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### Developments in diagnosis and treatment of obstructive sleep apnea

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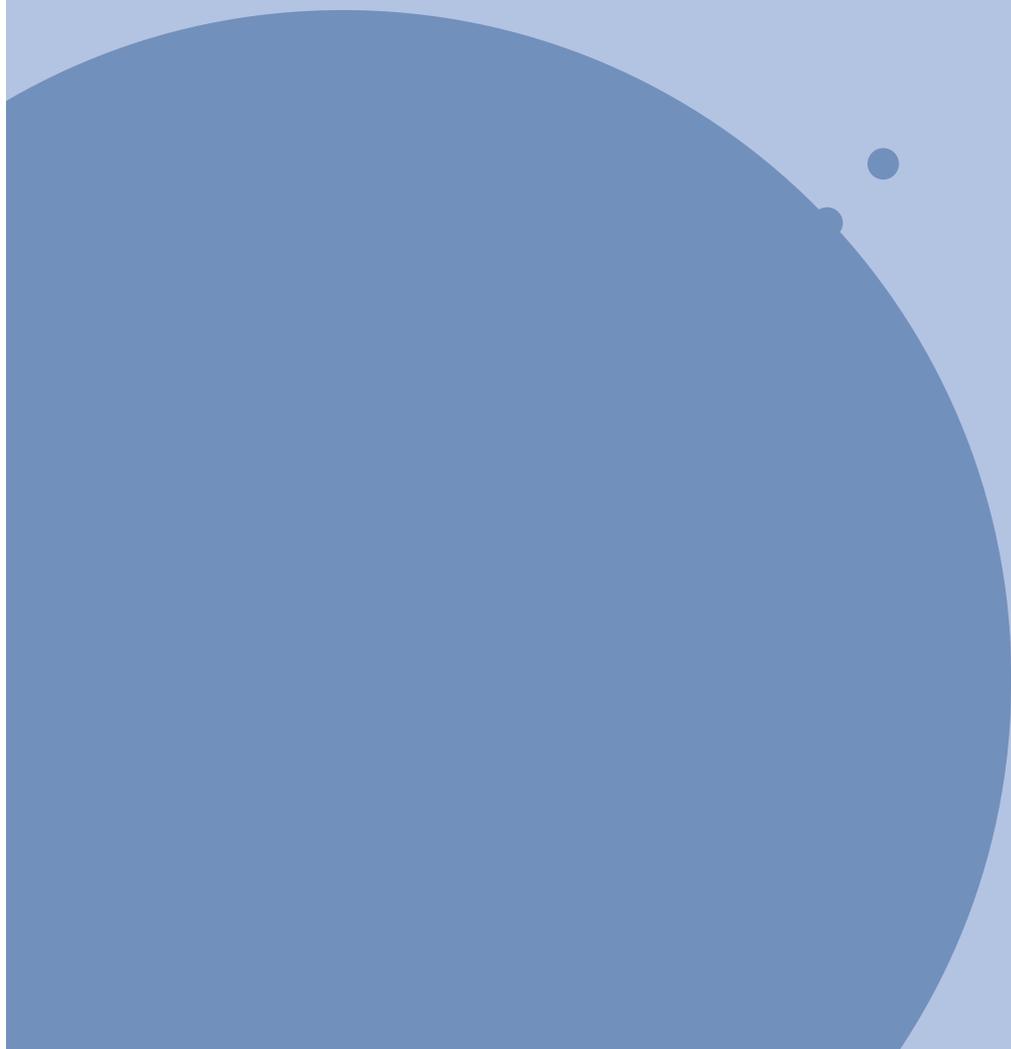
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# 10 Discussion and future perspectives



## DISCUSSION AND FUTURE PERSPECTIVES

Identification of phenotypes and endotypes contributes to a better understanding of the complex pathophysiology and heterogeneous clinical presentation of obstructive sleep apnea (OSA). As a result, the specificity and sensitivity of diagnostic tools could be increased. Another advantage of identification of these potential predictors is that they point in a specific treatment direction, as every treatment option tackles specific components influencing the upper airway patency. Consequently, treatment success might increase. Bearing this in mind, scientists are constantly seeking for predictors: risk factors associated with OSA and parameters influencing treatment outcome. The general aim of this thesis was to assess the value of potential predictors influencing OSA severity and treatment outcome.

