Oral appliance treatment in moderate and severe obstructive sleep apnoea patients non-adherent to CPAP

K. GJERDE*, S. LEHMANN*,†, M. E. BERGE*,‡, A.-K. JOHANSSON§ & A. JOHANSSON*,‡

*Department of Thoracic Medicine, Center for Sleep Medicine, Haukeland University Hospital, Bergen, †Department of Clinical Science, Section for Thoracic Medicine, Faculty of Medicine and Dentistry, University of Bergen, Bergen, ‡Department of Clinical Dentistry – Prosthodontics, Faculty of Medicine and Dentistry, University of Bergen, Bergen, and §Department of Clinical Dentistry – Cariology, Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway

SUMMARY The aim of this retrospective study was to evaluate the effect of individually adjusted custom-made mandibular advancement device/oral appliance (OA) in treatment of patients with moderate and severe obstructive sleep apnoea (OSA), who were non-adherent to continuous positive airway pressure (CPAP) therapy. During 2007-2013, 116 patients with moderate (n = 82) and severe (n = 34) OSA non-adherent to CPAP treatment were referred for dental management with an individually adjusted OA at a specialist sleep clinic. Ten of the participants (8.6%) were lost to follow-up, leaving the data set to consist of 106 patients (71 men/35 women, mean age 57 year, range 28-90). Nocturnal respiratory polygraphic recordings were performed at baseline and follow-up. Average time between baseline polygraphy and follow-up was 12 months. A successful OA treatment outcome was based on polygraphy at the follow-up and divided into three groups: 1 = AHI <5; 2 = 5 ≤ AHI <10 and >50% reduction in baseline AHI; and 3. >50% reduction in baseline AHI. If there was a ≤50% reduction in baseline AHI at the follow-up, the treatment was considered as a failure. The overall treatment success rate was 75%. There was no significant difference in success rates between patients in the moderate and severe categories (69% and 77%, respectively). Low oxygen saturation (SpO₂ nadir) had a high predictive value for OA treatment failure. OA treatment of patients non-adherent to CPAP is efficient and especially promising for the severe OSA group who are at greatest risks for developing serious comorbidities, if left untreated.

KEYWORDS: continuous positive airway pressure, mandibular advancement, medical device, obstructive sleep apnoea, oximetry, somnography

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Introduction

Obstructive sleep apnoea (OSA) is a common disorder, although prevalence varies widely in the literature. When using strict diagnostic criteria (full, attended nocturnal polysomnography), a recent systematic review reported prevalence among community-screened adult patients to range from 2% to 14%. The prevalence varied depending on the cut-off value of apnoea hypopnoea index (AHI), and for ≥5 events h⁻¹ and ≥15/h, the prevalence was 14% and 6%, respectively (1). Similar frequencies have been found in a large Norwegian population-based study where the estimated prevalence of OSA was 16% for AHI ≥ 5 and 8% for AHI ≥ 15 (2).

Patients suffering from moderate and severe OSA exhibit a range of comorbidities including cardiovascular disease, metabolic syndrome as well as depression. If their OSA is left untreated, the risk for all-cause mortality increases (3–6). Continuous positive airway pressure (CPAP) is a common treatment for OSA on the basis of its efficacy using objective mea-
sures (7). Despite its well-known benefits, adherence is generally poor and its use is often felt bothersome with little evidence on how its utility might be improved (8). It has therefore been deemed important to identify better tolerated treatment options (4).

Oral appliance (OA) treatment has long been used as measure against snoring and OSA. OA is in general inferior to CPAP in terms of reducing OSA parameters based on polygraphy especially in severe OSA. However, the greater efficacy of CPAP may not necessarily lead to a superior health outcome compared to treatment with OA. In this regard, it has been reported that OA adherence is in the range of 76% to 95%, which exceeds that of CPAP of which vary between 30% and 80% (9, 10). In contrast to CPAP, where data on adherence can be retrieved from device software, adherence to OA is usually self-reported and less accurate. However, in a recent report where adherence was measured via a built-in thermistor in the OA, 1-year results demonstrated a mean use rate of 6.4 ± 1.7 h per night in continuing users and a regular user rate of 83% (11). Consequently, OA adherence may actually be higher than for CPAP in treatment of OSA forming the basis for the suggestion of similar health outcomes on a group level for the two treatment modalities (12).

