SUPPELEMENT

Patient selection:

The University Medical Center Groningen includes most patients of the northeastern part of the Netherlands. Patients suspected having Obstructive Sleep Apnea Syndrome (OSAS) are referred to this hospital by general practitioners and physicians of pulmonary medicine, neurology and ear nose and throat surgery. For this randomized controlled trial we adopted the recommendations of the American Academy of Sleep Medicine to diagnose OSAS [1].

Patients over the age of 20 who were diagnosed with OSAS based on polysomnography were eligible for inclusion [2]. Besides patients required fulfilling predefined medical, psychological, and dental inclusion criteria.

<u>General criteria for inclusion:</u>

- Polysomnography showing an Apnea-Hypopnea Index (AHI) ≥ 5 in combination with:
    - Excessive daytime sleepiness that is not better explained by other factors or
    - Two or more of the following symptoms that are not better explained by other factors: choking or gasping during sleep, recurrent awakenings from sleep, unrefreshed sleep, daytime fatigue, impaired concentration.

<u>Medical and psychological criteria for exclusion:</u>

- Previous treatment of obstructive sleep apnea (Continuous Positive Airway Pressure (CPAP), oral appliance therapy, or uvulopalatopharyngoplasty)
- Morphological airway abnormalities requiring treatment (a compromised nasal passage, enlarged tonsils or adenoids, upper airway or pulmonary neoplasm, or upper airway soft-tissue or craniofacial abnormality)

- Endocrine dysfunction (hypothyroidism, acromegaly, or pituitary adenoma)
- A reported or documented history of severe cardiac or pulmonary disease (daytime respiratory insufficiency, severe chronic obstructive pulmonary disease (Tiffeneau index < 40%), type 2 heart failure, coronary disease, or severe cardiac arrhythmias)
- Moderate or severe periodic limb movement disorder (periodic limb movement index > 25).
- A psychological condition precluding informed consent (mental retardation or psychiatric disorder; e.g., depression or schizophrenia)

Dental criteria for exclusion from the study

- Extensive periodontal disease or tooth decay
- Active temporomandibular joint disease (including severe bruxism)
- Restrictions in mouth opening (< 25 mm) or advancement of the mandible (< 5 mm)
- Partial or complete edentulism (fewer than eight teeth in upper or lower jaw)

Patients who were eligible for inclusion were given a brochure with details about the study. All patients had 1 week to decide whether or not they wanted to participate. If patients decided to participate they needed to sign and return an informed consent form.

Randomization:

Each patient was given a serial number and diagnosis of disease severity. All patients were randomized for either MAD or CPAP therapy, by using Block randomization[3]. It was not possible to blind patients or clinicians for the treatment modality.

Interventions:

Before treatment, all patients were instructed to adopt conservative measures; specifically to avoid using depressants and to have at least 7-8 hours of sleep each night. Patients were encouraged to give up smoking and lose weight.

The oral appliance used in this study was the TAP appliance. (Thornton Adjustable Positioner type-1, Airway Management Inc., Dallas, TX, USA). This duo block MAD fixes the patients mandible in a forward position by a screw mechanism incorporated in the frontal area of the appliance. The patient could adjust the amount of mandibular advancement in 0.2mm increments. The maximum advancement of the mandible was determinded with a George-Gauge™ (H Orthodontics, Michigan City, IN, USA). At baseline the appliance was set at approximately 50% of patient's maximum protrusion. After a 2-week adaptation period, patients were instructed to advance their appliance until symptoms abated or until further protrusion of the mandible resulted in discomfort. After a 8-week follow-up period a checkup was arranged to further adjust the therapy if necessary. When OSAS symptomatology was improved or when further protrusion was not tolerated by the patient, a second polysomnographic study, with physical examination and subjective questionnaire evaluation, was performed. In patients showing an AHI<5, therapy was considered successful. In patients showing an AHI $\geq$ 5, the appliance was further adjusted by the physician. Four weeks after adjustments, another polysomnographic study, with physical examination and subjective questionnaire evaluation, was performed. This was continued until OSAS was successfully treated or until further adjustments were not tolerated by the patient. During follow-up the MAD was adjusted when necessary, if OSAS symptomatology appeared or when the patient experienced discomfort associated with wearing the appliance.

