ONLINE SUPPLEMENT

Inclusion criteria

1) Individuals who have been subjected to polysomnography and are diagnosed as having moderate (AHI 15 - 30) obstructive sleep apnea;
2) Aged ≥18 years;

Exclusion criteria

Medical and psychological exclusion criteria:

1) Patients previously treated for OSA (e.g. CPAP, MAD);
2) Morphologic abnormalities of the upper airway (e.g., a compromised nasal passage, enlarged tonsils or adenoids, or upper airway soft-tissue or craniofacial abnormality);
3) Reported or documented unstable endocrine dysfunction (hypothyroidism, acromegaly, or pituitary adenoma);
4) Reported or documented severe cardiovascular- or pulmonary co-morbidity (clinically concurrent cardiovascular disease (coronary artery disease, heart failure, cardiac arrhythmias, CVA within 6 months prior to randomization, daytime respiratory insufficiency, Severe Chronic Obstructive Pulmonary Disease (COPD) (GOLD 3 or 4; FEV1 / FVC<70% and FEV1 <50%));
5) Reported or documented psychological condition precluding informed consent (e.g., mental retardation, depression or schizophrenia);
6) Other diseases that may impact the evaluation of the results of the study according to the investigator's judgment.

Whether the patient has unstable endocrine dysfunction, severe cardiovascular- or pulmonary co-morbidity or a psychological condition precluding informed consent, was assessed based on patient's medical records.

Dental exclusion criteria:

1) Extensive periodontal disease or tooth decay;

2) Active temporomandibular joint disease (including severe bruxism);

3) Restrictions in mouth opening (<25mm) or advancement of the mandible <5mm);

4) Partial or complete edentulism (less than eight teeth in upper or lower jaw).

Study procedures and subjects

All consecutive patients aged ≥18 years with an AHI of 15-30 events/h based on polysomnography (PSG), and fulfilling the selection criteria based on medical records, were asked to participate in a multicenter parallel randomized controlled trial and subsequently invited for a screening visit. When indicated, spirometry and/or electrocardiogram (ECG) were performed during the screening visit in order to exclude severe cardiovascular- and/or pulmonary disease. During the screening visit a dental examination was performed to establish that patients were suitable candidates for MAD therapy. Patients meeting all in- and exclusion criteria were scheduled for a baseline visit, which included physical examination, 24-hour ambulatory blood pressure measurement (ABPM), blood- and urine sampling, and questionnaire evaluation. Subsequently, patients were randomized to either MAD or CPAP therapy.

Patients returned 3, 6 and 12 months after the start of therapy for follow-up measurements. A PSG was performed after 3 months to assess the effectiveness of the therapy. In case of unsuccessful treatment (i.e. <50% AHI reduction), adjustments to the therapy were

made and a second PSG was scheduled (approximately 6 months after the start of therapy). After 12 months, a final PSG was performed.

Patients switching to the other therapy (randomized therapy not being effective or patient unable to comply with randomized therapy) remained part of the study and were analyzed according to their initial therapy (intention-to-treat analysis).

Randomization and masking

Randomization to either MAD or CPAP therapy was performed using a computer program, thereby concealing the allocation sequence from the investigators. Minimization was used to minimize the imbalance between the number of patients in each over hypercholesterolemia, diabetes and hypertension status, thereby minimizing the possible effects of *a priori* cardiovascular differences between patients receiving MAD and CPAP therapy. Patients could not be blinded to the intervention they received.

Interventions

MAD: Patients randomized to the MAD group were treated with a custom-made titratable bibloc MAD (SomnoDent® MAS, SomnoMed Australia/Europe AG). To start, the mandible was set at approximately 60 to 70% of the patient's maximum advancement. The maximum advancement of the mandible was determined with a George-Gauge (H-Orthodontics, Michigan City, IN, USA) before MAD therapy was initiated. The forward position of the mandible with the appliance was adjusted to the convenience of the patient until symptoms abated or until further advancement caused discomfort.

CPAP: Patients randomized to the CPAP group were subjected to autoCPAP (Philips Respironics REMstar Auto A-Flex, provided by VitalAire BV The Netherlands) for three weeks, after which the appropriate fixed CPAP-pressure for each individual patient (device provided by the healthcare provider of the patient) was set by a skilled, specialized nurse (i.e., highest

pressure derived from the Hoffstein formula [1] or the 90%-criterion (mean pressure ≤90% of the time) of the autoCPAP). Patients were fitted with a comfortable mask prior to titration of the CPAP-pressure. During the study, patients were allowed to change their mask and to use chinstraps or a humidifier if desired.

Outcomes

Cost-effectiveness and cost-utility analysis

The incremental cost-effectiveness and -utility ratios (ICER/ICUR) were calculated after 12 months. ICER was based on the incremental costs and the effects on AHI reduction of MAD versus CPAP (MAD considered the alternative and CPAP the control/reference intervention). ICUR was based on the incremental costs and the effects on utility scores (EQ-5D-3L). The answers on the five domains of the EQ-5D-3L, can be converted into a single index value (also called utility value) between 0 and 1 (with 1 being the optimal health status). Different algorithms to calculate the utility values have been obtained using representative samples of the general population, thereby representing the societal perspective. For this study the Dolan algorithm was used as it is frequently used in international literature and studies, thereby facilitating international comparisons.[2] Quality adjusted life year (QALY) was calculated using the utility values multiplied with the survival time (in this analysis 1 year). Bootstrap resampling (5000 replications) was performed on the cost and effect pairs to calculate confidence intervals and to depict cost-effectiveness planes. Furthermore, cost-effectiveness acceptability curves were plotted to illustrate the probability of interventions studied being more cost-effective than the other therapy over a range of thresholds. In the Netherlands, no formal threshold for cost-effectiveness exists.

