

## Articles of the Month – October 2021

### MAD

J Clin Sleep Med. 2021 Oct 6.  
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### Functional imaging improves patient selection for mandibular advancement device treatment outcome in sleep-disordered breathing: a prospective study

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**Study objectives:** Mandibular advancement devices (MAD) are a non-invasive treatment option for patients with obstructive sleep apnea (OSA) and act by increasing the upper airway volume. However, the exact therapeutic mechanism of action remains unclear. The aim of this study was to assess MAD mechanisms using functional imaging, that combines imaging techniques and computational fluid dynamics (CFD) and assess associations with treatment outcome.

**Methods:** One hundred OSA patients were prospectively included and treated with a custom-made MAD at a fixed 75% protrusion. A low-dose CT scan was made with and without MAD for CFD analysis. Patients underwent a baseline and 3-month follow-up polysomnography to evaluate treatment efficacy. A reduction in apnea-hypopnea index (AHI)  $\geq 50\%$  defined treatment response.

**Results:** Overall, 71 patients completed both 3-month follow-up polysomnography and low-dose CT scan with CFD analysis. MAD treatment significantly reduced the AHI (16.5 (10.4-23.6) events/h to 9.1 (3.9-16.4) events/h,  $P < 0.001$ , median (Q1-Q3)) and significantly increased the total upper airway volume (8.6 (5.4-12.8)  $\text{cm}^3$  vs. 10.7 (6.4-15.4)  $\text{cm}^3$ ;  $P = 0.003$ ), especially the velopharyngeal volume (2.1 (0.5-4.1)  $\text{cm}^3$  vs. 3.3 (1.8-6.0)  $\text{cm}^3$ ;  $P < 0.001$ ). However, subanalyses in responders and non-responders only showed a significant increase in the total upper airway volume in responders, not in non-responders.

**Conclusions:** MAD acts by increasing the total upper airway volume, predominantly due to an increase in the velopharyngeal volume. Responders showed a significant increase in the total upper airway volume with MAD treatment, while there was no significant increase in non-responders. Findings add evidence to implement functional imaging using CFD in routine MAD outcome prediction.

**EADSM comment:** Interesting way forward to predict treatment response with MADs.

## Development of a physiological-based model that uses standard polysomnography and clinical data to predict oral appliance treatment outcomes in obstructive sleep apnea

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**Study objectives:** Oral appliance (OA) therapy is a well-tolerated alternative to continuous positive airway pressure (CPAP). However, it is less efficacious. A major unresolved clinical challenge is the inability to accurately predict who will respond to OA therapy. We recently developed a model to estimate obstructive sleep apnea (OSA) pathophysiological endotypes. This study aimed to apply this physiological-based model to predict OA treatment responses.

**Methods:** 62 men and women with OSA (aged 29-71y) were studied to investigate the efficacy of a novel OA device. An in-laboratory diagnostic followed by an OA treatment efficacy polysomnography were performed. 7 polysomnography variables from the diagnostic study plus age and body mass index were included in our machine learning based model to predict OA therapy response according to standard apnea-hypopnea index (AHI) definitions. Initially, the model was trained on data from the first 45 participants using 10-fold cross-validation. A blinded independent validation was then performed for the remaining 17 participants.

**Results:** Mean accuracy of the trained model to predict OA therapy responders vs. non-responders (AHI<5events/h) using 10-fold cross-validation was 91±8%. All 17 individuals were correctly classified in the independent blinded validation (AHI<5events/h); 59% (AHI<10events/h); 71% (50% reduction in AHI) and 82% (50% reduction in AHI to <20events/h).

**Conclusions:** While further evaluation in larger clinical datasets is required, these findings highlight the potential to use routinely collected sleep study and clinical data with machine learning based approaches underpinned by OSA endotype concepts to help predict treatment outcomes to OA therapy for people with OSA.

**EADSM comment:** Using available data from the polysomnographic sleep recording in addition to demographic data will become very useful in the light of the recent news that polysomnographic method will become easier to use in the clinic and therefore more available.

Sleep Med Rev. 2021 Aug;58:101513.

