Oral-appliance therapy obstructive sleep apnea-hypopnea syndrome

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Chapter 4

Oral appliances versus continuous positive airway pressure

Chapter 4.1

Effectiveness of obstructive sleep apnea-hypopnea therapy: a randomized parallel trial of oral-appliance versus continuous positive airway pressure therapy

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* Hoekema A, Stegenga B, Wijkstra PJ, van der Hoeven JH, Meinesz AF, de Bont LGM. Effectiveness of obstructive sleep apnoea therapy: a randomized parallel trial of oral-appliance versus continuous positive airway pressure therapy (submitted for publication).

Summary

Background Oral-appliance therapy is emerging as an alternative to continuous positive airway pressure (CPAP) as therapy for the obstructive sleep apnea-hypopnea syndrome (OSAHS). In clinical practice, however, oral appliances are used primarily for patients who do not respond to CPAP therapy. We hypothesized that an oral appliance is not inferior to CPAP in treating OSAHS effectively.

Methods We randomly assigned 103 OSAHS patients to oral-appliance or CPAP therapy. After eight weeks, treatment effect was assessed with polysomnography. Follow-up review was extended for patients requiring adjustments to therapy and ended with a patient's final polysomnographic evaluation or when a patient discontinued treatment. We then determined the proportion of patients for whom oral-appliance or CPAP therapy was effective. For the difference in effectiveness (oral-appliance minus CPAP therapy), a 95% two-sided confidence interval was calculated. Non-inferiority of oral-appliance therapy was considered established when the lower boundary of this interval exceeded -25%.

Results Treatment was effective for 39 of 51 patients using the oral appliance (76.5%) and for 43 of 52 patients using CPAP (82.7%). The lower boundary of the confidence interval of the difference in effectiveness was -21.7%, indicating that oral-appliance therapy met the criterion for non-inferiority. Subgroup analysis revealed that oral-appliance therapy was effective primarily in patients with non-severe disease (apnea-hypopnea index ≤30).

Conclusions In this randomized parallel trial, oral-appliance therapy was not inferior to CPAP as effective treatment of OSAHS. Subgroup analysis suggested that an oral appliance is particularly indicated for patients with non-severe disease.

Introduction

The obstructive sleep apnea-hypopnea syndrome (OSAHS) is characterized by disrupted snoring and repetitive upper-airway collapse.[1] Its neurobehavioral consequences include excessive sleepiness, an increased risk of accidents, and an impaired quality of life.[1,2] Cardiovascular consequences include hypertension and increased risk of ischemic heart disease, congestive heart failure, and stroke.[3,4] Continuous positive airway pressure (CPAP), the standard treatment,[2] improves blood pressure[5] and neurobehavioral outcomes,[2] but as it requires wearing an obtrusive device, patients may abandon or adhere poorly to therapy.[6,7]

Oral-appliance therapy is an alternative to CPAP that relieves upper airway collapse during sleep by modifying the position of the mandible, tongue, and pharyngeal structures.[8] Although effective, it is generally less effective than CPAP.[9-11] Nevertheless, many patients prefer an oral appliance to CPAP, and physiological and neurobehavioral outcomes are not substantially different between the therapies.[9,10]

Specific indications for oral-appliance therapy are indeterminate.[8,10,11] It is prescribed primarily for patients unwilling or unable to tolerate CPAP.[11] We hypothesized that an oral appliance is not inferior to CPAP in treating OSAHS effectively. Because there are indications that effectiveness of oral-appliance therapy is related to disease severity, we designed a randomized parallel trial to evaluate the treatment in OSAHS patients representing the entire spectrum of the disease.