Costs

Assuming that both MAD and CPAP have a lifespan of five years, device costs were uniformly depreciated over a five year period. Costs were studied from a societal perspective, including direct costs in- and outside the health care sector as well as indirect costs. The time horizon of this study encompassed one year, using 2015 as the reference year, therefore no discounting was applied on costs and effects. The following cost components were taken into account in the economic evaluation: direct medical costs, such as costs of treatment (including PSG), outpatient hospital visits, visits to general practitioner and other health care providers, and hospital stay. Direct costs outside the health care sector (direct non-medical costs) included travel expenses and parking costs. Indirect costs included income missed from being absent from paid work. Cost components were scored according to the Dutch standard guidelines for economic evaluations [3]. Additional detail on the cost components taken into account in the economic evaluation is provided in Table S1.

A case record form was used to register hospital related medical resource use. Indirect costs and medical resource use outside the hospital were measured using a questionnaire (adapted version from the iPCQ and iMCQ), which was filled out by patients at baseline and after 3, 6 and 12 months.

Costs of absenteeism (productivity loss) were calculated according to the human capital method based on the multiplication of working days per week, working hours per day, and mean Dutch salary costs (differentiated for men and women) [3].

All units of health care consumption, such as visits to the outpatient clinic and to the hospital (academic or periphery), were measured at patient level. Costs of health care consumption were calculated based on standard prices according to CVZ (Care insurance board**)** guidelines [3].

Polysomnography

The mean number of apneas and/or hypopneas was assessed during (ambulatory) PSG. Baseline polysomnographic outcomes were those obtained at the time of diagnosis. When the diagnostic sleep study was a polygraphy, PSG was performed before inclusion. Apneas and hypopneas were defined according to the American Academy of Sleep Medicine (AASM) criteria.

Questionnaires

Patients filled out questionnaires at baseline, and 3, 6 and 12 months after the start of therapy. The level of subjective EDS was measured with the Epworth Sleepiness Scale (ESS) [4]. This questionnaire assesses the propensity to fall asleep in eight separate situations. Quality of life was estimated using the 36-item health survey (SF-36) [5] and the functional outcomes of sleep questionnaire (FOSQ) [6], with higher scores implying better quality of life. Generic health status was assessed with the EQ-5D-3L. Current depression and anxiety was measured with the hospital anxiety and depression scale (HADS) [7]; a higher score representing higher states of anxiety and depression. Furthermore, subjective compliance, satisfaction with the current therapy and side-effects were monitored using self-reported questionnaires.

References

1. Miljeteig H, Hoffstein V. Determinants of continuous positive airway pressure level for treatment of obstructive sleep apnea. Am Rev Respir Dis 1993;147:1526-1530.

2. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-1108.

3. Zorginstituut Nederland. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg; 2015.

4. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-545.

5. Ware JE,Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-483.

6. Weaver TE, Laizner AM, Evans LK et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep 1997;20:835-843.

7. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-370.

Table S1. Outline of costs first year

	Costs	Source
MAD therapy		
MAD device Technical costs Somnodent	€579.- including depreciation over 5-yr period = €83.95	Correspondence
Fee for starting up MAD therapy	€348.-	Correspondence Websites health insurance companies
Check-up visit	€34.89 (NZa 234191 tariff per 1-1-2015)	Dutch Healthcare Authority (NZa)
Check-up visit including reparation	€70.16 (NZa 234192 tariff per 1-1-2015)	Dutch Healthcare Authority (NZa)
CPAP therapy		
CPAP device	€900.- including depreciation over 5-yr period = €135.95	Correspondence (VitalAire and SomnoMed Goedegebuure)
CPAP mask	Depends on type of mask	Website Vivisol
Chin straps	€21.26	Website Vivisol
Setting-up visit	€74.- (weighted mean reference price 2014, medical specialist replaced by nurse practitioner (hourly rate €35.07)	Reference [3]

Check-up by telephone	€18.50 (1/4 * €74-)	Reference [3]
Check-up visit	€37.- (1/2 * €74,-)	Reference [3]
Polysomnography	€236.80	Dutch Healthcare Authority (NZa)
Travel expenses	€0.19 per kilometer (car and public transport)	Reference [3]
Parking	€3.- per consult	Reference [3]
Health care costs		
General practitioner standard consult	€33.-	Reference [3]
Psychologist private practice	€94.-	Reference [3]
Psychologist hospital	€64.-	Reference [3]
Company doctor	€33.-	Reference [3]
Medical specialist	€91.-	Reference [3]
Paramedic	€33.-	Reference [3]
Social worker	€65.-	Reference [3]
Hospitalization day	€476.-	Reference [3]
Inpatient day psychiatric institution	€302.-	Reference [3]
Rehabilitation	€153.-	Reference [3]
Domestic home care	€20.-	Reference [3]
Salary		
Men	€37.90	Reference [3]
women	€31.60	Reference [3]

Table S2. Direct medical, direct non-medical and indirect costs (intention-to-treat analysis n=85)

	After 1 year	
	MAD n=43	**CPAP n=42**
Direct medical costs	4,573.3 ± 20,912.5	2,056.8 ± 2,534.0
Direct non-medical costs	54.7 ± 41.0	53.7 ± 40.2
Indirect costs	3,548.9 ± 11,434.7	5,132.3 ± 16,014.4

Data are displayed as mean±SD.

Direct medical costs: costs of treatment, visits to general practitioner and other health care providers, outpatient hospital visits, and hospital stay.

Direct non-medical costs: travel expenses and parking costs.

Indirect costs: absenteeism from paid work.