ORIGINAL ARTICLES

http://dx.doi.org/10.15331/jdsm.6250

Predicting Therapeutic Outcome of Mandibular Advancement Device Treatment in Obstructive Sleep Apnoea (PROMAD): Study Design and Baseline Characteristics

Annelies E.R. Verbruggen, MD[1,6]; Anneclaire V.M.T. Vroegop, MD, PhD[1,6]; Marijke Dieltjens, MBS, PHD[1,2,6]; Kristien Wouters, PhD[5]; Chloé Kastoer, MD[1,6]; Wilfried A. De Backer, MD, PhD[3,4,6]; Johan A. Verbraecken, MD, PhD[3,4,6]; Marc Willemen, Eng[3]; Paul H. Van de Heyning, MD, PhD[1,3,6]; Marc J. Braem, DDS, PhD[2,6]; Olivier M. Vanderveken, MD, PhD[1,3,6]

[1]Antwerp University Hospital, ENT Department and Head and Neck Surgery, Edegem, Antwerp, Belgium; [2]Antwerp University Hospital, Department of Special Dentistry Care, Edegem, Antwerp, Belgium; [3]Antwerp University Hospital, Multidisciplinary Sleep Disorders Centre, Edegem, Antwerp, Belgium; [4]Antwerp University Hospital, Department of Pulmonary Medicine, Edegem, Antwerp, Belgium; [5]Antwerp University Hospital, Department of Scientific Coordination and Biostatistics, Edegem, Antwerp, Belgium; [6]University of Antwerp, Faculty of Medicine and Health Sciences, Edegem, Antwerp, Belgium

Study Objectives: Oral appliances have gained their place in the treatment of obstructive sleep apnea (OSA) where custom-made titratable mandibular advancement devices (OAm) have become the oral appliance of choice. Retrospective studies assessing possible predictors of treatment outcome with OAm have been published but are lacking uniformity in their conclusions. The "PRedicting therapeutic Outcome of Mandibular Advancement Device treatment in OSA" (PROMAD) study aims at identifying predictive screening methods for treatment success with OAm, assessing the following upper airway (UA) evaluation methods: awake nasendoscopy including Müller manoeuvre, and drug-induced sedation endoscopy (DISE) will identify the level, degree, and pattern of UA collapse; while computed tomography (CT)-scan based computational fluid dynamics (CFD) will evaluate changes in UA volume and resistance.

Methods: PROMAD is a prospective, single-center cohort study that enrolled 100 consecutive patients with diagnosed OSA (5 events/h < apnea-hypopnea index (AHI) < 50 events/h) to be treated with a custom-made titratable OAm. Primary endpoints are the positive and negative predictive values of awake nasendoscopy including Müller manoeuvre, DISE, and CFD with and without the OAm, toward reduction in AHI. Univariate and multivariate analyses will be performed to determine which of the investigations and/or combinations thereof predict success.

Conclusions: PROMAD is a prospective trial to investigate the predictive potential of awake nasendoscopy including Müller manoeuvre, DISE, and CFD, and any combination thereof in the prediction of reduction of AHI with OAm in OSA patients. The results will allow translating the assessments into optimal OSA patient selection, leading to evidence-based decision making and targeted OAm treatment.

Clinical Trial Registration: Clinicaltrial.gov identifier: NCT01532050

Keywords: oral appliance, awake nasendoscopy, sleep endoscopy, computed tomography, computational fluid dynamics

Citation: Verbruggen AE, Vroegop AV, Dieltjens M, Wouters K, Kastoer C, De Backer WA, Verbraecken JA, Willemen M, Van de Heyning PH, Braem MJ, Vanderveken OM. Predicting therapeutic outcome of mandibular advancement device treatment in obstructive sleep apnoea (PROMAD): study design and baseline characteristics. *Journal of Dental Sleep Medicine* 2016;3(4):119–138.

INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent disease and public health issue, affecting approximately 34% of middle-aged men and 17% of middle-aged women in the United States.[1] The condition is characterized by periodic partial or complete obstruction of the upper airway (UA) during sleep, causing sleep fragmentation and hypoxemia.[2] The severity of OSA is expressed in terms of the number of apneas and hypopneas per hour of sleep, the apnea-hypopnea index (AHI). OSA poses a strong and independent risk factor for cerebro- and cardiovascular morbidity, associated with high rates of morbidity and mortality.[3–7]

Continuous positive airway pressure (CPAP) is the advised standard of treatment for patients diagnosed with AHI > 15 events/h.[8] However, its clinical effectiveness is limited by moderate patient acceptance and tolerance, leading to unsatisfactory compliance.[9–11] The most commonly used class of oral appliances, the mandibular advancement device (OAm), is recommended as a first-line therapy for patients with sleep-disordered breathing, having an AHI of up to 15 events/h, and in patients who fail or refuse treatment with CPAP.[12] The OAm is worn intra-orally during sleep and maintains the mandible in a protruded position, commonly with a design to additionally protrude the mandible in search for the most effective protrusion.[13–15] The aim is to prevent UA collapse during sleep by increasing the cross-sectional pharyngeal area, thereby reducing snoring and OSA.[16–19] However, there is a high interindividual variability in success rate with OAm as reported in the literature.[20] Optimal prediction of individual treatment outcome, improving the selection of OSA patients for OAm therapy, is therefore desirable from both therapeutic as well as financial perspectives, although it remains an unresolved key issue.

Table 1—Eligibility criteria.

Inclusion criteria	Exclusion criterion
• Age ≥18 years • Body mass index (BMI) ≤ 35 kg/m^2 • OSA as defined by the American academy of sleep medicine task force Diagnostic criteria: (A + B + D or C + D):[2] A. Anamnesis (at least one of the following criteria) 1. Unwanted sleepiness and/or fatigue in the daytime, unrefreshing sleep or insomnia 2. Nocturnal arousals with breathing stops, gasping 3. Snoring or breathing stops while sleeping, determined by the bed partner B. PSG: AHI ≥ 5 events/h of sleep and AHI < 50 events/h of sleep C. PSG: AHI ≥ 15 events/h of sleep and AHI < 50 events/h of sleep D. The condition cannot be explained by another sleep disorder, internal or neurological disorder, medication or drug use	• Absolute dental contraindications: - Functional restrictions of the temporomandibular joint - Insufficient dentition with pathological aspects - Insufficient retention for Respident Butterfly OAm use • Other sleep disorders (e.g. parasomnias) • Previous invasive UA surgery for sleep-disordered breathing (uvulopalatopharyngoplasty, palatal implants, maxillomandibular advancement, suspension or resection of the tongue base, hyoid suspension, genioglossus advancement) • Genetic disorders with craniofacial and/or UA anomalies • Use of benzodiazepine(s) and/or antidepressant(s) • Prior history of psychiatric disease (including alcohol abuse) • Known history of fibromyalgia or chronic fatigue syndrome • Not willing to participate and/or to give informed consent

Awake nasendoscopy including Müller manoeuvre as well as drug-induced sedation endoscopy (DISE) can be used to assess the anatomical level at which snoring and pharyngeal collapse with and without mandibular protrusion[21] will occur as well as the pattern of collapse and anatomical abnormalities. These techniques have been suggested as valuable prognostic indicators of successful OAm treatment in the individual patient.[22–24]

In the past, UA imaging techniques using a three-dimensional and dynamic approach have been applied to study the pathophysiological aspects of OSA.[18,25–29] Computer models have been developed according to the principles of computational fluid dynamics (CFD) using transformed data from three-dimensional computer tomography (CT) images of OSA patients. CFD models allow for evaluation of the airflow and the resistance within the pharynx of the individual OSA patient.[30,31] In previous studies, CFD is suggested as a potential adequate predictive tool for treatment outcome with OAm in OSA patients.[32–34]

The "PRedicting therapeutic Outcome of Mandibular Advancement Device treatment in obstructive sleep apnea" (PROMAD) trial aims at identifying the predictive power of awake nasendoscopy including Muller manoeuvre, DISE, and CT-scan based CFD in treatment outcome with OAm. Additionally, the effect of the combination of these techniques and their relative weight, in terms of predicting the treatment outcome with OAm therapy, is explored.

METHODS

Design

The PROMAD-study is a prospective, single-center, cohort study that evaluates 100 eligible OSA patients. The eligibility criteria are summarized in **Table 1**.

A comprehensive characterization of the patients comprises anthropometric data, polysomnography (PSG), awake nasendoscopy including Muller manoeuvre, DISE, and awake UA CT-scan with CFD.