Methods

Patient selection

Patients were recruited through the Department of Home Mechanical Ventilation of the University Medical Center Groningen, The Netherlands. Patients over age 20 who underwent polysomnography and were diagnosed as having OSAHS with at least five apneas or hypopnoeas per hour of sleep were eligible. To screen for any underlying disease, all eligible patients underwent a comprehensive physical evaluation, spirometry, thoracic radiography, electrocardiography, and blood tests. Patients were selected based on medical, psychological, and dental criteria. Patients with previous treatment of OSAHS, clearly reversible morphological airway abnormalities, endocrine dysfunction, a reported or documented history of severe cardiac or pulmonary disease, moderate or severe periodic limb-movement disorder, or a psychological condition precluding informed consent were excluded, as were patients whose dental status could complicate oral-appliance therapy.[12] The trial was approved by the Groningen University Medical Center's ethics committee (METc 2002/032). Written informed consent was obtained from patients before enrollment. Details on the recruitment and selection of patients

are provided in Appendix 1.

Study design

Patients were allocated to groups treated with an oral appliance or CPAP by using block randomization. Severity of disease was assessed based on the baseline polysomnographic study by using the apnea-hypopnea index (AHI): the mean number of apneas and hypopnoeas per hour of sleep. Patients were classified as having non-severe (AHI 5–30) or severe (AHI >30) OSAHS. The cooperating clinical epidemiologist (B. Stegenga) made computer-generated randomization sequences, balancing for disease severity. The randomization sequences were used for selecting random permuted blocks with lengths of two, four, and six.[13] The clinicians supervising oral-appliance and CPAP therapy were not informed about how randomization was performed. The randomization sequences were concealed and administered by Department of Oral and Maxillofacial Surgery staff. After each patient's serial number and diagnosis of disease severity was provided, the treatment was disclosed. It was not possible to blind patients or clinicians to treatment assignment. At baseline, each patient underwent a physical and neurobehavioral examination.

After patients had used an oral appliance or CPAP for eight weeks, the effect was assessed with a second polysomnographic study. For patients whose AHI was still ≥5, treatment was adjusted, if possible, to improve effectiveness, and the follow-up period was extended another four weeks. The effect was then assessed with a third polysomnographic study. This adjustment sequence continued until the AHI was <5 or until adjustments became uncomfortable for the patient. Follow-up review ended with a patient's final polysomnographic evaluation or when a patient discontinued treatment because of poor tolerance or another reason. At their final follow-up review, patients again underwent the physical and neurobehavioral examinations performed at baseline.

Treatment was considered effective when the AHI either was <5 or showed "substantial reduction,"[10] defined as reduction in the index of at least 50% from the baseline value to a value of <20 in a patient who had no symptoms while using therapy. Patients not meeting these criteria at their final review were considered "nonresponsive" to treatment. Patients who discontinued treatment for any reason were considered "nonadherent" to treatment.

Interventions

All patients were instructed to adopt conservative measures and to use their oral appliance or CPAP whenever they slept. The oral appliance (Thornton Adjustable Positioner, Airway Management, Inc., Dallas, TX, USA) positioned the patient's mandible in a forward and downward position. By turning a propulsion screw