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Link:

<https://reader.elsevier.com/reader/sd/pii/S1087079221000988?token=1DE7CE98A6972666D95047D8A7B58E2FF592409CCC2A4CAFB88D67C080109D66CE86E906432814777B8452040384A0C0&originRegion=eu-west-1&originCreation=20211102083618>

## **Treatment-emergent central sleep apnea associated with non-positive airway pressure therapies in obstructive sleep apnea patients: A systematic review**

Mathieu Berger<sup>1</sup>, Geoffroy Solelhac<sup>2</sup>, Christian Horvath<sup>3</sup>, Raphael Heinzer<sup>2</sup>, Anne-Kathrin Brill<sup>3</sup>

This systematic review summarizes the prevalence of treatment-emergent central sleep apnea (TECSA) occurring with therapies other than positive airway pressure (PAP) for the management of obstructive sleep apnea (OSA). We describe its natural course as well as the proposed underlying pathophysiological mechanisms and the clinical management of affected patients. A systematic search of PubMed, Embase, Web of science, and the Cochrane Library was performed until June 2020. Eighteen studies (n = 284 patients) were included. TECSA was observed in 31 patients with the use of four different medical devices (mandibular advancement device, hypoglossal nerve stimulation, tongue stabilizing device and nasal expiratory PAP) and after three different types of surgical treatments (tracheostomy, maxillofacial surgery and oro-nasal surgery). Due to the paucity of data available, it was not possible to establish a clear prevalence rate of TECSA for each alternative treatment. After the initiation of non-PAP treatments, a systematic reassessment of the treatment efficacy with follow-up sleep studies will be helpful to identify TECSA. A spontaneous resolution over time was described as well as a persistence of TECSA. In this case, treatment should focus on patients' specific underlying pathophysiology. Overall, the limited current literature suggests that this phenomenon is rare (<4%).

**EADSM comment:** An unusual phenomenon, but still important to be aware of, that central sleep apneas may increase, when obstructive sleep apneas are diminished with a non-PAP therapy.

Sleep Med Rev. 2021 Jul 1;60:101521.

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Link:

<https://reader.elsevier.com/reader/sd/pii/S1087079221001064?token=B40B31BD17F60AEA8F9393434E77C49731C6E1530C36F5474E8DAB38E9EF0520A6743DED20E150F0C1473EB451AE9087&originRegion=eu-west-1&originCreation=20211102084942>

## **Non-continuous positive airway pressure treatment options in obstructive sleep apnoea: A pathophysiological perspective**

Marcello Bosi<sup>1</sup>, Serena Incerti Parenti<sup>2</sup>, Antonio Sanna<sup>3</sup>, Giuseppe Plazzi<sup>4</sup>, Andrea De Vito<sup>5</sup>, Giulio Alessandri-Bonetti<sup>6</sup>

The phenotyping of the pathophysiology of obstructive sleep apnoea (OSA) lies at the core of tailored treatments and it is one of the most debated topics in sleep medicine research. Recent sophisticated techniques have broadened the horizon for gaining insight into the variability of the endotypic traits in patients with OSA which account for the heterogeneity in the clinical presentation of the disease and consequently, in the outcome of treatment. However, the implementation of these concepts into clinical practice is still a major challenge for both researchers and clinicians in order to develop tailored therapies targeted to specific endotypic traits that contribute to OSA in each individual patient. This review summarizes available scientific evidence in order to point out the links between endotypic traits (pharyngeal airway collapsibility, upper airway neuromuscular compensation, loop gain and arousal threshold) and the most common non-continuous positive airway pressure (CPAP) treatment options for OSA (mandibular advancement device, upper airway surgery, medication therapy, positional therapy) and to clarify to what extent endotypic traits could help to better predict the success of these therapies. A narrative guide is provided; current design limitations and future avenues of research are discussed, with clinical and research perspectives.

**EADSM comment:** Important overview about various indications for non-PAP therapies.

## **Mandibular advancement device design: A systematic review on outcomes in obstructive sleep apnea treatment**

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Obstructive Sleep Apnea (OSA) is often treated with Mandibular Advancement Devices (MADs). It is unclear whether particular design features are superior to others in terms of OSA alleviation. In order to facilitate clinical decision-making, this systematic review summarizes the objective and subjective outcomes of different available MAD designs. Studies comparing different MAD designs in OSA treatment were searched. After screening 1887 titles and abstracts, 20 original RCTs and six cohort studies were included. 14 articles were systematically reviewed in a meta-analysis. The decrease in AHI was significantly different between some of the MAD designs. The clinical relevance of the observed differences was however limited. Monoblock appliances performed more favorable, compared to bilateral thrust (effect size:-0.37; CI:-1.81 to 0.07). Midline traction appliances performed more favorable, compared to other designs. Custom appliances performed more favorable, compared to thermoplastic appliances (effect size:0.86; CI:-0.62 to 2.35). Furthermore, there were no clinically relevant differences between MAD designs in reduction of ESS, compliance, preference, side effects, and cost effectiveness. 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. We confirm custom MAD designs perform superior to thermoplastic MAD designs.