Objective baseline evaluation is performed by PSG, and in particular by assessing the AHI. Then treatment is initiated with a titratable custom-made duobloc OAm (Respident Butterfly, Respident, Orthodontic Clinics NV, Antwerp, Belgium). Re-evaluation by PSG with the OAm in situ is performed after 3 months and 1 year after treatment initiation.

Data analysis of the predictive value of awake nasendoscopy including Müller manoeuvre, DISE, and CT-scan based CFD consists of correlating baseline findings without the OAm in situ with changes in AHI following OAm treatment. Moreover the findings of these same investigations with the OAm in situ in 75% of the individual maximal protrusion will be correlated with the therapeutic outcome. Patients as well as investigators assessing the clinical, polysomnographic, and radiological response remain blinded to the data.

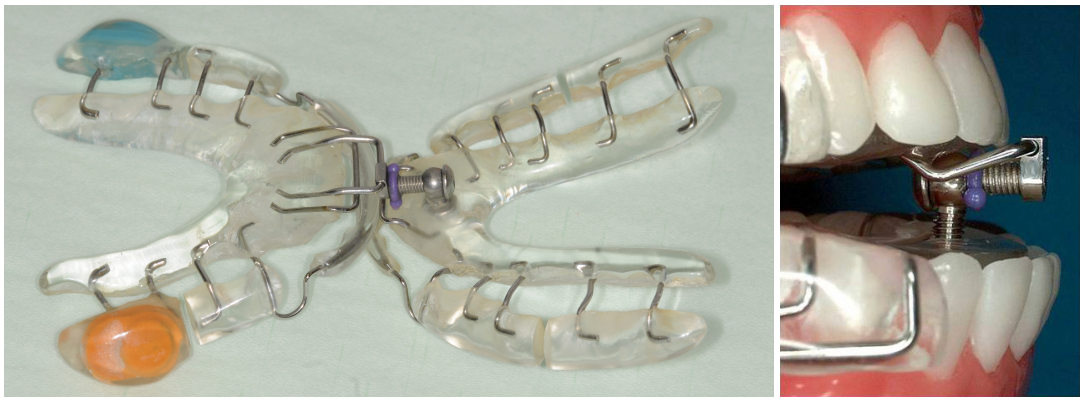
The institutional ethics committee has approved the study protocol and written informed consent is obtained from all participants.

The Mandibular Advancement Device

A custom-made, titratable, commercially available duobloc OAm with an interconnecting mechanism located in the frontal teeth area allowing for precise adjustment of mandibular protrusion was selected (Respident Butterfly, RespiDent, Orthodontic Clinics NV, Antwerp, Belgium).[35] The appliance consists of two clips (Antwerp DentalClip) (see **Figure 1**), attached to each other via a small screw system located in the frontal teeth area (Nelissen Titrator) allowing for additional gradual titration. The device is set at 75% of the individual maximal protrusion of each patient. The vertical opening, being the distance between the incisal edges of the upper and lower incisors, is kept constant during the treatment on a minimal distance.[36]

Two temperature-sensitive microsensors with on-chip integrated readout electronics were embedded in the OAm on opposites sides of the maxillary part, to objectively measure

Figure 1—The Respident Butterfly OAm, consisting of two clips (Antwerp Dental Clip), attached to each other in the frontal teeth area allowing adjustment of the mandibular protrusion in the horizontal plane, as well as in the vertical plane.



Two chips (Blue = Theramon; Orange = Air Aid Sleep) for objective measurement of compliance are embedded in the maxillary part.

the therapy compliance (TheraMon, Handelsagentur Gschladt, Hargelsberg, Austria[37–39]; and Air Aid Sleep, Air Aid GmbH & Co. KG, Frankfurt am Main, Germany[39]) (**Figure 1**).

Polysomnography

A standard full-night PSG is performed (Brain RT software, OSG, Belgium) at baseline to verify the inclusion PSG criteria and to fix the starting point of the study, followed by evaluation after 3 months and after 1 year of OAm therapy. The PSG provides information on respiration, oxygen saturation, and sleep state, as well as on body position, heart rhythm, limb movements and snoring. It comprises recording of respiratory data, including nasal airflow by using an external thermistor, nasal pressure by means of a nasal pressure cannula and respiratory effort through respiratory induction plethysmography. Oxygen saturation is monitored using a pulse oximeter with a finger probe. A microphone qualitatively records snoring, and body position is assessed with a piezoelectric sensor. The PSG includes electroencephalography (EEG), right and left electrooculography, electromyography of the genioglossus muscle and tibialis anterior muscle, and electrocardiography. All sleep records are scored manually according to the American Academy of Sleep Medicine criteria,[40] by the same qualified sleep technician. The sleep technician is blinded to the results of the other examinations.

Assessment of Subjective Complaints and Quality of Life

Subjective information is collected by digital versions of different relevant questionnaires. The Epworth Sleepiness Scale (ESS) is used to assess excessive daytime sleepiness.[41] The visual analogue scale (VAS) for snoring scores the snoring on a scale of 0 (no snoring) to 10 (partner leaves the bedroom). The Functional Outcomes of Sleep Questionnaire (FOSQ)[42] determines the functional status in adults with OSA. The Sleep Apnea Quality of Life Index (SAQLI)[43] questions the OSA-related quality of life. The Pittsburgh Sleep Quality Index (PSQI)[44] assesses sleep quality and disturbances. The Type D Scale-14 (DS14)[45] measures negative affectivity and social inhibition. The NEO-Five Factor Inventory (NEO-FFI[46]) explores the five domains of the adult personality. The Short Form Health Survey (SF-36)[47] investigates the patients' health status. The Beck Depression Inventory (BDI)[48] evaluates mood disturbances.

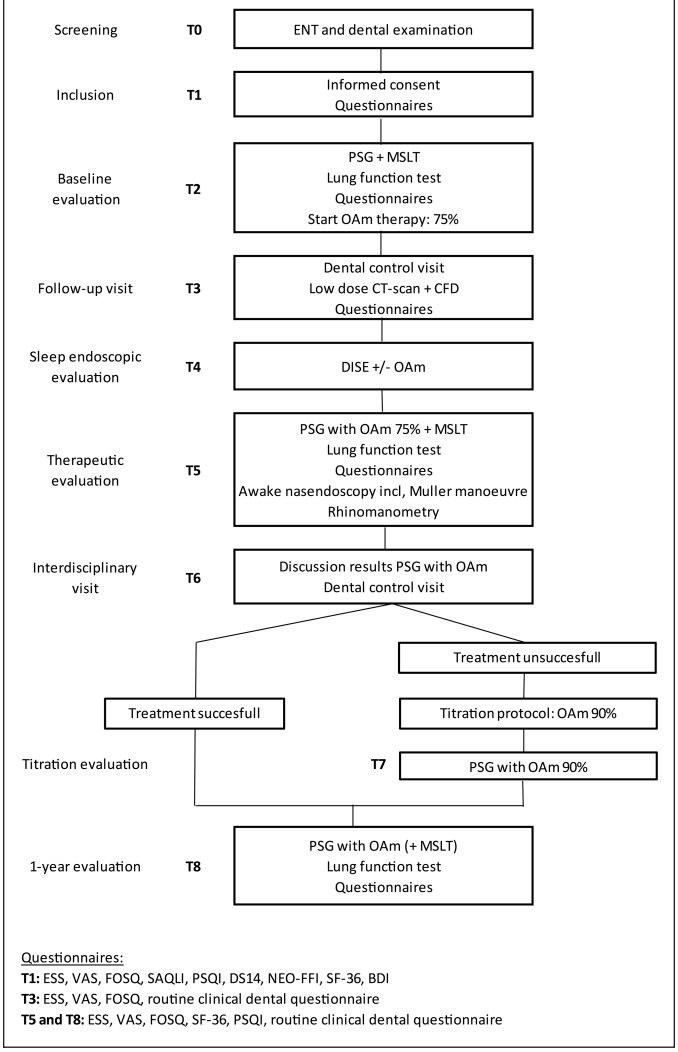
Study Protocol

As illustrated in **Figure 2**, at T0, patients are screened and complete assessment of the patient status is performed, including medical history, standard ear-nose-throat clinical examination with awake upright nasendoscopy including the Muller manoeuvre and rhinomanometry. The patient is then referred to the dental sleep professional for a general dental examination including an orthopantomography. If the patient meets the eligibility criteria and wants to participate in the PROMAD-study, informed consent is obtained and dental impressions are taken (T1). Different questionnaires, as specified in the previous section, were digitally filled out using touch screen technology.