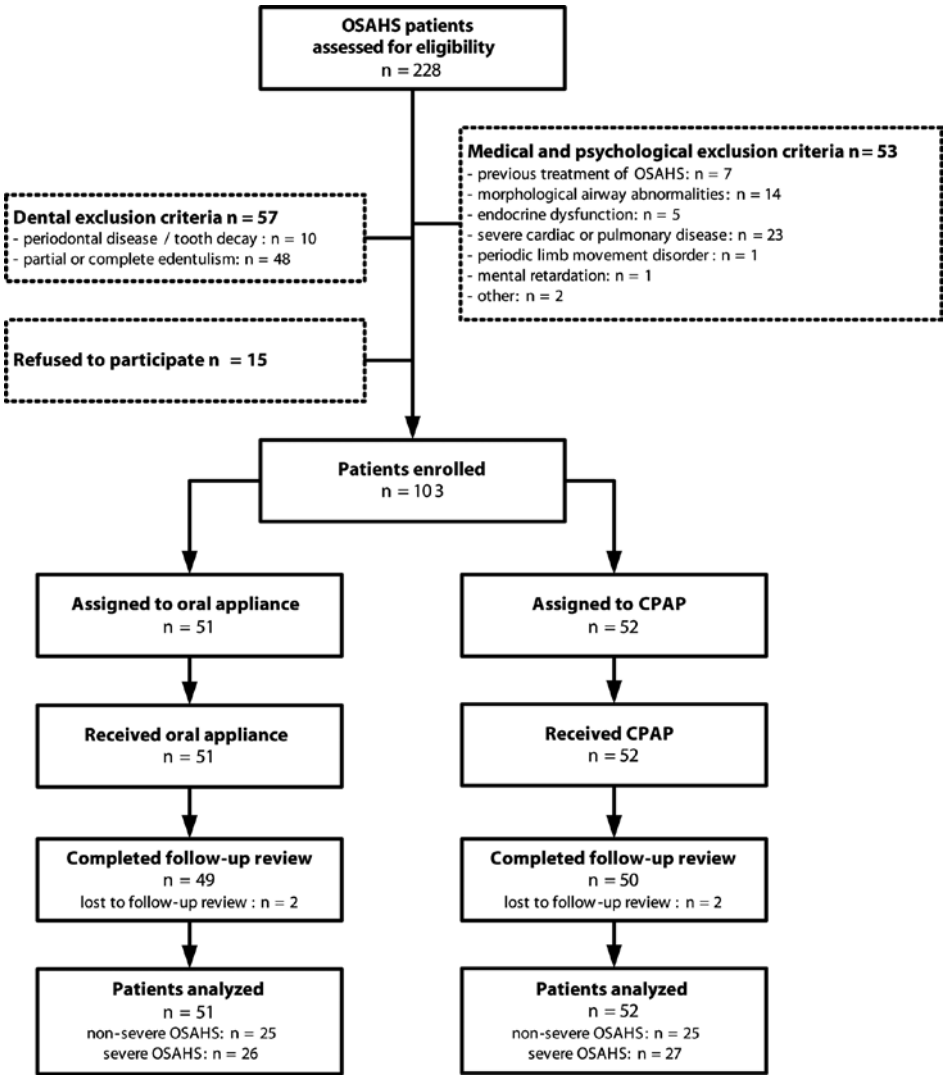

FIGURE 1. Flow diagram of patients through each stage of the trial.

Of the 103 patients included, two patients in the oral-appliance group and in the CPAP group did not return for the follow-up polysomnography and neurobehavioral examinations (lost to follow-up review).

Abbreviations: CPAP = continuous positive airway pressure, OSAHS = obstructive sleep apnea-hypopnea syndrome.

incorporated anteriorly in the appliance, patients could adjust mandibular advancement in 0.2-mm increments. Patients advanced the mandible until symptoms abated or until further advancement caused discomfort. CPAP-titration aimed at abolishing: all signs of apneas, hypopneas, and snoring—was performed during an afternoon nap.[14] Details of the interventions, conservative measures, and treatment adjustments are provided in Appendix 1.

Polysomnography

Polysomnography (Embla® A10 digital recorder, Medcare, Reykjavik, Iceland) for baseline and follow-up evaluations was conducted while patients slept at home. All polysomnographic studies were evaluated according to standardized criteria and scored by one neurophysiologist (J.H. van der Hoeven) who was unaware of the patient's treatment assignment (see Appendix 1).

Physical and neurobehavioral examination

Physical examination included documentation of height, weight, neck circumference, alcohol consumption, tobacco use, and current medications. For the neurobehavioral examination (see Appendix 1), patients completed questionnaires addressing OSAHS-related symptoms,[15,16] health perceptions,[17] and presence of anxiety or depression.[18] At final follow-up review, patients completed a questionnaire assessing treatment usage and grading their satisfaction with treatment on a ten-point scale.

Analysis

In assessing non-inferiority of oral-appliance to CPAP therapy, non-inferiority was defined as a difference between the proportions of treatment effectiveness of less than 25%. With a one-sided significance level of 5%, a power of 90%, and an assumed proportion of treatment effectiveness of 90%, a minimum of 46 patients would be required in each treatment group. Calculation of the sample size was performed with the PASS 2000 software package (NCSS, Kaysville, UT, USA). No interim analysis was conducted during the study period.