Oral appliance treatment is considered to be equally effective as CPAP in mild to moderate sleep apnoea, if titrated sufficiently (12–14). In severe OSA, CPAP is always the first-line treatment because it has a well-documented efficacy in reducing apnoeic events. Nevertheless, some studies report promising results even when using OA in patients with severe OSA (14–16). In addition, reports on antihypertensive effects and reduced cardiovascular mortality with OA treatment indicate a similar outcome to that of CPAP (17, 18).

The major risk groups for health complications among OSA patients are those with moderate and especially severe disease. Considering the high non-adherence rate to CPAP as well as the diverging results of surgical interventions (19), it is important to explore other conservative treatment alternatives more closely.

The aim of this study was to evaluate the effect of OA treatment in patients with moderate and severe OSA who were non-adherent to CPAP and to assess factors predicting treatment success/failure. Our hypothesis was that OA treatment was superior in patients with moderate compared to severe OSA.

### Materials and methods

The baseline diagnosis of OSA and follow-up investigations were performed by respiratory medicine or ENT specialists at the Departments of Thoracic Medicine and Otolaryngology at Haukeland University Hospital, Bergen, Norway, supported by a medical examination that included home respiratory polygraphy (*). Sleep recordings were analysed by experienced respiratory medicine, and ENT specialists and scoring rules were in accordance with the 2007 American Academy of Sleep Medicine manual (20). The criteria for mild OSA were AHI 5–14.9, for moderate OSA ≥15–29.9 and for severe OSA AHI ≥30 (21).

During the years 2007 to 2013, 127 consecutive patients were identified with a baseline diagnosis of moderate or severe OSA who had received OA treatment due to non-adherence to CPAP. Non-adherence to CPAP treatment was defined as less than 5 h usage/night during a period of at least three months (22, 23). All OA patients were treated by dentists with extensive training and experience in Dental Sleep Medicine.

Within the selected group of OA-treated OSA patients previously non-adherent to CPAP, inclusion criteria comprised subjects who had had a sleep study performed at baseline before CPAP and who attended the follow-up appointment including new sleep study using the OA (n = 116). The polygraphy recordings included AHI, oxygen desaturation index (ODI) and oxygen saturation parameters: mean (SpO2 mean), nadir (SpO2 nadir) and percentage time below 90% (SpO2 <90%). Data on body mass index (BMI), previous snoring/OSA surgery, smoking habits and comorbidities, that is hypertension, other cardiovascular diseases, diabetes, were retrieved from the patients’ medical records.

### Success criteria

A successful OA treatment outcome was based on polygraphy at the follow-up and divided into three groups based on the following criteria: 1 = AHI < 5; 2 = 5 ≤ AHI < 10 and more than 50% reduction in baseline AHI; and 3 = AHI > 50% reduction in base-
line AHI. If there was a ≤ 50% reduction in baseline AHI at the follow-up, the treatment was considered as a failure (Table 1).

**Oral appliance treatment**

Maxillary and mandibular impressions (†) and an occlusal protrusive wax or silicone index using George Gauge bite fork™ (‡) were made. The baseline fitting index of the OA was made at 50–80% of maximum protrusive capacity. The appliances were custom-made, and in the majority of patients a dual-block adjustable type (n = 89) (§) but in a few cases a generic-type non-adjustable mono-block appliance (n = 17) was delivered. The latter type of appliance was in several cases switched to the adjustable type in order to alleviate titration. Approximately 4–8 weeks after insertion of the appliance, the first evaluation of subjective effect was performed, and if not satisfactory, titration of the appliance was carried out. Titrations were performed until the patient reported a positive subjective effect (e.g. reduced sleepiness/snor- ing improved sleep) of the OA or until all possible adjustments were exhausted, after which follow-up objective overnight polygraphy was carried out.