At T2, a baseline full-night PSG in the sleep laboratory is performed, including lung function testing, arterial blood gas analysis, and a clinical questionnaire as routinely used in the sleep laboratory (see **Appendix 1** for the English translated version). In the 19 days prior to the baseline PSG, the patients fill out each day an ESS questionnaire on paper, a sleep diary with the sleeping and waking times, and the PSQI. The day after T2, PSG is followed by a multiple sleep latency test (MSLT) and the start of the OAm therapy upon fitting of the OAm in the 75% protrusive position of the individual patient.

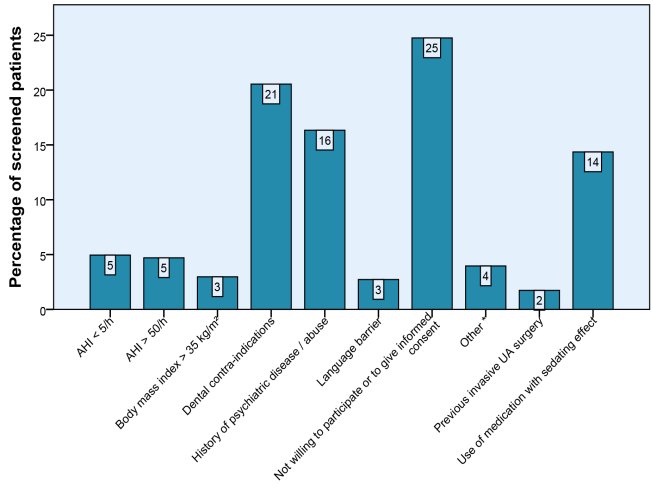
A first follow-up visit is planned 1 month after the start of OAm therapy (T3) and includes a dental checkup with control of the protrusive position at 75%. Subsequently, a low-dose CT scan of the head and neck region is made with and without the OAm in the 75% protrusive position, for CFD analysis including level diagnosis. At this time, subjective information is again collected through digital versions of the following questionnaires: ESS, VAS for snoring, FOSQ, and a clinical

Figure 2—Study flow chart of the PROMAD-study.



Questionnaires:
T1: ESS, VAS, FOSQ, SAQLI, PSQI, DS14, NEO-FFI, SF-36, BDI
T3: ESS, VAS, FOSQ, routine clinical dental questionnaire
T5 and T8: ESS, VAS, FOSQ, SF-36, PSQI, routine clinical dental questionnaire

Figure 3—Reasons for non-participation.



*Medical history, medical contraindications, other complaints, fibromyalgia, no previous PSG available.

dental questionnaire (see **Appendix 2**) as routinely used in our multidisciplinary clinic. Between 1 and 3 months after T2, a DISE (T4) is performed with and without the OAm in the 75% protrusive position.

Three months after initiating OAm therapy (T5), a full-night PSG is performed with the OAm in the 75% protrusive position, including lung function testing, arterial blood gas analysis, and the routine clinical sleep questionnaire, as described before. Prior to T5, the patient fills out again the sleep diary and the ESS each day for 19 days, as well as the PSQI. Other subjective information is again collected through digital versions of the following questionnaires: ESS, VAS for snoring, FOSQ, SF-36, PSQI, and the routine clinical dental questionnaire. Prior to the PSG, a dental examination is conducted with control of the 75% protrusive position of the OAm. The next day, MSLT, rhinomanometry, and awake nasendoscopy including Muller manoeuvre are performed.

Four weeks after T5, an interdisciplinary visit at the dental and medical outpatient clinic is scheduled (T6) and the results of the PSG evaluation with the OAm are discussed with the patient. From this point on, patients and investigators are not blinded anymore to the results of the investigations. In case the remaining AHI with the OAm in situ is higher than 5 events/hour, the study protocol requires further adjustment of protrusion in order to lower the AHI: the patient is invited to participate in a titration protocol with advancement of the mandible to 90% of the baseline maximal protrusion. The OAm is then fixed in this 90% protrusive position. After a habituation and adaptation period of 2 months, an additional PSG is performed to assess the effect of the 90% protrusive position on AHI (T7).

One year after initiation of treatment a PSG is scheduled in all study patients, with the OAm in either 75% or 90% protrusive position, depending on the patient (T8). Also lung function testing and arterial blood gas analysis are performed. In case of previously pathological MSLT results, the PSG is followed by MSLT the next day. At this time, the patient is also examined by the dental sleep professional to check the condition of the OAm as well as its protrusive position. The questionnaires as on T5 are completed again.

Data collection occurs at screening (T0), at baseline assessment (T2), 1-month follow-up (T3), during DISE (T4), at 3-month follow-up (T5), after titration if needed (T7), and 1 year (T8) after starting therapy. Objective and subjective compliance are verified at T3, T5, and T8.

Study Population and Enrolment

The PROMAD investigators screened consecutively 402 OSA patients diagnosed with recent PSG, from January 2012 until March 2014 at the Antwerp university hospital (UZA, Belgium). Patients were referred to the special care dentistry unit for treatment with an OAm. A group of 202 of these patients did not fulfil the eligibility criteria as defined by the PROMAD study protocol, and 58 (29%) of these patients had more than one reason for non-participation. One hundred invited patients declined to participate because of personal considerations or the inability to comply with the time demands of the protocol (**Figure 3**). One hundred eligible patients were enrolled, of whom 38 patients had mild OSA (5 events/h < AHI < 15 events/h), 41 patients had moderate OSA

Table 2—Baseline characteristics of the study population.

Age (years)	47.4 ± 11.5
Gender	83% male
Body mass index, BMI (kg/m²)	26.9 ± 3.3
Neck circumference (cm)	39.5 ± 3.0
AHI at inclusion (events/h)	21.0 ± 11.2
Visual Analogue Scale for snoring, VAS (0–10)	7 ± 2
Epworth Sleepiness Scale, ESS (0–24)	9 ± 5

Data are expressed as mean ± standard deviation or percentages.

(15 events/h < AHI < 30 events/h), and 21 patients had severe OSA (30 events/h < AHI < 50 events/h). The baseline characteristics of the patients are summarized in **Table 2**. The last baseline PSG was performed in June 2014.

Multiple Sleep Latency Test (MSLT)

The MSLT is an objective assessment of the tendency to fall asleep, and requires EEG evaluation of the participants. The day after the PSG, the patient is lying on a bed in a quiet, darkened room and is instructed to fall asleep. The test is conducted according to the standard practice of the American Academy of Sleep Medicine.[49] The time required to reach the first epoch of any sleep stage is determined in a 20-minute period every 2 hours during the day for a total of 4 test sessions. The mean sleep latency is then calculated and is considered pathological if it is less than 8 minutes and normal if it is longer than 10 minutes. Nineteen days prior to the testing, the patient is asked to keep a sleep diary reporting the patient's sleeping and waking times.

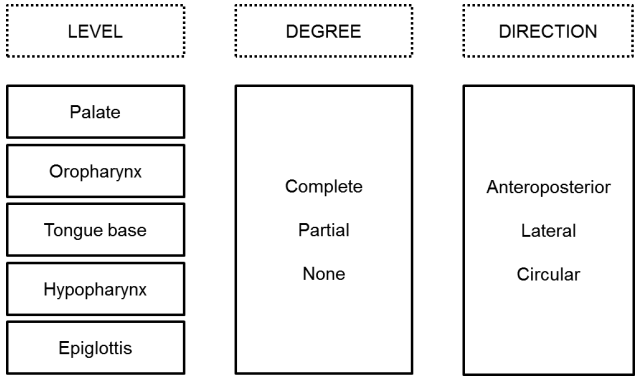
Imaging with Computational Fluid Dynamics Analysis

All patients undergo a low-radiation dose CT scan with and without the OAm in 75% of the protrusive position, to evaluate the UA geometry. This scan is performed while awake and in supine position during one breath hold at the end of a normal inspiration. The scanned area starts at the nasopharynx and extends down to the larynx. Based on these images, three-dimensional computer-aided design models of the segments of interest can be reconstructed using a commercial software package (Mimics, Materialise, Leuven, Belgium), based on Hounsfield units. These models are then exported and used for detailed analysis of the anatomical parameters, volume meshing, and CFD simulation, as previously described.[30,32,33] CFD outcome parameters describe changes in volume of the UA as well as changes in resistance of the simulated amount of air passing through this airway.