CPAP titration was performed during an afternoon nap in the outpatient clinic by a skilled nursing consultant [4]. Patients were fitted with a comfortable CPAP mask before titration. The CPAP device used during titration was the Breas PV10 (Molnlycke, Sweaden.) After two weeks patients returned for a

checkup and after a 8 week period another polysomnographic study, with physical examination and subjective questionnaire evaluation, was performed. If the AHI > 5, CPAP was adjusted if possible and raised by 1 or 2 cm H_2O. A third polysomnographic study was performed 4 weeks after the adjustments. This was continued until OSAS was successfully treated or until further adjustments were not tolerated by the patient.

Patients were monitored at 3 months, 1-year, 2-year and 10-year follow-up by polysomnography. In case of recurrence of clinical symptoms polysomnography was also repeated in between these standard evaluation time points. Patients who were successfully treated continued their therapy. Patients who were not successfully treated were offered the alternative therapy, either CPAP or MAD.

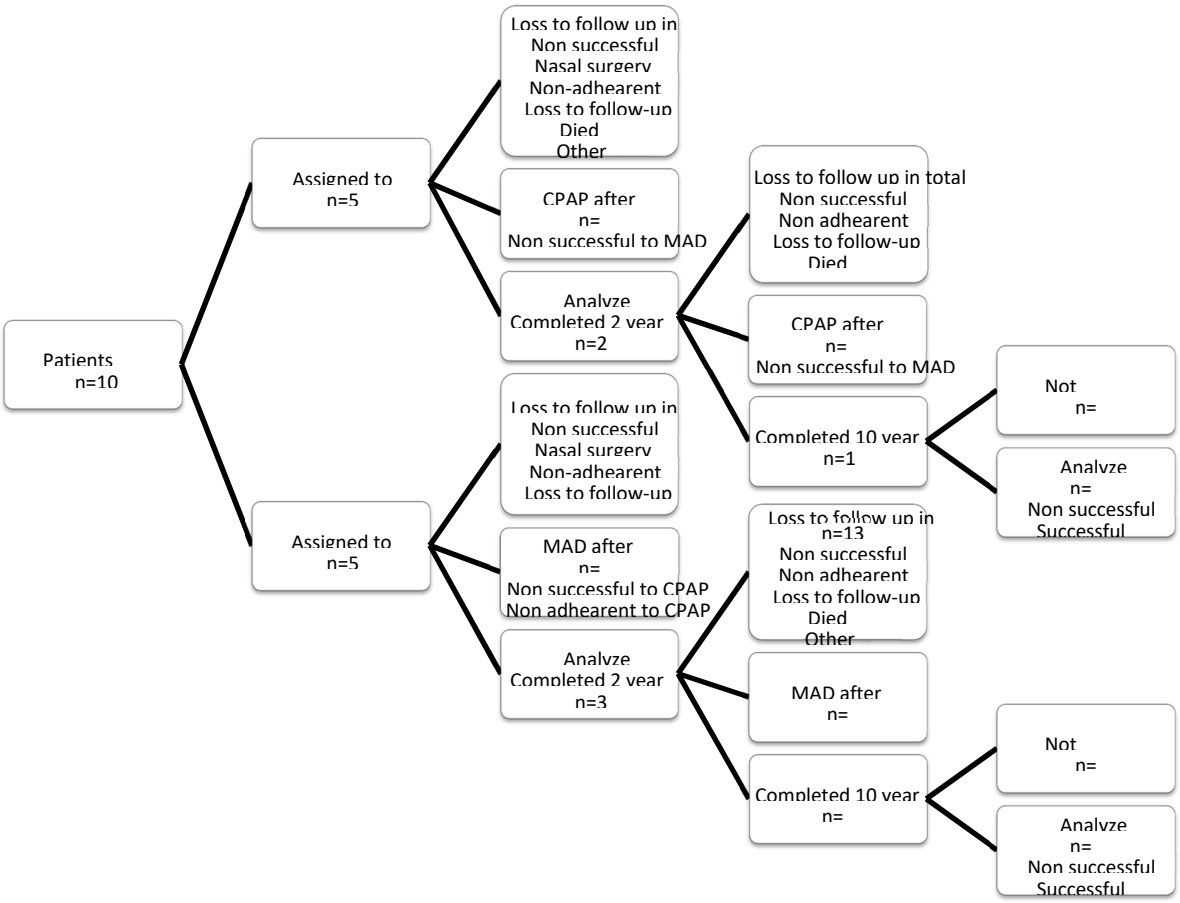

Figure S1: Study flowchart

Table S1: BMI and Neck circumference Mandibular Advancement Device (MAD) (n=14) and Continuous Positive Airway Pressure (CPAP) group