The primary outcome measure was the proportion of patients whose oral-appliance or CPAP therapy was effective (intention-to-treat analysis). Patients lost to follow-up review were considered "nonadherent" to treatment (worst-case scenario). Secondary outcome measures were polysomnographic and neurobehavioral outcomes at final follow-up review. To determine the relative effectiveness of oral-appliance therapy, primary and secondary outcomes were compared to those with CPAP. Comparison of the proportions of effectiveness between the groups was also performed as a function of disease severity to provide insight into the major indications for oral-appliance therapy (prespecified subgroup analyses).

Statistical analyses were performed by using the Statistical Package for the Social

TABLE 1. Baseline characteristics of 103 patients treated with an oral appliance or CPAP.

Variable	Oral appliance* (n = 51)	CPAP* (n = 52)
Male / female ratio	43 / 8	49 / 3
Non-severe OSAHS (no. patients)	25	25
Severe OSAHS (no. patients)	26	27
Age (years)	49 ± 10	49 ± 10
Body-mass index (kg/m^2)	32 ± 6	33 ± 6
Neck circumference (cm)	44 ± 4	45 ± 4
Consumption of alcohol (no. patients)	34	40
Smoking (no. patients)	20	17
Sedative medication (no. patients)†	3	1
Antihypertensive medication (no. patients)	20	21
Hypertension (no. patients)‡	39	42
Blood pressure (mm Hg): - systolic	150 ± 21	151 ± 20
- diastolic	93 ± 13	91 ± 12

* Plus-minus values are means ± standard deviations.
† After starting oral-appliance therapy one patient stopped using sedative medication completely, and two other patients stopped using sedative medication at night.
‡ Hypertension was defined as either the use of antihypertensive medication or a systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg.[19]
Abbreviations: CPAP = continuous positive airway pressure, OSAHS = obstructive sleep apnea-hypopnea syndrome.

Sciences (version 12.0, SPSS Inc, Chicago, IL, USA). Means and standard deviations, or medians and interquartile ranges in skewed distributions, are reported. For the difference between the proportions of effectiveness of the therapies (oral-appliance minus CPAP therapy), a 95% two-sided confidence interval was calculated. Non-inferiority of oral-appliance therapy was considered established when the lower boundary of this confidence interval exceeded -25%. Secondary outcomes were compared by calculating effect sizes with two-sided 95% confidence intervals. For comparing outcomes with skewed distributions, Mann-Whitney U tests were used. All tests were two-sided and *p*-values <0.05 indicated significance.

Results

Between September 2002 and May 2005, 103 patients were enrolled (Table 1). Randomization yielded an oral-appliance group of 51 patients and a CPAP group of 52 patients (figure 1). Of the oral-appliance group, 47 patients completed

TABLE 2. Polysomnographic outcomes of 103 patients treated with an oral appliance or CPAP.

Variable	Baseline*		Follow-up review*		Difference in effect at follow-up review: effect size (95% CI) or p-value‡
	Oral appliance (n = 51)	CPAP (n = 52)	Oral appliance (n = 47)†	CPAP (n = 47)†	
Total sleep time (min)	408 ± 70	390 ± 80	425 ± 64	405 ± 68	0.31 (-0.10 to 0.71)
Sleep efficiency (%)§	88 ± 10	86 ± 16	86 ± 8	86 ± 10	0.00 (-0.40 to 0.40)
AHI (no/hour)	39 ± 31	40 ± 28	2 (0–10)	0 (0–3)	*p*=0.006
minSaO_2 (%)	78 ± 9	78 ± 10	88 ± 6	90 ± 6	-0.33 (-0.73 to 0.08)
Non-REM sleep stage 1 & 2 (%)‖	65 ± 13	68 ± 15	53 ± 10	54 ± 10	-0.08 (-0.48 to 0.33)
Non-REM sleep stage 3 & 4 (%)‖	14 ± 9	13 ± 12	20 ± 8	22 ± 8	-0.18 (-0.58 to 0.23)
REM sleep (%)‖	21 ± 8	19 ± 7	27 ± 7	24 ± 6	0.39 (-0.03 to 0.79)

