internal grant No. 4995/2/08.03.2016 of "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania and the COFUND-ERA-HDHL ERANET Project, European and International Cooperation - Subprogram 3.2 - Horizon 2020, PNCDI III Program - Biomarkers for Nutrition and Health - “Innovative technological approaches for validation of salivary AGEs as novel biomarkers in evaluation of risk factors in diet-related diseases”, grant no 25/1.09.2017.

References

1. Gauthier L, Almeida F, Arcache P (2012) Position paper by Canadian dental sleep medicine professionals regarding the role of different health care professionals in managing obstructive sleep apnea and snoring with oral appliances. Can Respir J 19(5): 307-309.
2. Aarab G, Lobbezoo F, Hamburger HL (2010) Effects of an oral appliance with different mandibular protrusion positions at a constant vertical dimension on obstructive sleep apnea. Clin Oral Investig 14(3): 339-345.
3. Benoist L, De Ruiter M, De Lange J (2017) A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea. Sleep Medicine 34: 109-117.
4. Cilil VR, Sapana Varma NK, Gopinath S (2015) Efficacy of custom-made oral appliance for treatment of obstructive sleep apnea. Contemp Clin Dent 6(3): 341-347.
5. Filiz K, Bülent Ç, Güven SF (2014) Management of Obstructive Sleep Apnea in an Edentulous Lower Jaw Patient with a Mandibular Advancement Device. Case Reports in Dentistry Article ID 436904.

6. Hoekema A, Stegenga B, Wijkstra PJ (2008) Obstructive sleep apnea therapy. J Dent Res 87(9): 882-887.
7. Johal A, Haria P, Manek S (2017) Ready-made versus custom-made mandibular repositioning devices in sleep apnea: a randomized clinical trial. Journal of Clinical Sleep Medicine 13(2): 175-182.
8. Kaur A, Chand P, Singh RD (2012) Computed tomographic evaluation of the effects of mandibular advancement devices on pharyngeal dimension changes in patients with obstructive sleep apnea. Int J Prosthodont 25(5): 497-505.
9. Miljuš D, Tihacek-Šojic L, Milic-Lemic A (2014) Treatment of obstructive sleep apnea patients using oral appliances - our experience. Vojnosanit Pregl 71(7): 623-626.
10. Nerfeldt P, Friberg D (2016) Effectiveness of Oral Appliances in Obstructive Sleep Apnea with Respiratory Arousals. J Clin Sleep Med 12(8): 1159-1165.
11. Phillips CL, Grunstein RR, Darendeliler MA (2013) 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 187(8): 879-887.
12. Sari E, Menillo S (2011) Comparison of Titratable Oral Appliance and Mandibular Advancement Splint in the Treatment of Patients with Obstructive Sleep Apnea. ISRN Dent 581692.
13. Schütz TC, Cunha TC, Moura-Guimaraes T (2013) Comparison of the effects of continuous positive airway pressure, oral appliance and exercise training in obstructive sleep apnea syndrome. Clinics 68(8): 1168-1174.
14. Sutherland K, Takaya H, Qian J (2015) Oral Appliance Treatment Response and Polysomnographic Phenotypes of Obstructive Sleep Apnea. Journal of Clinical Sleep Medicine 11(8): 861-886.
15. Teixeira AO de B, Abi-Ramia LBP, Almeida MA de O (2013) Treatment of obstructive sleep apnea with oral appliances. Progress in Orthodontics 14: 10.
16. Tihacek-Sojic L, Andjelkovic M, Milic-Lemic A (2012) The effectiveness of oral appliances in elderly patients with obstructive sleep apnoea treated with lorazepam, a pilot study. J Oral Rehabil 39(10): 785-790.
17. Bandodkar AJ, Wang J (2014) Non-invasive wearable electrochemical sensors: a review. Trends Biotechnol 32: 363-371.
18. Arakawa T, Kuroki Y, Nitta H, Chouhan P, Toma K (2016) Mouthguard biosensor with telemetry system for monitoring of saliva glucose : A novel cavitas sensor. Biosens Bioelectron 84: 106-111.
19. Ilea A, Andrei V, Feurdean CN (2019) Saliva, a Magic Biofluid Available for Multilevel Assessment and a Mirror of General Health-A Systematic Review. Biosensors (Basel) 9(1): pii: E27. doi: 10.3390/bios9010027
20. Zilberman Y, Sonkusale SR (2015) Microfluidic optoelectronic sensor for salivary diagnostics of stomach cancer. Biosens Bioelectron 67: 465-471.
21. Ciui B, Tertis M, Feurdean CN, Ilea A, Sandulescu R (2019) Cavitas electrochemical sensor toward detection of N-epsilon (carboxymethyl)lysine in oral cavity. Sens. Actuators B Chem 281: 399-407.
22. Ilea A, Băbţan AM, Boşca BA, Crişan M, Petrescu NB (2018) Advanced glycation end products (AGEs) in oral pathology. Arch Oral Biol 93: 22-30.