Treatment	Variable	Baseline	1-year follow-up	2-year follow-up	10-year follow-up
MAD	Body Mass Index (kg/m2)	32.4±6.6	32.3±6.3	32.1±6.6	31.3±5.9
CPAP	Body Mass Index (kg/m2)	33.2±3.6	33.1±3.7	33.9±4.2	32.5±4.8
MAD	Neck circumference (cm)	43.6±3.7	43.1±3.4	42.9±3.7	43.8±3.8
CPAP	Neck circumference (cm)	44.6±3.2	44.3±2.6	44.6±2.6	44.4±2.8

Values are means ± standard deviations

No significant differences calculated

Table S2A: Functional Outcomes of Sleep Questionnaire Mandibular Advancement Device (MAD) group (n=14)

Subject	Range	Baseline	3-months follow-up	1-year follow-up	2-year follow-up	10-year follow-up
General productivity (GP)	1-4	2.9±0.6	3.8±0.4*	3.6±0.7*	3.9±0.2*	3.7±0.4*
Social outcome (SO)	1-4	2.8±0.9	3.8±0.4*	3.6±0.8*	3.8±0.5*	3.6±0.6*
Activity level (AC)	1-4	2.5±0.8	3.6±0.5*	3.4±0.9*	3.7±0.4*	3.4±0.7*
Vigilance (VI)	1-4	2.6±0.8	3.7±0.4*	3.4±0.8*	3.8±0.4*	3.5±0.5*
Intimate relationships and sexual activity (SE)	1-4	2.6±1.0	3.1±1.4	3.2±1.0	2.4±1.6	2.9±1.5
Total score (Tot)	5-20	13.4±3.0	18.2±2.1*	17.1±3.5*	17.6±1.9*	17.7±2.1*

Values are means ± standard deviations

** Values are significantly different from baseline (p<0.05)*

Table S2B: Functional Outcomes of Sleep Questionnaire Continuous Positive Airway Pressure (CPAP) group (n=17)

Subject	**Range**	**Baseline**	**3-months follow-up**	**1-year follow-up**	**2-year follow-up**	**10-year follow-up**
General productivity (GP)	1-4	3.0±0.7	3.7±0.4*	3.8±0.3*	3.6±0.5*	3.9±0.3*
Social outcome (SO)	1-4	3.1±0.8	3.7±0.7*	3.9±0.3*	3.9±0.3*	3.9±0.2*
Activity level (AC)	1-4	2.7±0.8	3.5±0.6*	3.5±0.7*	3.7±0.4*	3.7±0.4*
Vigilance (VI)	1-4	2.2±0.7	3.6±0.5*	3.6±0.6*	3.6±0.5*	3.8±0.3*
Intimate relationships and sexual activity (SE)	1-4	2.9±1.0	3.0±1.3	3.0±1.5	3.2±1.3	3.6±0.98*
Total score (Tot)	5-20	13.7±3.0	17.5±2.8*	17.8±2.2*	18.1±2.2*	18.8±1.1*

Values are means ± standard deviations

** Values are significantly different from baseline (p<0.05)*

References

1. 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.

2. Ramar K, Dort LC, Katz SG, et al. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2015;11(7):773-827.

3. Altman DG. Designing research. In: Altman DG, ed. Practical statistics for medical research. London: Chapman & Hall. 1991:74-106.

4. Doff MH, Hoekema A, Wijkstra PJ, et al. Oral appliance versus continuous positive airway pressure in obstructive sleep apnea syndrome: a 2-year follow-up. Sleep. 2013;36(9):1289-96.