### Predictors for OSA

At which healthcare practitioner patients first present themselves with OSA-related complaints, varies broadly. It could be at the general practitioner for snoring issues or excessive daytime sleepiness, at the psychologist for depression or fatigue, at the dentist for bruxism, or at any medical specialist with vague complaints. Therefore, it is important that all of these health practitioners are aware of the possible symptoms of OSA to prevent unnecessary care and high healthcare costs. The heterogeneity of OSA-related complaints makes early diagnosis difficult. The detection of specific risk factors and predictors could be of added value in this process. Since the majority (95%) of patients with OSA report disruptive snoring, using snoring sounds as a diagnostic tool could potentially be of great value. As described in **chapter 2**, during a drug-induced sleep endoscopy (DISE), the duration of a snoring event is associated with complete concentric collapse of the soft palate, which is a negative predictor for surgical treatment outcome. One of the reasons that we perform a DISE prior to upper airway surgery is to determine if this negative predictor is present. Therefore, this outcome could be of great value, but first needs to be confirmed in a representative OSA population during natural sleep. We concluded that it is not feasible to predict the obstruction site of the upper airway, assessed during DISE, based on snoring sounds. More intelligent methods like machine learning, however, may perform better in recognizing collapse sites. Since, in general, people visit the dentist once or twice a year and oral inspection is routinely performed, the dentist could potentially assist in early detection of dental parameters and other specific characteristics (e.g., large tonsils) that increase the risk of developing OSA, and

subsequently ask targeted questions. Based on the findings of our study, within the limitations as described in **chapter 3**, it seems not feasible yet to screen for OSA by phenotyping patients with regard to dental parameters. Although with these studies we could not yet determine specific diagnostic leads, we do think that future research should point in the direction of the analysis of snoring sounds and the role of the dentist. Given the 95% prevalence of snoring complaints in the OSA population and the yearly dentist visits, the influence of discovering a diagnostic lead in the general dental practice would be major.

### **Predictors for treatment outcome – Mandibular advancement device (MAD)**

MADs are widely used in the treatment of OSA, but have a broad range with regard to treatment outcome. The majority of MADs is custom-made. Consequently, in case of therapy failure or intolerance, the MAD goes to waste. This thesis focused especially on prediction and optimization of MAD treatment. In **chapters 3 and 4**, potential phenotypes, including dental characteristics and positional OSA (POSA), were investigated with regard to their influence on MAD treatment outcome. Both did not seem to predict MAD treatment outcome. We are of the opinion that the validity of these findings should be investigated prospectively with a larger cohort. Another tool to screen for MAD treatment eligibility could be the use of DISE findings. This hypothesis was investigated in **chapters 5-7**. The jaw thrust maneuver is known not to be fully reproducible and therefore less reliable with regard to objective study outcomes and its predictive value. As an alternative, the added value of a temporary non-custom MAD was explored. Both maneuvers (jaw thrust and a temporary MAD) seemed to mimic the treatment effect of a MAD as reported in the literature. To validate this outcome, we used the same temporary MAD during DISE. Patients were instructed to use the temporary MAD directly after DISE for at least 3 months, followed by a polysomnography (PSG) to determine its treatment effect. This study showed that if the obstruction of the upper airway in supine position completely disappeared while applying the MAD during DISE. Patients were 6.3 times more likely to be a responder than with persisted obstruction during DISE. The finding of the preliminary predictive value of this temporary MAD with regard to MAD treatment outcome is a key finding. In particular because in another study, in which we have investigated the similarity of this temporary MAD with a custom MAD with regard to objective and self-reported outcomes, we concluded that the MADs were similar