Drug-Induced Sedation Endoscopy

Drug-induced sedation endoscopy (DISE) is performed by an experienced ENT surgeon in a semi-dark and silent operating theatre with the patient lying in supine position in a hospital bed.[50] The OAm in 75% protrusive position is placed intra-orally and verified by the dental sleep professional, prior to the intravenous administration of sedative drugs. Artificial sleep is induced by an intravenous bolus administration of 1.5 mg midazolam and a target-controlled infusion of Propofol (2.0–3.0 µg/mL).[50] During the procedure, standard cardiovascular monitoring is carried out. The level of sedation is continuously assessed by a bispectral index (BIS) monitoring system (BIS VISTA monitor; Aspect Medical Systems Inc., Norwood, USA) which involves a leaf of four sensor electrodes (BIS Quatro; Aspect Medical Systems Inc., Norwood, USA) attached to the forehead. It records values between 0, when there is no brain activity, and 100, representing the patient is fully awake.[51] DISE assessment in the PROMAD study protocol is conducted at BIS values between 50 and 70.

Figure 4—A standard scoring system for DISE, classified per UA level.



A flexible fiberoptic nasopharyngoscope (Olympus END-GP, diameter 3.7 mm, Olympus Europe GmbH, Hamburg, Germany) is inserted transnasally, and the different levels of the UA are observed. The presence of UA collapse is reported using a standard scoring system (**Figure 4**),[23] assessing the level, the degree, and the direction of the collapse pattern.[23] First, the UA dimensions are assessed with the OAm positioned intra-orally during at least 5 minutes with BIS values between 50 and 70. Next, the OAm is removed by the dental sleep professional, allowing assessment of the UA in a baseline setting without any mandibular repositioning, and with a minimal duration of 5 minutes. Thereafter, the dental sleep professional brings the mandible in the maximal protrusive position by pulling it gently forward, also referred to as the chin-lift manoeuvre. This phase lasts for 2 minutes and allows for the observation of the effects of maximal protrusive positioning on the UA collapse patterns.

Awake Nasendoscopy Including Müller Manoeuvre

At screening (T0) and the day after the PSG with the OAm in situ (T5), a nasopharyngoscopy is performed with a flexible fiberoptic nasopharyngoscope (Olympus END-GP, diameter 3.7 mm, Olympus Europe GmbH, Hamburg, Germany) by a single ENT surgeon and while the patient is awake. At T5, the endoscopy is performed with and without the OAm in situ, both in supine and upright position. In each of the 4 phases of this examination, the patient is asked to simulate snoring and to perform a Müller manoeuvre. For this manoeuvre, both nose and mouth are occluded and the patient is asked to inhale maximally. During the awake endoscopy, the degree, the level,

Table 3—Treatment response definitions ranged from most liberal to most strict.

Definition 1:	Δ AHI ≥ 50%[38]
Definition 2:	Δ AHI ≥ 50% or AHI < 5 events/h
Definition 3:	Δ AHI ≥ 50% and AHI < 5 events/h[57]
Definition 4:	AHI < 5 events/h[38]
Definition 5:	Δ AHI ≥ 50% and AHI < 10 events/h[55,56]

and the pattern of UA collapse are observed and scored using the same scoring system as during DISE.[23]

Treatment Outcome Measures

The PROMAD study will explore the predictive value of awake nasendoscopy including Müller manoeuvre, DISE and CFD with and without the OAm in the 75% protrusive position on treatment outcome, determined on T5. For those patients who are unsuccessfully treated at T5, the predictive value of the baseline findings during the investigations will be further analyzed on treatment outcome at T7 with the OAm in 90% protrusion.

Regarding the AHI, several definitions of success can be found in the literature,[38,52–58] with or without requirement for symptomatic improvement. In the PROMAD study, we will analyze the data according to five various definitions of success, shown in **Table 3**. Since patients are included based on an AHI ≥ 5 events/h, the main definition of treatment response is that "Δ AHI ≥ 50% or AHI < 5 events/h".

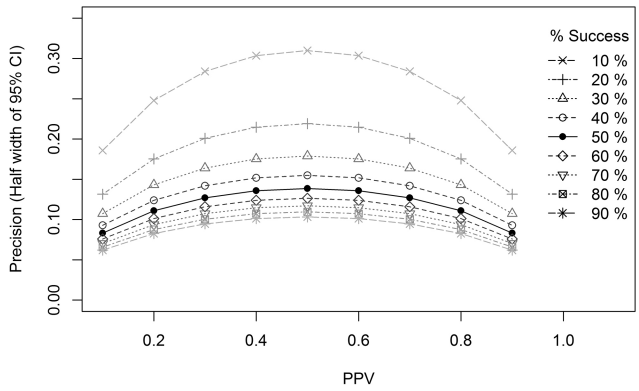
Data Collection and Statistical Analysis

Data are stored in Open Clinica (Open Clinica LLC, Waltham, USA, Version: 3.1.4.1), an open source clinical trial software for electronic data capture and clinical data management. Data will be statistically analyzed using R statistical software (R version 3.0.1, R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics for clinical characteristics of patients will be presented as mean ± standard deviation for continuous, normally distributed variables and median, Q1-Q3 for non-normally distributed variables. Unpaired t-tests will be used to compare baseline measurements between responders and non-responders when data are normally distributed. Nonparametric tests will be used in case the variables are not normally distributed. Categorical variables will be analysed using χ^2 tests. Multiple logistic regression models will be used to predict response versus non-response based on baseline measurements of the screening procedures correcting for confounding factors. Sensitivity, specificity, and positive (PPV) and negative predictive value (NPV) will be calculated for each of the screening measurements together with their 95% confidence interval. A p value of < 0.05 will be considered statistically significant.

Sample Size Justification

To accurately estimate the positive predictive value (PPV), we included 100 subjects in the study. In **Figure 5**, the precision for the PPV is presented for different response rates with 100 subjects: with a response rate of 50%, we are able to estimate a

Figure 5—Presentation of the precision for the estimation of the PPV for different response rates with 100 subjects.



PPV of 0.5 with a precision (i.e., half width of 95% confidence interval, CI) of 0.125. For a lower or a higher PPV, the precision is improved. Since we expect the response rate to be lower than in studies with a preselected group of patients,[35] a response rate of 50% seems realistic. In case the response rate turns out to be higher, the precision reduces, if the response rate is lower, the precision improves.

This study is not powered to reveal differences in odds for each individual measurement in the screening procedure. Instead our goal is to find a combination of screening measurements that can predict treatment success. Results need to be confirmed in a second trial, which will be powered based on the odds ratios and prevalence rates found in the current study.

DISCUSSION

OAm therapy is increasingly used in clinical practice to treat snoring and OSA and has emerged as a valuable alternative for CPAP treatment. The OAm therapy is proven to be efficient in reducing snoring and obstructive breathing events, and it has shown beneficial effects on associated health outcomes such as daytime sleepiness. However, a major issue confronting OAm therapy is that one-third of the patients undergoing such a therapy do not show a beneficial response in terms of reduction in AHI. The inability to adequately and consistently predict treatment outcome potentially results in suboptimal patient selection. Predicting the effectiveness of OAm therapy in the individual patient is a clinical challenge and is important from both treatment and cost-benefit point of view. Ideally the selection procedure has to be accurate, feasible, easily accessible and cost-effective.

However, the search for a predictive model is complicated. First, there are the variety of mechanisms that underlie OSA, such as UA dilator muscle response, ventilator control instability, and anatomic compromise.[59] The interaction between those mechanisms is complex and not yet completely understood. Second, there is the mode of action of the OAm, with both anatomical and functional aspects determining treatment efficacy. The relative contributions of these factors will differ among patients, impeding straightforward prediction of

treatment outcome. A single structural or functional assessment may prove to be inadequate to accurately predict treatment outcome in all patients. The combination of patient characteristics, structural, and functional assessments may therefore increase the predictive value of the individual techniques. Third, a complicating factor is the use of a variety of definitions of treatment success in literature (see **Table 3**). Treatment success is variously expressed as a reduction in AHI below a specific value or by a percentage reduction in AHI from baseline, with or without requirement for symptomatic improvement. In the PROMAD study, data will be evaluated using different definitions of success (see **Table 3**). A commonly used surgical criterion of success that is not mentioned in **Table 3** is "Δ AHI ≥ 50% and postoperative AHI < 20 events/h": the original criterion, however, as published by Sher,[58] was stated as a change in apnea index (AI) or respiratory disturbance index (RDI) of at least 50% and a post-surgery AI below 10 events/h or a post-surgery RDI below 20 events/h. As those parameters currently have become obsolete in describing success, this criterion is not listed in the table. Other commonly used criterions of success not mentioned in our listing are "AHI < 10 events/h."[54] and "Δ AHI ≥ 50% or AHI < 10 events/h."[53] These definitions are not used because they are not suitable to the sample as the inclusion criterion for participation to the study is baseline AHI > 5 events/h. The main definition of treatment response used in the PROMAD study, being "Δ AHI ≥ 50% or AHI < 5 events/h," is rather unusual but dictated by one of the main inclusion criteria, namely baseline AHI ≥ 5 events/h.