* Plus-minus values are means ± standard deviations; values with additives in parentheses are medians with interquartile ranges.
† The median treatment period from baseline until final follow-up review was 68 (interquartile range 60–96) days in the oral-appliance group and 63 (interquartile range 60–88) days in the CPAP group.
‡ Polysomnographic outcomes at follow-up review were compared by calculating effect sizes with two-sided 95% confidence intervals (effect size reported with confidence interval in parenthesis). For comparing outcomes with skewed distributions, Mann-Whitney U tests were used (with significant differences *p*-values reported).
§ Sleep efficiency is the total sleep time expressed as a percentage of the total time in bed.
‖ Sleep stages are expressed as a percentage of total sleep time.
Abbreviations: AHI = apnea-hypopnea index, CI = confidence interval, CPAP = continuous positive airway pressure, minSaO_2 = lowest oxyhemoglobin saturation during sleep, REM = rapid-eye-movement.

polysomnographic evaluation; seven required adjustment of their appliance after eight weeks of treatment. At final follow-up review, mean advancement of the mandible was 81 ± 19% of maximum advancement. Of patients using CPAP, 47 completed polysomnographic evaluation; seven required pressure adjustment after eight weeks of treatment. At final review, mean pressure was 8.1 ± 1.9 cm H_2O. The median period to final review was 68 (interquartile range 60–96) days in the oral-appliance group and 63 (interquartile range 60–88) days in the CPAP group (p>0.05).

Treatment effectiveness

Polysomnographic outcomes were available for 47 patients in each group. At final review, the CPAP group had a significantly lower AHI than the oral-appliance group (Table 2). Two patients using oral-appliance therapy had an increase in their AHI, from 15 to 17 and from 9 to 19, respectively. No other adverse events occurred. There were no significant differences in other polysomnographic outcomes at final review (Table 2).

Neurobehavioral outcomes were available for 49 patients in the oral-appliance group and 50 in the CPAP group; none was available for two patients lost to follow-up review in each group. There were no significant differences between groups at final review (Table 3).

Oral-appliance therapy was effective for 39 patients (76.5%); of the other twelve patients, eight were "nonresponsive," two were "nonadherent," and two were lost to follow-up review. In the CPAP group, treatment was effective for 43 patients (82.7%); of the other nine patients, two were "nonresponsive," five were "nonadherent," and two were lost to follow-up review. The difference in effectiveness was -6.2% and the lower boundary of the confidence interval was -21.7%, indicating that oral-appliance therapy met the criterion for non-inferiority (Table 4).

Satisfaction and treatment usage

In each group, 41 patients were "satisfied" or "very satisfied" with treatment. On the ten-point scale, patients graded their satisfaction as a mean 7.6 ± 1.9 points in the oral-appliance group and 7.4 ± 2.1 points in the CPAP group (p>0.05). There were no significant differences in reported treatment usage. Of the 49 patients completing follow-up review of oral-appliance therapy, 42 reported wearing the appliance seven nights each week (mean 6.7 ± 1.0 days); 46 wore it five or more hours each night (mean 6.9 ± 1.0 hours). Of the 50 patients completing follow-up review of CPAP therapy, 42 reported using CPAP for seven nights each week (mean 6.7 ± 0.8 days); 44 used CPAP five or more hours each night (mean 6.5 ± 1.6 hours).

Treatment effectiveness in relation to OSAHS severity

For non-severe OSAHS, treatment was effective for 21 of the 25 patients using

TABLE 3. Neurobehavioral outcomes of 103 patients treated with an oral appliance or CPAP.