**Statistical analyses**

Differences between the moderate and severe OSA groups and between treatment outcome groups (success or failure) were tested by means of the Mann–Whitney U-test. Wilcoxon signed rank test was used to analyse intra-individual differences between baseline and follow-up regarding AHI, ODI and oxygen saturation parameters. Logistic regression analysis was performed with the most strict treatment success criteria applied as dependent variable at the follow-up (success: AHI < 5, failure: AHI ≥ 5). The following criteria were used for selection of independent variables: (i) theoretical relevance and (ii) significant findings according to Spearman correlation analysis between the dependent and the recorded baseline variables. All independent variables were dichotomized before entered into the regression model. Unadjusted and adjusted odds ratios were calculated. Additionally, forward conditional method was calculated. Analyses to account for missing values were performed using multiple imputations. A P-value less than 0.05 was considered statistically significant.

**Results**

Of the 116 participants, 10 patients (8.6%) were lost to follow-up (three died and seven did not show up for their follow-up appointment). Thus, the total data set in the study included 106 patients (71 men, 35 women, mean = 57 year, range 28–90) who all had both a baseline and a follow-up polygraphy, except for two patients who reported non-adherence at the follow-up (recorded as failures). Seventy-four patients were diagnosed as having moderate OSA, and 32 patients had severe OSA. At baseline, there were no significant differences regarding age, BMI, gender, smoking habits and recorded comorbidities between the two severity groups (Table 2). Average time between the baseline sleep study and follow-up was 12 months (range 2–60 months, s.d. 11).

Baseline and follow-up AHI, ODI and SpO2 parameters (average, nadir and percentage sleep time below 90%) in the two groups are shown in Table 3. The moderate group showed a significantly lower AHI (P < 0.01) and ODI (P = 0.01) at follow-up compared to the severe group. The average decrease in AHI units between baseline and follow-up was 15.8 and 32.2 in the moderate and severe group, respectively. The decrease in AHI units was significantly greater in the severe compared to the moderate group (P < 0.001). The percentage AHI decrease was however about the same in both OSA groups; moderate 76% and severe 79%, and not significantly different.
**Table 2.** Baseline characteristics of the population studied: age, BMI, gender (males), commenced surgery (for snoring/OSA), smoking (present or previous) and comorbidities (smoking, hypertension, cardiovascular disease, diabetes) in the moderate \((n = 74)\) and severe \((n = 32)\) OSA groups

|                  | Moderate OSA |                                            | Severe OSA |                                            |
|------------------|--------------|---------------------------------------------|------------|---------------------------------------------|
|                  | Age (year) (s.d.) | BMI (s.d.) | Male gender, n (%) | Surgery, n (%) | Smoking, n (%) | Hypertension, n (%) | Cardiovascular, n (%) | Diabetes, n (%) |
|                  | 57 (12-0) | 28-2 (4-2) | 46 (62) | 32 (43) | 27 (37) | 34 (46) | 13 (18) | 8 (11) |
|                  | NS | NS | NS | NS | NS | NS | NS | NS |
|                  | 57 (12-2) | 29-5 (4-3) | 25 (78) | 18 (56) | 13 (41) | 18 (56) | 7 (22) | 1 (3) |

NS, not significant; BMI, body mass index.

**Table 3.** Apnoea hypopnoea index, ODI and oxygen saturation at baseline and follow-up in the moderate \((n = 74)\) and severe \((n = 32)\) OSA groups

|                  | Moderate OSA |                                            | Severe OSA |                                            |
|------------------|--------------|---------------------------------------------|------------|---------------------------------------------|
|                  | AHI (s.d.) | ODI (s.d.) | SpO2 mean (s.d.) | SpO2 nadir (s.d.) | <90% | AHI (s.d.) | ODI (s.d.) | SpO2 mean (s.d.) | SpO2 nadir (s.d.) | <90% |
|                  | 21-2 (4-0) | 17-4 (8-0) | 93.4 (1-5) | 80.0 (5-9) | 8.0 (9-3) | 41-4 (9-9) | 35-1 (14-2) | 92.8 (2-5) | 76-8 (4-8) | 19-1 (17-8) |
| Follow-up        | NS          | NS       | NS          | NS          | NS          | NS          | NS          | NS          | NS          | NS |
|                  | 8-1 (7-7) | 7-8 (7-1) | 93-4 (1-6) | 83-1 (5-6) | 6-5 (11-3) | 17-4 (15-7) | 14-9 (13-7) | 92-6 (1-7) | 80-6 (6-5) | 13-8 (17-2) |