Previous research, mostly relying on retrospective analysis, showed several anthropometric, polysomnographic, physiologic, and anatomical factors to be associated with OAm success (see **Table 4**). However, those studies lack uniformity, are mostly underpowered, and the results are not always consistent. Furthermore, the indicators of success have often not been tested prospectively, prior to appliance construction. Therefore, the proof on predictability is still rather limited and research is ongoing. In this study, each distinct investigation gives rise to several variables that are prospectively collected and of which the predictive value will be analyzed. For example, for the findings during DISE we will perform an extensive analysis based on the level, the degree, the direction, and specific collapse patterns. A strength of the present study is that data of the investigations are collected in baseline circumstances as well as with the OAm in situ in 75% of the maximal individual protrusion. Thus predictability can be investigated in a prospective way, based on baseline findings as well as based on the findings with the OAm in situ. In addition, collection of the data from awake nasendoscopy, DISE, and CFD was performed in a blind fashion, meaning that the treating dentist and sleep physician were blinded to the results of the other investigations. As such, included patients were treated with the OAm in a fixed degree of protrusion regardless of the results of the investigations.

The screening of possible candidates for the study took a long time as a result of the strict eligibility criteria that caused the exclusion of many patients. However, a rigorous screening is necessary to obtain a homogeneous group of patients to achieve accurate predictive factors, without interaction of confounding factors biasing the study outcome. We had to screen 402 patients during 27 months to include 100 patients in the study who fulfilled all criteria for inclusion and exclusion in the PROMAD trial. The most common reason for exclusion is dental-related pathology as found in 83 patients (20%), including an insufficient number of teeth, periodontal disease, fragile crown and bridge restorations, limited protrusive capacity, and dentition with pathological aspects. It is important to mention that we evaluated this contraindication as a function of the particular type of OAm used in this study for which an optimal dentition is required to guarantee adequate retention. Therefore, the absolute rate of dental contraindications for OAm in general will be lower than in the present study. Compared to the literature, the present rate of exclusion on dental aspects is clearly lower than the 34% reported earlier in 2002[77]. A history of psychiatric disease or alcohol or substance abuse was found in 17% of the patients (n = 66). A study performed in 6 European countries including Belgium, reported a prevalence of 25% for a lifetime presence of any

Table 4—Patients factors, as reported in the literature, with beneficial effect on OAm outcome.

Clinical parameters
• Younger age[60–63]
• Female gender[63,64]
• Smaller neck circumference[65]
• Lower body mass index[57,60,66]
• Lower Mallampati score[57]
Polysomnographic parameters
• Lower baseline AHI[64,65]
• Supine dependent OSA[64,67,68]
• A successful titration night with remotely controlled mandibular positioner[55]
Cephalometric parameters
• Smaller mandibular-hyoid distance[54,69]
• Smaller incisor overjet[60]
• Shorter soft palate length[54,63,70]
• Maxillary prognathia[60,71]
• Retrognathic mandible[62,71]
• Less erupted maxillary molars[60]
• Longer pharynx and/or smaller soft palate[60]
• Higher tongue height[62]
• Larger mandibular plane to cranial base angle[65]
• Larger retropalatal airway space[65]
• Increased cranial base angulation[63]
• Smaller upper to lower facial height ratio[72]
• Smaller oropharyngeal cross-sectional area[54,60,71]
• Shorter upper facial height[61]
• Larger tongue/oral cross sectional area ratio[61]
Endoscopic parameters
• Open airway during Müller manoeuvre[73]
• Improvement of UA patency on MRI after mandibular advancement during Müller manoeuvre[56]
• Resolution of airway obstruction with manual mandibular advancement during DISE[74]
• Improvement of the UA patency with the use of a simulation bite in maximal comfortable protrusion[75]
Functional parameters
• Lower nasal resistance on posterior rhinomanometry[66]
• Primary oropharyngeal collapse with upper-airway closing pressure[76]
Computational fluid dynamics
• Decrease in airway resistance[32]
• Enlargement in UA volume[32]

mental disorder, including anxiety disorders, mood disorders, and alcohol dependence.[78]

In a previous study, we found a prevalence of 18% to 32% of residual excessive sleepiness based on ESS-scores despite successful OAm treatment (AHI < 5 events/h).[79] In the PROMAD-study, MSLTs are additionally performed to obtain the prevalence of residual excessive sleepiness in a prospective way and based on objective tests as well. This is performed in a homogenous group of patients without confounding factors such as medical or psychiatric comorbidities and vigilance-influencing medication.

CONCLUSIONS

The PROMAD study prospectively identifies which of the several previously published predictive factors of success with OAm therapy would adequately forecast success of OAm. It is a prospective nonrandomized observational study that evaluates pre-defined baseline parameters for their ability to predict clinical and polysomnographic response to OAm treatment in OSA patients. Given the prospective nature of data in the PROMAD study, we will be able to fully characterize these patients and identify important and potentially new predictive factors for treatment outcome with OAm. The advantages of each of the individual pre-treatment investigations will be combined with the aim of translating it into an optimal selection procedure, leading to an evidence based decision making and targeted treatment of patients with OSA.

ABBREVIATIONS

AHI, apnea-hypopnea index
BDI, Beck depression index
BIS, bispectral index
BMI, body mass index
CFD, computational fluid dynamics
CI, confidence interval
CPAP, continuous positive airway pressure
CT, computer tomography
DISE, drug-induced sedation endoscopy
DS14, type D scale-14
EEG, electroencephalography
ESS, Epworth Sleepiness Scale
FOSQ, functional outcomes of sleep questionnaire
MSLT, Multiple Sleep Latency Test
NEO-FFI, NEO-Five factor inventory
NPV, negative predictive value
OAm, mandibular advancement device
OSA, obstructive sleep apnea
PPV, positive predictive value
PROMAD, predicting therapeutic outcome of mandibular advancement treatment in obstructive sleep apnea
PSG, polysomnography
PSQI, Pittsburgh Sleep Quality Index
SAQLI, sleep apnea quality of life index
SF-36, short form health survey
UA, upper airway
VAS, visual analogue score

REFERENCES

1. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177:1006–14.
2. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22:667–89.
3. Vanderveken OM, Boudewyns A, Ni Q, et al. Cardiovascular implications in the treatment of obstructive sleep apnea. *J Cardiovasc Transl Res* 2011;4:53–60.
4. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046–53.
5. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet* 2009;373:82–93.
6. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005;353:2034–41.
7. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J Am Coll Cardiol* 2008;52:686–717.
8. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* 1981;1:862–5.
9. Grote L, Hedner J, Grunstein R, Kraiczi H. Therapy with nCPAP: incomplete elimination of sleep related breathing disorder. *Eur Respir J* 2000;16:921–7.
10. Lindberg E, Berne C, Elmasry A, Hedner J, Janson C. CPAP treatment of a population-based sample--what are the benefits and the treatment compliance? *Sleep Med* 2006;7:553–60.
11. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008;5:173–8.
12. Kushida CA, Morgenthaler TI, Littner MR, et al. Practice parameters for the treatment of snoring and Obstructive Sleep Apnea with oral appliances: an update for 2005. *Sleep* 2006;29:240–3.
13. Dieltjens M, Vanderveken OM, Heyning PH, Braem MJ. Current opinions and clinical practice in the titration of oral appliances in the treatment of sleep-disordered breathing. *Sleep Med Rev* 2012;16:177–85.
14. Gagnadoux F, Fleury B, Vielle B, et al. Titrated mandibular advancement versus positive airway pressure for sleep apnoea. *Eur Respir J* 2009;34:914–20.
15. Fleury B, Rakotonanahary D, Petelle B, et al. Mandibular advancement titration for obstructive sleep apnea: optimization of the procedure by combining clinical and oximetric parameters. *Chest* 2004;125:1761–7.
16. Randerath WJ, Verbraecken J, Andreas S, et al. Non-CPAP therapies in obstructive sleep apnoea. *Eur Respir J* 2011;37:1000–28.
17. Tsuiki S, Lowe AA, Almeida FR, Kawahata N, Fleetham JA. Effects of mandibular advancement on airway curvature and obstructive sleep apnoea severity. *Eur Respir J* 2004;23:263–8.
18. Chan AS, Sutherland K, Schwab RJ, et al. The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. *Thorax* 2010;65:726–32.
19. Kato J, Isono S, Tanaka A, et al. Dose-dependent effects of mandibular advancement on pharyngeal mechanics and nocturnal oxygenation in patients with sleep-disordered breathing. *Chest* 2000;117:1065–72.
20. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. *Sleep* 2006;29:244–62.
21. Vanderveken OM, Vroegop AV, van de Heyning PH, Braem MJ. Drug-induced sleep endoscopy completed with a simulation bite approach for the prediction of the outcome of treatment of obstructive sleep apnea with mandibular repositioning appliances. *Operative Techniques in Otolaryngology-Head and Neck Surgery* 2011;22:175–82.
22. Battagel JM, Johal A, Kotecha BT. Sleep nasendoscopy as a predictor of treatment success in snorers using mandibular advancement splints. *J Laryngol Otol* 2005;119:106–12.