Variable	Range	Direction of improvement	Baseline* Oral appliance (n = 51)
Epworth sleepiness scale	0–24	-	13 ± 6
Functional outcomes of sleep questionnaire			
- general productivity	1–4	+	3.0 ± 0.7
- social outcome	1–4	+	2.9 ± 0.9
- activity level	1–4	+	2.6 ± 0.8
- vigilance	1–4	+	2.6 ± 0.8
- intimate relationships & sexual activity§	1–4	+	2.6 ± 1.0
- total score	5–20	+	14 ± 3
Medical outcomes study 36-item short-form health survey			
- physical functioning	0–100	+	71 ± 23
- social functioning	0–100	+	66 ± 23
- role physical	0–100	+	25 (0–75)
- role emotional	0–100	+	100 (33–100)
- mental health	0–100	+	71 ± 18
- vitality	0–100	+	39 ± 19
- bodily pain	0–100	+	75 ± 27
- general health perception	0–100	+	58 ± 21
- health change	0–100	+	40 ± 25
Hospital anxiety and depression scale			
- anxiety	0–21	-	4.0 (3.0–8.0)
- depression	0–21	-	5.0 (3.0–8.0)

* Plus-minus values are means ± standard deviations, values with additives in parentheses are medians with interquartile ranges.
† The median treatment period from baseline until final follow-up review was 68 (interquartile range 60–96) days in the oral-appliance group and 63 (interquartile range 60–88) days in the CPAP group.
‡ Neurobehavioral outcomes at follow-up review were compared by calculating effect sizes with two-sided 95% confidence intervals (effect size reported with confidence interval in parenthesis). For comparing outcomes with skewed distributions, Mann-Whitney U tests were used (with significant differences *p*-values reported).
§ At baseline, this item was completed by 48 patients in the oral-appliance group and 47 patients in the CPAP group. At follow-up review, this item was completed by 47 patients in the oral-appliance group and 46 patients in the CPAP group.

Baseline*	Follow-up review*		Difference in effect at follow-up review: effect size (95% CI) or p-value‡
CPAP (n = 52)	Oral appliance (n = 49)†	CPAP (n = 50)†	
14 ± 6	7 (2–10)	6 (4–12)	NS
3.0 ± 0.8	3.5 ± 0.6	3.5 ± 0.7	0.10 (-0.30 to 0.49)
3.0 ± 1.0	3.6 ± 0.7	3.6 ± 0.7	0.01 (-0.38 to 0.41)
2.7 ± 0.8	3.3 ± 0.6	3.3 ± 0.7	-0.12 (-0.52 to 0.27)
2.4 ± 0.9	3.2 ± 0.8	3.3 ± 0.8	-0.08 (-0.47 to 0.32)
2.9 ± 1.0	2.9 ± 1.1	3.1 ± 1.1	-0.21 (-0.61 to 0.20)
14 ± 4	17 ± 3	17 ± 3	-0.05 (-0.44 to 0.34)
67 ± 24	79 ± 22	81 ± 19	-0.09 (-0.48 to 0.31)
69 ± 24	80 ± 21	79 ± 21	0.05 (-0.34 to 0.45)
25 (0–100)	100 (25–100)	100 (44–100)	NS
100 (33–100)	100 (67–100)	100 (59–100)	NS
68 ± 18	77 ± 17	75 ± 16	0.15 (-0.24 to 0.55)
39 ± 22	64 ± 21	61 ± 20	0.12 (-0.27 to 0.52)
78 ± 26	80 ± 27	82 ± 24	-0.10 (-0.49 to 0.30)
55 ± 23	65 ± 21	61 ± 23	0.21 (-0.19 to 0.60)
38 ± 25	74 ± 27	74 ± 26	0.02 (-0.38 to 0.41)
5.0 (3.0–8.0)	3.0 (2.0–6.5)	3.5 (1.8–7.0)	NS
7.0 (4.0–10.0)	2.0 (1.0–7.0)	3.0 (1.0–8.5)	NS

Abbreviations: CI = confidence interval, CPAP = continuous positive airway pressure, NS = not significant.

oral-appliance therapy (84.0%) and 20 of the 25 patients using CPAP (80.0%). Within this subgroup, oral-appliance therapy met the criterion for non-inferiority (Table 4). For severe OSAHS, oral-appliance therapy did not meet the criterion for non-inferiority; oral-appliance therapy was effective for 18 of 26 patients (69.2%) and CPAP for 23 of 27 patients (85.2%) (Table 4).