AHI, apnoea hypopnoea index; ODI, oxygen desaturation index; SpO2 mean, mean oxygen saturation level; SpO2 nadir, lowest oxygen saturation level; SpO2 <90%, percentage of total sleep time with oxygen saturation level below 90%.

\*P < 0.5; \**P < 0.01; \***P < 0.001

**Table 4.** Apnoea hypopnoea index at follow-up and reduction in AHI units between baseline and follow-up in the moderate and severe OSA groups divided into successful and failed OA treatment

|                  | Moderate OSA |                                            | Severe OSA |                                            |
|------------------|--------------|---------------------------------------------|------------|---------------------------------------------|
|                  | n | Mean | Range | s.d. |
|                  | AHI at follow-up | | | |
| Success\*        | 57 | 5-0 | 0 to 13-5 | 3-1 |
| Decrease in AHI units | 57 | 15-8 | 8-5 to 29-0 | 4-2 |
| Percentage reduction in AHI between baseline and follow-up | 57 | 76 | 52-3 to 100-0 | 13-8 |
| Failure\†        | 15 | 19-8 | 10-5 to 36-9 | 8-4 |
| Decrease in AHI units | 15 | 2-2 | -14-9 to 11-4 | 9-0 |
| Percentage reduction in AHI between baseline and follow-up | 15 | 8 | -71-4 to 47-9 | 41-3 |
|                  | AHI at follow-up | | | |
| Success\*        | 22 | 9-1 | 0 to 24-6 | 7-2 |
| Decrease in AHI units | 22 | 32-2 | 21-4 to 49-7 | 8-1 |
| Percentage reduction in AHI between baseline and follow-up | 22 | 79 | 50-8 to 100-0 | 14-2 |
| Failure\†        | 10 | 35-7 | 17-5 to 67-7 | 13-7 |
| Decrease in AHI units | 10 | 6-1 | -6-0 to 18-2 | 7-6 |
| Percentage reduction in AHI between baseline and follow-up | 10 | 15 | -19-4 to 44-0 | 20-8 |

AHI, apnoea hypopnoea index.

\*Success criteria: 1, 2 or 3.

\†Failure criterion: ≤50% reduction in baseline AHI at the follow-up (Table 1).

The treatment success rate with the criterion 3 applied (>50% reduction in AHI) was 75% for the whole group (79/106 patients), comprising 77% and

between the two groups (Table 4). Self-reported adherence rate of the OA at the follow-up was 98% (104/106 patients).
69% of the moderate and severe groups, respectively. AHI < 5 (criterion 1) was recorded in 43% of patients in the moderate and 25% in the severe group, while it was 38% for both groups together. The combined figures for criteria 1 and 2 (5 ≤ AHI < 10 and more than 50% reduction in baseline AHI) were 70% and 50%, for the moderate and severe groups respectively. There was no significant difference in treatment outcome between the moderate and severe groups using the above-mentioned success criteria (Fig. 1). AHI at baseline and at follow-up after OA treatment in the successful group (criterion 1, 2 or 3, n = 79) and in the failure group (≤ 50% reduction in baseline AHI at follow-up, n = 25) for each participant is shown in Fig. 2a and b.

In bivariate analyses between treatment outcome (success or failure) and baseline parameters, the success group, including both moderate and severe OSA, had lower prevalence of cardiovascular disease (P < 0.05), and a tendency for lower age and BMI
Baseline AHI or gender did not differ between success and failure groups.