23. Vroegop AV, Vanderveken OM, Dieltjens M, et al. Sleep endoscopy with simulation bite for prediction of oral appliance treatment outcome. *J Sleep Res* 2013;22:348–55.
24. Ryan CF, Love LL, Peat D, Fleetham JA, Lowe AA. Mandibular advancement oral appliance therapy for obstructive sleep apnoea: effect on awake calibre of the velopharynx. *Thorax* 1999;54:972–7.
25. Stuck BA, Maurer JT. Airway evaluation in obstructive sleep apnea. *Sleep Med Rev* 2008;12:411–36.
26. Ikeda K, Ogura M, Oshima T, et al. Quantitative assessment of the pharyngeal airway by dynamic magnetic resonance imaging in obstructive sleep apnea syndrome. *Ann Otol Rhinol Laryngol* 2001;110:183–9.
27. Schwab RJ, Pasirstein M, Pierson R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. *Am J Respir Crit Care Med* 2003;168:522–30.
28. Yucel A, Unlu M, Haktanir A, Acar M, Fidan F. Evaluation of the upper airway cross-sectional area changes in different degrees of severity of obstructive sleep apnea syndrome: cephalometric and dynamic CT study. *AJNR Am J Neuroradiol* 2005;26:2624–9.
29. Kyung SH, Park YC, Pae EK. Obstructive sleep apnea patients with the oral appliance experience pharyngeal size and shape changes in three dimensions. *Angle Orthod* 2005;75:15–22.
30. Vos W, De Backer J, Devolder A, et al. Correlation between severity of sleep apnea and upper airway morphology based on advanced anatomical and functional imaging. *J Biomech* 2007;40:2207–13.
31. Jeong SJ, Kim WS, Sung SJ. Numerical investigation on the flow characteristics and aerodynamic force of the upper airway of patient with obstructive sleep apnea using computational fluid dynamics. *Med Eng Phys* 2007;29:637–51.
32. De Backer JW, Vanderveken OM, Vos WG, et al. Functional imaging using computational fluid dynamics to predict treatment success of mandibular advancement devices in sleep-disordered breathing. *J Biomech* 2007;40:3708–14.
33. Van Holsbeke C, De Backer J, Vos W, et al. Anatomical and functional changes in the upper airways of sleep apnea patients due to mandibular repositioning: a large scale study. *J Biomech* 2011;44:442–9.
34. Zhao M, Barber T, Cistulli P, Sutherland K, Rosengarten G. Computational fluid dynamics for the assessment of upper airway response to oral appliance treatment in obstructive sleep apnea. *J Biomech* 2013;46:142–50.
35. Dieltjens M, Vanderveken OM, Hamans E et al. Treatment of obstructive sleep apnea using a custom-made titratable duobloc oral appliance: a prospective clinical study. *Sleep Breath* 2013;17:565–72.
36. Vroegop AV, Vanderveken OM, Van de Heyning PH, Braem MJ. Effects of vertical opening on pharyngeal dimensions in patients with obstructive sleep apnoea. *Sleep Med* 2012;13:314–6.
37. Dieltjens M, Braem MJ, Vroegop AV, et al. Objectively measured vs self-reported compliance during oral appliance therapy for sleep-disordered breathing. *Chest* 2013;144:1495–502.
38. Vanderveken OM, Dieltjens M, Wouters K, De Backer WA, Van de Heyning PH, Braem MJ. Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. *Thorax* 2013;68:91–6.
39. Kirshenblatt S, Chen H, Lowe A, Pliska B, Almeida F. Microsensor technology to monitor compliance with removable oral appliances. *Sleep Breath* 2013;17:879–94.
40. Iber C, Ancoli-Israel S, Chesson AL Jr., Quan SF, for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine, 2007.
41. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540–5.
42. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep* 1997;20:835–43.
43. Flemons WW, Reimer MA. Development of a disease-specific health-related quality of life questionnaire for sleep apnea. *Am J Respir Crit Care Med* 1998;158:494–503.
44. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
45. Denollet J. DS14: standard assessment of negative affectivity, social inhibition, and Type D personality. *Psychosom Med* 2005;67:89–97.
46. Costa PT, McCrae RR. Revised NEO Personality Inventory and NEO Five Factor Inventory: Professional Manual. Odessa, FL: Psychological Assessment Resources, 1992.
47. Ware JE, Jr. SF-36 health survey update. *Spine* 2000;25:3130–9.
48. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–71.
49. Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep* 2005;28:113–21.
50. De Vito A, Carrasco Llatas M, Vanni A, et al. European position paper on drug-induced sedation endoscopy (DISE). *Sleep Breath* 2014;18:453–65.
51. Babar-Craig H, Rajani NK, Bailey P, Kotecha BT. Validation of sleep nasendoscopy for assessment of snoring with bispectral index monitoring. *Eur Arch Otorhinolaryngol* 2012;269:1277–9.
52. 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.
53. Schmidt-Nowara W, Lowe A, Wiegand L, Cartwright R, Perez-Guerra F, Menn S. Oral appliances for the treatment of snoring and obstructive sleep apnea: a review. *Sleep* 1995;18:501–10.
54. Eveloff SE, Rosenberg CL, Carlisle CC, Millman RP. Efficacy of a Herbst mandibular advancement device in obstructive sleep apnea. *Am J Respir Crit Care Med* 1994;149:905–9.
55. Remmers J, Charkhandeh S, Grosse J, et al. Remotely controlled mandibular protrusion during sleep predicts therapeutic success with oral appliances in patients with obstructive sleep apnea. *Sleep* 2013;36:1517–25.
56. Sanner BM, Heise M, Knoben B, et al. MRI of the pharynx and treatment efficacy of a mandibular advancement device in obstructive sleep apnoea syndrome. *Eur Respir J* 2002;20:143–50.
57. Tsuiki S, Ito E, Isono S, et al. Oropharyngeal crowding and obesity as predictors of oral appliance treatment response to moderate obstructive sleep apnea. *Chest* 2013;144:558–63.
58. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep* 1996;19:156–77.
59. Verbraecken JA, De Backer WA. Upper airway mechanics. *Respiration* 2009;78:121–33.
60. Liu Y, Lowe AA, Fleetham JA, Park YC. Cephalometric and physiologic predictors of the efficacy of an adjustable oral appliance for treating obstructive sleep apnea. *Am J Orthod Dentofacial Orthop* 2001;120:639–47.
61. Mostafiz W, Dalci O, Sutherland K, et al. Influence of oral and craniofacial dimensions on mandibular advancement splint treatment outcome in patients with obstructive sleep apnea. *Chest* 2011;139:1331–9.
62. Liu Y, Park YC, Lowe AA, Fleetham JA. Supine cephalometric analyses of an adjustable oral appliance used in the treatment of obstructive sleep apnea. *Sleep Breath* 2000;4:59–66.
63. Ng AT, Darendeliler MA, Petocz P, Cistulli PA. Cephalometry and prediction of oral appliance treatment outcome. *Sleep Breath* 2012;16:47–58.
64. Marklund M, Stenlund H, Franklin KA. Mandibular advancement devices in 630 men and women with obstructive sleep apnea and snoring: tolerability and predictors of treatment success. *Chest* 2004;125:1270–8.
65. Mehta A, Qian J, Petocz P, Darendeliler MA, Cistulli PA. A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. *Am J Respir Crit Care Med* 2001;163:1457–61.
66. Zeng B, Ng AT, Qian J, Petocz P, Darendeliler MA, Cistulli PA. Influence of nasal resistance on oral appliance treatment outcome in obstructive sleep apnea. *Sleep* 2008;31:543–7.