Discussion

This randomized parallel trial indicates that an oral appliance is not inferior to CPAP for effective treatment of OSAHS. The difference in effectiveness (6.2%) met the predefined criterion for non-inferiority. Unlike studies showing greater improvement in oxyhemoglobin saturation with CPAP than with oral appliances,[9,10] polysomnography showed no significant differences except for the AHI. Non-inferiority of oral-appliance therapy was supported by a lack of significant differences in neurobehavioral outcomes, confirming findings in most reports comparing these therapies.[9,10] Patients' satisfaction and treatment usage were similar in the two groups.

Although both therapies produced substantial improvement in most polysomnographic and neurobehavioral outcomes evaluated, oral-appliance therapy was primarily successful for patients with non-severe disease. For patients with severe OSAHS, CPAP was superior. This finding may explain why the AHI was relatively higher in the oral-appliance group at final review.

Our results show a relatively more positive effect of oral-appliance therapy than those in previous studies. Variables correlating with increased effectiveness of oral appliances have included being female,[20] being young,[21] no obesity,[21] and non-severe disease.[20,22] However, our patients, while demographically comparable to those in most of these studies,[9,10] were generally more obese and had more severe disease. Therefore, other factors must explain the difference. First, effectiveness of oral appliances usually increases with greater advancement of the mandible, and mean mandibular advancement in our study was generally more extended than in most previous studies.[10] Secondly, patients could adjust mandibular advancement in increments—a design speculated to increase therapeutic effectiveness.[23] However, studies in which different oral appliances that reposition the mandible were compared have not demonstrated differences in physiological outcomes as a result of appliance design.[10] Thirdly, our definition of "effective treatment" comprised a criterion based on polysomnographic and clinical outcomes. Treatment was considered effective when the AHI was <5 or the baseline index value was reduced by at least 50% to a value of <20 in a patient free of symptoms while using therapy. If the rigid criterion of an AHI <5 defines effective treatment, our data suggest non-inferiority of oral-appliance therapy only in patients with non-severe OSAHS (see

TABLE 4. Proportions of effective treatments with an oral appliance or with CPAP.

	Oral appliance*	CPAP*	Difference (95% CI)†
Effective treatment‡			
Total population (n = 103)	39 / 51 (76.5%)	43 / 52 (82.7%)	-6.2% (-21.7 to 9.4)
Non-severe OSAHS (n = 50)	21 / 25 (84.0%)	20 / 25 (80.0%)	4.0% (-17.7 to 25.4)
Severe OSAHS (n = 53)	18 / 26 (69.2%)	23 / 27 (85.2%)	-16.0% (-37.1 to 6.8)

* Values are the number of effective treatments divided by the total number of patients in the treatment group. Values in parentheses are the percentages of effective treatments.
† Differences in effectiveness between oral-appliance and CPAP therapy (oral-appliance minus CPAP therapy) are reported as percentages with two-sided 95% confidence intervals in parenthesis.
‡ Treatment was considered effective when the apnea-hypopnea index either was <5 or showed "substantial reduction," defined as reduction in the index of at least 50% from the baseline value to a value of <20 in a patient who had no symptoms while using therapy.
Abbreviations: CI = confidence interval, CPAP = continuous positive airway pressure, OSAHS = obstructive sleep apnea-hypopnea syndrome.

Appendix 2). However, all previous studies comparing oral-appliance and CPAP therapy used an AHI <10 as the criterion for effective treatment.[9,10] Had we used that criterion for our patients with a baseline index ≥10, we would have obtained similar results in terms of effectiveness of oral-appliance therapy when compared with the criterion for effectiveness used in this study (see Appendix 2). We suggest that the relatively more positive effect of oral-appliance therapy we observed is best explained by greater mandibular advancement.