The outcome on the univariate evaluation of factors potentially predicting treatment failure is shown in Table 5, and the results from the logistic regression analyses are presented in Table 6. In the unadjusted analyses, all selected independent variables, except gender and SpO2 <90%, were significantly correlated to the success criteria applied, while in the fully adjusted analyses none of the variables predicted treatment failure/success. When applying the forward conditional method, SpO2 nadir turned out to be significant (OR = 0.36, p = 0.001) (Table 6); Nagelkerke R2 was 0.18 and the sensitivity (correctly classified successfully treated) and specificity (correctly classified failures) was 37% and 93%, respectively. The predicted probability for all variables and for SpO2 nadir is illustrated by the receiver operating characteristic (ROC) curve where the area under the curve (AUC) was 0.66 for SpO2 nadir while AUC for all the variables combined was 0.79 (Fig. 3).

The 10 patients lost to follow-up did not differ significantly compared to those who completed the study regarding age, gender, BMI, diagnosis (severe or moderate OSA), baseline AHI/ODI, snoring/OSA surgery, smoking habits, hypertension/cardiovascular diseases and diabetes.

### Discussion

This retrospective study of 106 moderate and severe OSA patients non-adherent to CPAP showed an overall success rate of 75% using the criterion 3 (> 50% reduction in baseline AHI) (Table 1). This success rate compares favourably with that reported in recent reviews (9, 24), although most previous studies only included patients with mild to moderate OSA. Using the success criteria applied in this study, comparison of treatment outcome between the moderate and severe group showed no significant differences, albeit that a numerically higher proportion of patients reached AHI < 5 in the moderate group. What constitutes clinically acceptable success criteria for OSA treatment is much debated (9, 25). Although the moderate group had a significantly lower AHI (mean = 5) compared to the severe group (mean = 9) at follow-up, the latter experienced a considerably higher decrease in AHI units compared to the former (32 vs. 16 units). The clinical implication of this is unclear, but one may speculate that such a dramatic decrease of apnoeic events in the severe group may have a positive impact on health status even if not reaching the level of AHI < 5.

In category 2 success, it was required a 50% reduction in baseline AHI in addition to be below AHI 10 at follow-up. The reason for refinement of the criteria was that it was desired not only to appraise the cut-off point of 10 but also to make sure that the reduction had the commonly stated opinion that a 50% reduction in baseline AHI has a clinical benefit in the treatment of sleep apnoea patients (Table 1). There are only a few studies reporting on OA treatment of severe OSA. In this regard, and using similar criteria (> 50% reduction in baseline AHI) and follow-up time as in the present study, severe OSA treated with OA showed 44% (26) and 58% (14) success at 1-year follow-up. The higher success rate in this study (67%) may have several explanations, for example study design (retrospective study bias) and participant selections. When the most strict treatment success criteria

| Table 5. Correlations between success (AHI <5 at follow-up, n = 40) or failure (AHI ≥5 at follow-up, n = 66) and background variables and their dichotomizations |
|---------------------------------------------------------------|
| **Baseline variables** | **Dichotomization** | **Success AHI <5** |
|------------------------|---------------------|-------------------|
| Gender                 | Man                 | 0.07              |
|                        | Woman               | 0.05 (NS)         |
| Age                    | ≤69 year            | 0.20              |
|                        | >69 year            | 0.04              |
| BMI                    | ≤27.5               | 0.23              |
|                        | >27.5               | 0.02              |
| AHI                    | 15–25               | 0.20              |
|                        | > 25                | 0.04              |
| ODI                    | ≤20                 | 0.33              |
|                        | >20                 | 0.001             |
| SpO2 nadir             | <85%                | 0.38              |
|                        | ≥85%                | 0.001             |
| SpO2 <90%              | ≥10%                | 0.24              |
|                        | <10%                | 0.04              |
| Cardiovascular/        | No                  | 0.26              |
| diabetes disease       | Yes                 | 0.007             |