**EADSM comment:** Subclassification of MAD designs is complicated, because various brands lacks clear views regarding which design details that are important for the efficacy, but also the side effects. This makes it almost impossible to compare the efficacy between devices, at present. Instead, various types of differences in design details should be compared separately in future research.

Sleep Breath. 2021 Sep 13.

doi: 10.1007/s11325-021-02483-0. Online ahead of print.

Link: Impact of oral appliance therapy on quality of life (QoL) of obstructive sleep apnea (OSA) patients — a systematic review and meta-analysis (springer.com)

## **Impact of oral appliance therapy on quality of life (QoL) in patients with obstructive sleep apnea - a systematic review and meta-analysis**

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**Purpose:** Treatment of patients with obstructive sleep apnea (OSA) using mandibular advancement appliances enhances the airway and may be an alternative to continuous positive airway pressure (CPAP) in individuals with reduced adherence to CPAP therapy. The effectiveness as well as improved patient compliance associated with these appliances may improve the quality of life in patients with OSA. The aim of this systematic review of studies was to determine the improvement in quality of life amongst patients with OSA who were treated with an oral appliance.

**Methods:** The research study was registered on the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021193386). A search was carried out using the search engines Google Scholar, PubMed, Ovid, Cochrane Trial Registry, and LILACS. Patients with OSA treated with oral appliance therapy to advance the mandible were studied. Twenty-five studies were identified through the literature search and all had varying control groups for assessment of quality of life. Seventeen studies were included for the quantitative synthesis.

**Results:** QoL, evaluated by the Functional Outcomes of Sleep Questionnaire (FOSQ), significantly improved in patients treated with oral appliance therapy. There was a mean difference of 1.8 points between the baseline scores and the scores following treatment with an oral appliance.

**Conclusion:** Overall, a significant improvement in the QoL was observed with the Functional Outcomes of Sleep Questionnaire, following oral appliance therapy.

**EADSM comment:** Previous studies and meta-analyses have not shown clear effects on quality of life from MAD therapy, when comparing with a placebo intervention. This meta-analysis shows effects in FOSQ scores before and after MAD therapy.

Link: Partner perceptions are associated with objective sensor-measured adherence to oral appliance therapy in obstructive sleep apnea (wiley.com)

## Partner perceptions are associated with objective sensor-measured adherence to oral appliance therapy in obstructive sleep apnea

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The aims of the present prospective clinical study were to determine objective, sensor-measured adherence to a mandibular advancement device (MAD) in patients with obstructive sleep apnea (OSA) and to identify partner-specific adherence-related factors. A total of 77 eligible participants with mild, moderate, or severe OSA and who were non-adherent to continuous positive airway pressure (mean age 56.2 years) participated in the study (32.5% women). The mean (range) observation time between MAD delivery and final follow-up was 8.3 (3.4-16.5) months. The mean apnea-hypopnea index (AHI) was 26.6 events/hr at baseline and 12.5 events/hr at the 8-month follow-up (both  $p < 0.001$ ). The mean sensor-measured adherence at the 8-month follow-up was 60.1% for  $\geq 4$  hr/night of appliance use for  $\geq 5$  days/week. Average usage was 6.4 hr/night, when worn. The mean reduction in the AHI was significantly greater in the "good adherence" ( $\Delta 17.4$ ) than the "poor adherence" group ( $\Delta 11.0$ ;  $p < 0.05$ ). From the partner's perspective, the appliance had a positive effect on sharing a bedroom in the good- (55%) compared to the poor-adherence group (25%;  $p < 0.05$ ) and on their relationship (51.7% versus 17.9%, respectively;  $p < 0.05$ ). Regression analyses identified the partner's snoring and apneas to be the most significant factor predicting good adherence to MAD (odds ratio 4.4, 95% confidence interval 1.4-14.0). In conclusion, social factors, like partner perceptions, were positively associated with adherence, which indicate that partner's attitudes and support may be a resource that can be utilised to improve adherence in oral appliance treatment of OSA.

**EADSM comment:** Study highlighting the importance of the bed partner in the assessments of OSA therapies.

## INDICATIONS FOR TREATMENT OF OSA

Sleep Med. 2021 Oct 1;88:1-6.