Three factors distinguish our study from previous trials comparing these therapies. First, we included patients with severe OSAHS. Although oral appliances tend to decrease in effectiveness with increasingly severe disease,[24] recent studies suggest a future role for oral-appliance therapy of severe OSAHS.[22,25] By including patients with severe disease, we report results from a population covering the entire disease spectrum. Secondly, we used a parallel study design rather than a crossover design.[9,10] Crossover studies may not permit derivation of an unbiased estimate of treatment effect.[26] Moreover, carry-over effects and failure to return to baseline status may be anticipated when comparing oral-appliance and CPAP therapy in crossover studies. Thirdly, we evaluated the effectiveness of treatment with an intention-to-treat analysis. As only one previous study appropriately used an intention-to-treat analysis,[9] most reported trials may have incorporated bias when comparing these therapies.[10]

It could be reasoned that the definition of effectiveness used in this study is not compatible with the goals of optimal CPAP-titration. Although, treatment was always aimed at attaining an AHI <5, this could not always be accomplished due

to limitations in mandibular protrusion with oral-appliance therapy or pressure intolerance with CPAP. Patients with an AHI ≥5 at follow-up review for whom treatment was nonetheless considered effective had an index in the range of five to 20. These patients may be at risk for a cardiovascular event.[27] This situation applied to ten patients in the oral-appliance group and three in the CPAP group, all with severe OSAHS (see Appendix 2). Evidence that patients with severe OSAHS could be at particular cardiovascular risk may support primary oral-appliance therapy only for patients with non-severe disease.[3,4] As cardiovascular outcomes exceeded the scope of our study, this possibility must be substantiated.

Two factors affect the external validity of our results. Approximately 25% of eligible patients were excluded because of edentulism, the main reason disqualifying patients from oral-appliance therapy.[12] Additionally, 10% of eligible patients were excluded because of a history of severe cardiac or pulmonary disease; oral-appliance therapy often requires a longer adjustment period than CPAP, and for those patients the delay is undesirable. These factors must be considered in overall evaluations of oral-appliance therapy.

We believe the non-inferiority margin we used met the two major requisite conditions:[28] that the smallest expected effect of a control treatment (*i.e.*, CPAP) over placebo should exceed the non-inferiority margin;[2] and that the non-inferiority margin should not exceed the difference between active treatments judged clinically important. Most previous studies comparing these therapies showed differences in effectiveness ≥25%,[9,10] and all but one concerned only non-severe OSAHS patients.[29] We also accounted for the variability in the difference of effectiveness because we used the lower boundary of the corresponding confidence interval to decide on non-inferiority. Moreover, oral-appliance and CPAP therapy are reversible treatments that can be evaluated by polysomnography and discontinued readily should treatment fail. Considering these factors, we deemed the non-inferiority margin of 25% appropriate.

A potential limitation of our study was that the subgroup analysis showing that oral-appliance therapy was effective primarily in patients with non-severe disease was not based on a power calculation. Another was that adherence to therapy was assessed only with self-reports because oral-appliance usage cannot be assessed covertly in any reliable way. Self-reports usually overestimate the use of treatment by one hour per night.[30] When we adjusted for this factor, adherence to treatment was still adequate.[31] Undoubtedly a factor in our study was that a placebo effect may account for some changes in neurobehavioral outcomes,[2] especially among patients with non-severe OSAHS.[7,9] The placebo effect, however, has been demonstrated to affect the outcome of oral-appliance and CPAP therapy to a similar extent.[9] Additionally, two patients using oral-appliance therapy had

an increase in their AHI. These factors emphasize that effects of oral-appliance therapy must always be evaluated with polysomnography.

As obesity-related OSAHS has become increasingly prevalent,[32] the concept of CPAP as preferred primary therapy is being reassessed. Several authors,[10,33] although not all,[34] advocate oral-appliance therapy for non-severe disease—a view supported by disappointing results obtained with CPAP therapy for non-severe or asymptomatic OSAHS.[6,7] Those findings are reinforced by our study.

This randomized parallel trial showed that an oral appliance was not inferior to CPAP for the effective treatment of OSAHS. However, CPAP was more effective in improving the AHI and was superior to oral-appliance therapy for patients with severe disease. As these findings suggest that oral-appliance therapy is indicated primarily for patients with non-severe OSAHS, we recommend it be considered, alongside CPAP therapy, as treatment for patients with mild to moderate disease. The patient's preferences and the cost should be considered in choosing between treatments. Among patients with severe disease, oral-appliance therapy should be considered for patients unwilling or unable to tolerate CPAP.

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