R, Spearman’s rho; P, significance level; AHI, apnoea hypopnoea index; ODI, oxygen desaturation index; SpO2 mean, mean oxygen saturation level; SpO2 nadir, lowest oxygen saturation level; SpO2 <90%, percentage of total sleep time with oxygen saturation level below 90%.
were applied (AHI<5 at follow-up polygraphy), a number of baseline variables were significantly correlated to success in the unadjusted regression model. The anthropometric and polygraphic variables which have been reported as good predictors of successful OA treatment (9) are affirmative to those found in our unadjusted regression analyses (Table 6). In the adjusted model, none of the included variables turned out to be significant which may be explained of the inherent cross-correlations that exist between them and a reduced power in the analyses due to many variables in the model. However, in the final model (using the forward conditional method), only SpO2 nadir remained in the model with OR 0·36 demonstrating a low sensitivity (40%) but a high specificity (93%). It has been stated that more research is needed to define the patients who will benefit from MAD treatment (9) and it would also be of significance to identify those who do not. Interpretation of the findings from the regression analyses may be that low oxygen saturation in OSA is an important predictor for OA failure in patients non-adherent to CPAP. This preliminary finding needs to be corroborated in future studies.

Patient categories with deep oxygen desaturations in conjunction with breathing cessations are typically those with pre-existing chronic diseases of the chest affecting gas exchange, such as chronic obstructive pulmonary disease (COPD), congestive heart failure and pulmonary hypertension. There is good evidence that oxygenation deficits rather than breathing cessations per se predicts mortality in patients with OSA (27). Furthermore, survival effects of positive airway pressure treatment in patients with OSA with chronic lung disease are documented (28), whereas research on OA treatment outcomes in COPD is lacking. The
current results therefore support treatment with positive airway pressure methods, rather than OA treatment, in patients with severe oxygen desaturations from the diagnostic sleep studies, independent of OSA severity judged by the AHI only. However, it has to be remembered that all participants were PAP-non-adherent and findings may not be generalized to the treatment decisions in treatment-naive patients with OSA.

Our definition of PAP non-adherence (less than 5 h per night over 3 months treatment) is based on publications demonstrating clinical meaningful responses on sleepiness, daily functioning and reductions in blood pressure in patients achieving at least 5–6 h adherence to CPAP per night (22, 23). In the current study, all participants have been treated with auto-CPAP devices, which automatically adjust the delivered pressures needed to avoid breathing cessations. No patients have been manually titrated in an overnight laboratory setting. Subjects with large desaturations at initial sleep study, who should be encouraged to PAP treatment despite adherence problems, could, when other causes of non-adherence have been excluded, undergo manually PAP titration in a sleep laboratory to ensure better treatment tolerance. In cases of CPAP non-adherence, other forms of pressure support such as bilevel or adaptive servo-ventilation are often better accepted by subjects with chronic heart and lung disease.

The drawbacks of this study are several, and maybe the largest weakness is that we did not obtain adequate data related to subjective outcome of the treatment. Epworth Sleepiness Scale was recorded, but not consistently so in all instances. Details of adherence, such as number of nights and total hours of usage, to OA treatment was neither assessed which is another weakness but of the total of 116 patients who were prescribed OA treatment only two were recorded as non-adherent at the follow-up. Patients non-adherent to CPAP treatment are found to exhibit many barriers against its usage (29), and some of these may well be applicable to the use of an OA as well, although was apparently not so considering the seemingly high self-reported adherence of 98%.

Considering that the enrolled patients in this study were failures with the gold standard treatment for OSA (CPAP), we conclude that our results are very promising and especially so for severe OSA patients who are at greatest risks for serious medical consequences, if untreated. Low oxygen saturation (SpO2 nadir) had a high predictive value for OA treatment failure irrespective of baseline AHI. Limited to the success criteria applied and to our surprise, the hypothesis that OA treatment is superior in patients with moderate compared to severe OSA was rejected. Future prospective and well-designed studies are warranted in order to confirm the findings from this study.

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Ethical approval
The Regional Ethical Committee of Western Norway deemed the project not to require a formal ethical approval (protocol no: 2009/1229).

Conflict of interest
None.
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Correspondence: Anders Johansson, Department of Clinical Dentistry – Prosthodontics, Faculty of Medicine and Dentistry, University of Bergen, Post Box 7800, 5009 Bergen, Norway. E-mail: Anders.Johansson@uib.no