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Link:

<https://reader.elsevier.com/reader/sd/pii/S1389945721004846?token=2D40CFBAF74A8685D635EC29C4310475989E13644E7B83501D8715EA76EF4D94D1812984C8997DACDF373CB817F4F87F&originRegion=eu-west-1&originCreation=20211101152943>

### OSA patients not treated with PAP - Evolution over 5 years according to the Baveno classification and cardiovascular outcomes

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**Introduction:** The evolution of patients with obstructive sleep apnea (OSA) non-eligible for PAP-therapy at diagnosis is unknown. Currently, the severity of OSA is based on the apnea-hypopnea index (AHI), but its prognostic relevance has raised concerns. The Baveno classification may allow a better stratification of severity and therapeutic guidance in OSA.

**Methods:** Patients with  $AHI \geq 5/h$  in 2015, classified into Baveno groups A and B and non-eligible for PAP therapy at diagnosis and over 5 years, were analyzed. Patients were reclassified into Baveno groups (A-D) and changes in groups over 5 years were explored. Patients in Baveno groups C and D, who developed major cardiovascular comorbidities (CVC) or end-organ damage (EOD group), were compared with patients in Baveno groups A and B (non-EOD group). To identify predictors of the development of major CVC or EOD, a logistic regression analysis was performed.

**Results:** There were 76 patients, 58% male, mean age  $51.9 \pm 10.1$  years, mean body mass index (BMI) of  $30.3 \pm 5.0$  kg/m<sup>2</sup> and median AHI of 8.9 (5.9-12.0) events/h. At diagnosis, 46% and 54% of patients were classified into Baveno group A and group B, respectively. In total, 21% of patients developed major CVC or EOD (Baveno group C or D); higher age ( $p = 0.011$ ) and BMI ( $p = 0.004$ ) and a higher percentage of central apneas ( $p = 0.012$ ) at diagnosis significantly predicted it, while sex, sleepiness, insomnia, AHI, ODI and T90 were not.

**Conclusions:** A significant percentage of patients non-eligible for PAP-therapy at diagnosis of OSA developed CVC or EOD; higher age and BMI and a higher percentage of central apneas were significant predictors.

**EADSM comment:** Important data showing that treatment is important also for some patients with lower degrees of indications. This study indicates that older and obese patients might constitute such a group of patients. Maybe MADs could be a suitable therapy for some of those?

## SYMPTOMS OF OSA

J Sleep Res. 2021 Jul 29;e13431.

doi: 10.1111/jsr.13431. Online ahead of print.

Link: How sleepy patients differ from non-sleepy patients in mild obstructive sleep apnea? (wiley.com)

### How sleepy patients differ from non-sleepy patients in mild obstructive sleep apnea?

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To aim is investigate whether demographic, polysomnographic or sleep behaviour data differ between non-sleepy, sleepy and very sleepy patients with mild obstructive sleep apnea. The study population consisted of 439 consecutive adult patients diagnosed with mild obstructive sleep apnea ( $5 \leq$  apnea-hypopnea index  $< 15$ ) after a complete polysomnographic evaluation. The patients were divided into three groups based on subjective sleepiness: very sleepy (Epworth Sleepiness Scale  $\geq 16$ ,  $n = 59$ ); sleepy ( $10 <$  Epworth Sleepiness Scale  $< 16$ ,  $n = 102$ ); and non-sleepy (Epworth Sleepiness Scale  $\leq 10$ ,  $n = 278$ ). Demographic, polysomnographic and sleep behaviour data were compared between the groups. There were no statistically significant differences in breathing abnormality indices and most of the demographic features between the groups. The number of arousals was significantly higher in the very sleepy group compared with the non-sleepy group ( $140.8 \pm 105.2$  versus  $107.6 \pm 72.2$ ). Very sleepy patients reported feeling sleepy during the daytime more often (42.4% versus 31.7%) and sleeping significantly less during the week compared with non-sleepy patients. Also, a significantly higher proportion of sleepy (47.1%) and very sleepy patients (44.1%) reported taking naps during weekends compared with non-sleepy patients (35.6%). In a regression analysis, also total sleep time ( $\beta = 0.045$ ), sleep efficiency ( $\beta = -0.160$ ), apnea index ( $\beta = -0.397$ ), apnea-hypopnea index in supine position ( $\beta = 0.044$ ), periodic limb movement index ( $\beta = 0.196$ ) and periodic limb movement-related arousal index ( $\beta = -0.210$ ) affected subjective daytime sleepiness. The results suggest that excessive daytime sleepiness in patients with mild obstructive sleep apnea appears to be related to inadequate sleeping habits (i.e. insufficient sleep during working days) and decreased sleep quality rather than differences in breathing abnormalities.

**EADSM comment:** Interesting data about relationships between sleepiness, sleep apnea and poor sleep habits.