67. Marklund M, Persson M, Franklin KA. Treatment success with a mandibular advancement device is related to supine-dependent sleep apnea. *Chest* 1998;114:1630–5.

68. Yoshida K. Influence of sleep posture on response to oral appliance therapy for sleep apnea syndrome. *Sleep* 2001;24:538–44.

69. Yoshida K. Prosthetic therapy for sleep apnea syndrome. *J Prosthet Dent* 1994;72:296–302.

70. Lee CH, Kim JW, Lee HJ, et al. Determinants of treatment outcome after use of the mandibular advancement device in patients with obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg* 2010;136:677–81.

71. Mayer G, Meier-Ewert K. Cephalometric predictors for orthopaedic mandibular advancement in obstructive sleep apnoea. *Eur J Orthod* 1995;17:35–43.

72. Liu Y, Zeng X, Fu M, Huang X, Lowe AA. Effects of a mandibular repositioner on obstructive sleep apnea. *Am J Orthod Dentofacial Orthop* 2000;118:248–56.

73. Chan AS, Lee RW, Srinivasan VK, Darendeliler MA, Grunstein RR, Cistulli PA. Nasopharyngoscopic evaluation of oral appliance therapy for obstructive sleep apnoea. *Eur Respir J* 2010;35:836–42.

74. Johal A, Hector MP, Battagel JM, Kotecha BT. Impact of sleep nasendoscopy on the outcome of mandibular advancement splint therapy in subjects with sleep-related breathing disorders. *J Laryngol Otol* 2007;121:668–75.

75. Vroegop AV, Vanderveken OM, Dieltjens M, et al. Sleep endoscopy with simulation bite for prediction of oral appliance treatment outcome. *J Sleep Res* 2013;22:348–55.

76. Ng AT, Qian J, Cistulli PA. Oropharyngeal collapse predicts treatment response with oral appliance therapy in obstructive sleep apnea. *Sleep* 2006;29:666–71.

77. Petit FX, Pepin JL, Bettega G, Sadek H, Raphael B, Levy P. Mandibular advancement devices: rate of contraindications in 100 consecutive obstructive sleep apnea patients. *Am J Respir Crit Care Med* 2002;166:274–8.

78. Alonso J, Angermeyer MC, Bernert S, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl* 2004:21–7.

79. Verbruggen AE, Dieltjens M, Wouters, K et al. Prevalence of residual excessive sleepiness during effective oral appliance therapy for sleep-disordered breathing. *Sleep Med* 2014;15:269–72.

ACKNOWLEDGMENTS

The authors are grateful to the administrative and organizational support of Ms. Nadine De Kerpel. Furthermore, we thank the co-workers of the Sleep Laboratory of the Antwerp University Hospital for conducting the polysomnographic examinations.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication May, 2016
Submitted in final revised form September, 2016
Accepted for publication September, 2016
Address correspondence to: Annelies Verbruggen, Antwerp University Hospital (UZA), Wilrijkstraat 10, 2650 Edegem, Antwerp, Belgium; Tel: +32 3 821 52 21; Fax: +32 3 821 42 71; Email: annelies.verbruggen@uza.be

DISCLOSURE STATEMENT

This was not an industry supported study. This study was funded by a 3-year grant of the Flemish government agency for Innovation by Science and Technology (IWT-090864). Marc Braem and Olivier Vanderveken are promotors of the SomnoMed Research Grant at the University Hospital of Antwerp. Olivier Vanderveken is consultant for Inspire Medical Systems, Nyxoah and Philips Electronics. Paul Van de Heyning and Olivier Vanderveken received research support at the Antwerp University Hospital from Inspire Medical Systems. Olivier Vanderveken has got research support from ReVent and Nyxoah for clinical trials. He received research support in terms of free devices for an RCT with sleep position trainer in 20 patients from Nightbalance NV, Delft, the Netherlands; and he received lecture fees by Inspire Medical Systems, SomnoMed and Nightbalance. Johan Verbraecken received lecture fees from SomnoMed and AstraZeneca and is consultant for Jazz Pharmaceuticals. The other authors have indicated no financial conflicts of interest.

APPENDICES

Appendix 1: Sleep questionnaire as routinely used in the sleep laboratory

NAME: _____ DATE: _____/_____/ _____

FIRST NAME: _____ SEX: M / F

DATE OF BIRTH:_____ / _____/_____ AGE: _____

ADDRESS:_____

TELEPHONE: HOME: _____ WORK: _____

PROFESSIONAL SITUATION: _____
(or previous job)

MARITAL STATUS: single / married / living together

FAMILY DOCTOR (+address): _____
_____
_____

SPECIALIST: _____ SPECIALTY:_____

REASON FOR REFERRAL TO SLEEP ANALYSIS: _____
_____
_____

PLEASE ANSWER EACH FOLLOWING QUESTION (circle the right answer)

1) Do you often feel tired during the day?
   0: no 1: yes

2) Are you restless at night?
   0: no 1: yes

3) Do you snore?
   0: no snoring in any given position
   1: intermittent and discrete snoring only when lying on the back
   2: constant and clear snoring only when lying on the back
   3: constant or loud snoring in all positions
   4: socially unacceptable snoring (sleeping together is impossible, disturbing for surroundings)

4) Are you sleepy during the day?
   0: no sleepiness
   1: mild sleepiness present
   2: sleepiness disturbs the daily activities (driving a car, professional,…)
   3: daily activities impossible

Appendix 1 continues on the following page

APPENDICES (*continued*)

5) Do you sometimes fall asleep during the day?
   0: never
   1: < 1× a week
   2: > 1× a week
   3: daily

6) Do you suffer from morning headaches?
   0: never
   1: < 1× a week
   2: > 1× a week
   3: daily

7) Do you suffer from loss of memory?
   0: no 1: yes

8) Do you wake up at night after falling asleep?
   0: no
   1: sometimes When?_____

9) Do you feel fresh and alert in the morning after awaking?
   0: no 1: mostly

10) Do you feel more tired in the morning as opposed to when you go to sleep?
   0: no 1: mostly

11) How deep is your sleep; deep or superficial (superficial in case you awaken easily)?
   0: deep 1: superficial

12) Has your partner noticed pauses in your breathing while you are asleep?
   0: no 1: yes

   If yes, specify: 0 when lying on the back
   0 in all positions

13) Do you feel anxious at night or do you have breathing problems?
   0: never
   1: < 1× a week
   2: > 1× a week
   3: daily

14) Do you sometimes feel unpleasant pins and needles in your legs, which make you move your legs?
   0: no 1: yes

15) Does your bedpartner notice any uncontrolled leg movements in your sleep? (e.g. kicking with your legs)
   0: no 1: yes

Appendix 1 continues on the following page

APPENDICES (*continued*)

16) Are you satisfied with your sleep?
0: no 1: yes

If not, what is the main problem?
0 difficulty falling asleep
0 difficulty sleeping through the night
0 waking up too early

17) When did your complaints about snoring start?_____

18) Have you gained weight the last few years? Y / N
_____kg / _____years

19) Have you previously sought help for your snoring problem?
0: no 1: yes

If yes, which help or which treatments?_____
Have these treatments helped you?_____

20) Use of alcohol:
Number of glasses beer and/or wine a week?
Before :_____
Now :_____

Do you use any alcohol before bedtime?
0: no 1: yes

21) Use of coffee:_____cups of coffee a day (number)

22) Smoking habits:
- how much do you smoke a day?_____
- for how many years?_____years

If you have stopped smoking:
- Number of years stopped:_____
- Started smoking at the age of_____
- Stopped smoking at the age of_____
- How much did you smoke a day?_____

Appendix 1 continues on the following page

APPENDICES (*continued*)

23) Illnesses and operations? (circle the right answer or fill in)

Throat-Nose-Ear:
- extraction of polyps: Y / N
- extraction of tonsils: Y / N
- runny nose: Y / N
- blocked nose: Y / N
- nasal septum deviation: Y / N
- allergies: Y / N Which:_____

Heart:
- heart rhythm disorder: Y / N
- myocardial infarction: Y / N When:_____
- high blood pressure: Y / N

Lungs:
- chronic bronchitis: Y / N
- asthma: Y / N

Nervosity, depression, overworked? (circle)

Do you have back problems (or in the past)? Y / N

Other illnesses?_____

Which operations have you got?_____

24) Have you ever got a serious traffic accident? Y / N

How many times have you been involved in a traffic accident?_____times

How many times in the last year have you been able to just avoid an accident?_____times

25) Medication?