(**chapter 7**). The impact hereof is twofold: 1. the use of this temporary MAD during DISE predicts its own treatment success and, given the similarity, also that of a custom MAD; and 2. without performing a DISE with this MAD *in situ*, the findings with regard to this temporary MAD are still of added value. Patients could directly start treatment and experience the (subjective) benefits and possible disadvantages of MAD treatment within the first months, before a more expensive custom MAD would be produced. These findings create major screening opportunities and subsequently might increase treatment success of a MAD. Consequently, this temporary MAD could be an efficient and cost-effective means for screening treatment eligibility. If our other study would have confirmed the similarity between a jaw thrust and this temporary MAD, accordingly the predictive value of the jaw thrust for MAD treatment would have been proved. However, in our study, that was not the case. Future studies with larger cohorts should be performed to investigate the feasibility and cost-effectiveness of performing a DISE with this new-generation MAD and of providing patients with it without performing a DISE. In addition, it should be investigated for which patients and in which kind of clinical centers this would be of added value.

### **Predictors for treatment outcome – Hypoglossal nerve stimulation (HNS)**

Compared to MAD treatment, HNS is relatively new and less widely applied, and inclusion criteria are strict.

The conclusion in **chapter 8**, that pre-treatment severity (if the apnea-hypopnea index (AHI) is at least 15 events/hr) does not influence treatment effect or patient satisfaction, support a broader indication for HNS therapy. This concerns patients with an AHI above 50 and even above 65 events/hr sleep, for whom this treatment is now often not available. This is a key finding, since these are the patients with the highest disease burden, for whom not many effective treatment options are available in case of CPAP failure. This study was possible due to a large-scale registry and underlines its added value. A future recommendation would be to create more registries, especially in case of new treatment options, to more easily perform large-scale studies. In **chapter 9**, we evaluated the feasibility of a daytime titration PSG as an alternative for the conventional titration during the night to optimize treatment outcome of HNS. Our findings suggest the implementation of daytime titrations as standard of care. This will contribute to easier logistics and better

working circumstances for sleep technicians without jeopardizing titration quality, an optimization of a treatment modality.

## **Predictors - Biomarkers**

In this thesis, many potential predictors, mostly phenotypes, for OSA severity and specific treatment options were investigated. Relatively less studied is the role of biomarkers, an endotype, in predicting OSA severity and serving as follow-up marker for treatment response. In the literature, the association of lipid metabolism-related biomarkers with OSA has already been described. Identification of more OSA-related biomarkers from blood, collected by venipuncture, could provide a less expensive, less time consuming and more patient friendly diagnostic tool than the current gold standard PSG. Replacement of PSG with accurate biomarkers would provide a worldwide opportunity for all OSA clinics to simplify standard baseline and follow-up screening for specific purposes. Therefore, research should be aimed at identifying biomarkers associated with OSA by investigating if they are in agreement with PSG outcomes, pre- and post-treatment, and if OSA treatment does result in improvement of these markers associated with cardiovascular and metabolic diseases.

In this thesis, the main investigated phenotypes were snoring sounds, dental parameters and position dependency. Snoring sounds do not predict the presence of an obstruction at each level of the upper airway as found during DISE. Dental parameters do not contribute to screening for OSA and MAD treatment success as they do not correlate with OSA severity or MAD treatment outcome. POSA does not predict whether or not a patient is a suitable candidate for MAD treatment.

In addition to the predictive value of these phenotypes, we have investigated the predictive value of specific maneuvers and tools during DISE. The investigated new-generation MAD predicts its own treatment success and, given the similarity with the regular custom MAD, also that of a custom MAD.

Pre-treatment OSA severity and day-time titrations do not influence NHS treatment outcome, consequently the indication of HNS could be broadened and logistics for follow-up could be easier with better work circumstances for somnotechnologists without jeopardizing titration quality.