Do you regularly use:
- nose sprays Y / N
- puffs for the airways Y / N
- blood pressure medication Y / N
- sleeping pills Y / N

Write down every medication you are taking at the moment:
- _____
- _____
- _____
- _____

Appendix 1 continues on the following page

APPENDICES (*continued*)

26) Height:_____cm Weight:_____kg

Neck size (or size of your shirt):_____cm

Blood pressure:_____/_____mm Hg

27) Libido (sexual drive)
0: normal 1: less than normal

28) How often do you have to go to the toilet at night?_____times.

29) Concentration problems?
0: no 1: yes

30) Do you suffer from heartburn or a burning sensation after a meal? During the day or at night? (circle)
0: never
1: < 1× a week
2: > 1× a week
3: daily

31) What time do you normally go to bed?____h____

What time do you normally get up?____h____

32) For the ladies:
0: I am before menopause
1: I am in menopause ("hot flushes,"…)
2: I am past menopause

33) Remarks of spouse:
_____
_____
_____

34) Comments, miscellaneous:
_____
_____
_____

APPENDICES (*continued*)

Appendix 2: Routine dental questionnaire

1. How do you score your health in general?
   Excellent - very good - good - moderate - bad

2. How do you score your oral health in general?
   Excellent - very good - good - moderate - bad

3. Have you had facial pain in the past month (meaning: pain in the face, the temporal region, the jaws, frontal to or in the ear)?
   Yes - No
   >>> ***If not, go to question 14*** <<<

4. a. How many years ago did you experience facial pain for the first time?
   1 - 2 - 3 - 4–5 - 5–7 - 8–10 - >10

   b. How many months ago did you experience facial pain for the first time?
   1 - 2 - 3 - 4–5 - 5–7 - 8–10 - >10

5. Is the facial pain continuously or intermittently present, or was it a one-time occurrence?
   Continuously - intermittently - one-time occurrence

6. Did you ever visit a doctor, a dentist, a chiropractor or any other health professional for the facial pain?
   - No
   - Yes, in the past 6 months
   - Yes, more than 6 months ago

7. How do you score the facial pain that you feel at this moment, on a scale from 0 to 10, with 0 meaning 'no pain' and 10 meaning 'the worst possible pain'?

8. How do you score the intensity of the worst facial pain you experienced in the past 6 months, on a scale from 0 to 10, with 0 meaning 'no pain' and 10 meaning 'the worst possible pain'?

9. How do you score the average intensity of the facial pain you experienced in the past 6 months, on a scale from 0 to 10, with 0 meaning 'no pain' and 10 meaning 'the worst possible pain'? (meaning the usual pain you experienced on moments of pain)

10. What is the approximate number of days in the past 6 months that you could not carry out your normal activities (school, work, housework) due to the facial pain?

11. Score on a scale of 0 to 10 the extent to which the facial pain influenced your daily activities in the past 6 months, with 0 meaning 'no hindrance' and 10 meaning 'not capable of any activity'.

12. Score on a scale of 0 to 10 the extent to which the facial pain influenced your participation in social, recreational and familial activities with 0 meaning 'no hindrance' and 10 meaning 'not capable of any activity'.

13. Score on a scale of 0 to 10 the extent to which the facial pain influenced your work (incl. housework) with 0 meaning 'no hindrance' and 10 meaning 'not capable of any activity'.

Appendix 2 continues on the following page

APPENDICES (*continued*)

14. a. Have your temporal joints ever been locked or fixed, causing your mouth not to fully open or close?
Yes - No
>>> ***If not, go to question 15 a*** <<<

b. Was this limitation of movement to such an extent that you had difficulties eating?
Yes - No

15. a. Do the joints make a clicking or popping sound when opening or closing the mouth or during chewing?
Yes - No

b. Do the joints make a scraping or grinding sound when opening or closing the mouth or by chewing?
Yes - No

c. Have you ever been told or are you aware of the fact that you grind your teeth or clench the jaws when you are asleep?
Yes - No

d. Do you grind the teeth of clench the jaws during the day?
Yes - No

e. Do you have painful or stiff jaw muscles in the morning upon awakening?
Yes - No

f. Do you hear noises or ringing in the ears?
Yes - No

g. Does your bite feel uncomfortable or different than how it normally feels?
Yes - No

16. a. Do you suffer from rheumatoid arthritis, lupus erythematodes or another systemic joint disease?
Yes - No

b. Does any family member suffer from one of the former diseases?
Yes - No

c. Have you had or do you have swollen or painful joints, other than the temporal joints?
Yes - No
>>> ***If not , go to question 17 a*** <<<

d. Was it or is it a persistent pain, during at least one year?
Yes - No

17. a. Have you recently had an injury in the face?
Yes - No
>>> ***If not, go to question 18*** <<<

b. Was the facial pain already present prior to the injury?
Yes - No

18. Have you suffered from headache or migraine during the past 6 months?
Yes - No

Appendix 2 continues on the following page

APPENDICES (*continued*)

19. a. Are you hindered or impeded during chewing by the current problem with the joints?
Yes - No

b. Are you hindered or impeded during drinking by the current problem with the joints?
Yes - No

c. Are you hindered or impeded during physical exercise by the current problem with the joints?
Yes - No

d. Are you hindered or impeded upon eating of hard food by the current problem with the joints?
Yes - No

e. Are you hindered or impeded upon eating of soft food by the current problem with the joints?
Yes - No

f. Are you hindered or impeded upon smiling or laughing by the current problem with the joints?
Yes - No

g. Are you hindered or impeded during sexual activities by the current problem with the joints?
Yes - No

h. Are you hindered or impeded upon brushing your teeth of cleansing the face by the current problem with the joints?
Yes - No

i. Are you hindered or impeded upon swallowing by the current problem with the joints?
Yes - No

j. Are you hindered or impeded upon talking by the current problem with the joints?
Yes - No

k. Are you hindered or impeded in your usual facial expression by the current problem with the joints?
Yes - No

20. a. To what extent have you been hindered by headache in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

b. To what extent have you been hindered by chest pain in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

c. To what extent have you been hindered by low back pain in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

d. To what extent have you been hindered by sore muscles in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

e. To what extent have you been hindered by difficulties in breathing in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

f. To what extent have you been hindered by dizziness in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

Appendix 2 continues on the following page

APPENDICES (*continued*)

g. To what extent have you been hindered by nausea or stomach problems in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

h. To what extent have you been hindered by a hot-cold feeling in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

i. To what extent have you been hindered by a numbness or tingling anywhere in your body in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

j. To what extent have you been hindered by the sensation of an obstruction in the throat in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

k. To what extent have you been hindered by a sense of physical weakness in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

l. To what extent have you been hindered by a heavy feeling in the arms and legs in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

m. To what extent have you been hindered by difficulties falling asleep in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

n. To what extent have you been hindered by waking up early in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

o. To what extent have you been hindered by a restless or disturbed sleep in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

p. To what extent have you been hindered by unpleasant thoughts or not getting rid of certain thoughts in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

q. To what extent have you been hindered by a loss of libido or not enjoying sexual activities in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

r. To what extent have you been hindered by a lack of energy in the past week in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

s. To what extent have you been hindered by suicidal thoughts in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

t. To what extent have you been hindered by a poor appetite in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

u. To what extent have you been hindered by weeping easily in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

v. To what extent have you been hindered by feeling entangled or trapped in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

Appendix 2 continues on the following page

APPENDICES (*continued*)

w. To what extent have you been hindered by blaming yourself all sorts of things in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

x. To what extent have you been hindered by feeling lonely in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

y. To what extent have you been hindered by being upset in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

z. To what extent have you been hindered by worrying too much about things in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

aa. To what extent have you been hindered by not being interested in anything in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

bb. To what extent have you been hindered by a feeling of emptiness in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

cc. To what extent have you been hindered by feeling desperate about the future in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

dd. To what extent have you been hindered by thinking about death or dying in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

ee. To what extent have you been hindered by feeling worthless in the past week, including today?
Not at all - slightly - moderately - quite a bit - extremely

21. How well do you take care of your general health?
Excellent - very good - good - moderate - bad

22. How well do you take care of your oral health?
Excellent - very good - good - moderate - bad