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Original Article

ORIGINAL ARTICLE

Health outcomes of continuous positive airway pressure versus mandibular advancement device for the treatment of severe obstructive sleep apnea: an individual participant data meta-analysis

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Abstract

Study Objectives: The impact of therapy with continuous positive airway pressure (CPAP) and mandibular advancement device (MAD) has not been directly compared in patients with severe obstructive sleep apnea (OSA). The purpose of this individual participant data meta-analysis was to compare the treatment effects of CPAP and titratable MAD on sleepiness, quality of life, sleep-disordered breathing severity, and sleep structure in patients with severe OSA.

Methods: Randomized controlled trials (RCTs) that included severe OSA patients were identified in order to compare the impact of the two treatments. Individual data from severe OSA patients were extracted from the databases and pooled for analysis.

Results: Of the seven studies identified, three crossover RCT and one parallel-group RCT corresponding to 151 patients and 249 observations (125 in the CPAP treatment arm and 124 in the MAD treatment arm) were included in the analysis. Titratable MAD had a similar impact to CPAP on major patient-centered outcomes (sleepiness and quality of life). CPAP was more effective in reducing AHI and ODI. However, the two treatments had a similar impact on sleep structure with an increase of N3 and REM sleep. Finally, treatment adherence and preference were largely in favor of MAD.

Conclusion: This meta-analysis suggests that MAD represents an effective alternative treatment in severe OSA patients intolerant to CPAP or who prefer alternate therapy.

Statement of Significance

Mandibular advancement device therapy (MAD) is the main alternative therapy for OSA. Numerous trials and meta-analyses have compared CPAP and MAD on various OSA outcomes. However, none of the previously published studies have compared CPAP and MAD exclusively in patients with severe OSA. In the present work, individual data of severe OSA patients were extracted from previously published RCTs comparing CPAP and MAD. Titratable MAD and CPAP had a similar impact on major patient-centered outcomes (sleepiness and quality of life) and sleep structure while CPAP was more effective in reducing AHI and ODI. However, treatment adherence and preference were largely in favor of MAD treatment. This meta-analysis suggests that MAD represents an effective alternative treatment option in all OSA patients, including those with severe OSA.

Key words: sleep apnea; mandibular advancement device; continuous positive airway pressure

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Clinical trials

- Treatment of Sleep Apnea Syndrome With nCPAP Versus Oral Appliance; https://www.clinicaltrials.gov/ct2/show/NCT00152672?term=NCT00152672&draw=2&rank=1; NCT00152672
- Randomised controlled trial of the effect of mandibular advancement splint (MAS) versus positive airway pressure (PAP) therapy on blood pressure in obstructive sleep apnoea; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=82021&isReview=true; ACTRN 12607000289415.
- Oral Appliance Therapy in Obstructive Sleep Apnea; https://www.clinicaltrials.gov/ct2/show/NCT00950495?term=NCT00950495&draw=2&rank=1; NCT00950495
- Effektivität der OSA-Behandlung mittels MAD- und CPAP-Therapie bezüglich der autonomen Funktion am Tage; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00007772; DRKS00007772

Introduction

Mandibular advancement device (MAD) therapy has emerged as the main alternative therapy for obstructive sleep apnea (OSA). Numerous randomized control trials (RCT) have demonstrated a reduction of the apnea/hypopnea index (AHI) and improvement of major health outcomes, including daytime sleepiness, quality of life (QoL) or blood pressure with MAD therapy [1]. Several RCTs and meta-analyses have compared MAD to continuous positive airway pressure (CPAP), the gold standard treatment, in parallel or crossover study designs [2–5]. MAD is generally less effective in decreasing AHI than CPAP, but is usually associated with higher adherence. Finally, both treatments have been shown to have a similar impact on major clinical outcomes, including sleepiness, QoL, and cardiovascular outcomes.

The RCTs that have compared these two treatments have different designs, different inclusion criteria and used different MAD devices. Some studies only included patients with mild-to-moderate OSA, while others included patients with moderate-to-severe OSA. Of note, none of the studies compared CPAP and MAD exclusively in severe OSA patients. This gap in our knowledge has led to discrepancies regarding the use of MAD for the treatment of OSA according to different clinical guidelines around the world. The joint guideline of the American Academy of Sleep Medicine (AASM) and American Academy of Dental Sleep Medicine (AADSM) is silent on OSA severity, and recommends considering prescription of MAD for patients with OSA who are intolerant of CPAP therapy or who prefer alternate therapy [6]. In the 2015 guidelines, it was acknowledged that most of the studies included in the retained statement did not provide sub-analyses of results based on different levels of OSA severity. These recommendations, therefore, do not provide guidance for treating OSA patients with specific severity levels [6]. On the other hand, the most common statement from scientific societies, including the European Respiratory Society (ERS), is to consider MAD as an appropriate first-line therapy for patients with mild-to-moderate OSA with minimal daytime symptoms and no significant cardiovascular comorbidities and as an alternative therapy for severe OSA patients who are unable to tolerate CPAP [7].

The aim of this study was to perform a meta-analysis based on individual data from patients with severe OSA included in RCTs comparing custom-made titratable duobloc MAD and CPAP. The primary objective was to compare the impact of the two treatments on sleepiness and major health outcomes, including sleep architecture and quality of life. The secondary objective was to evaluate the effects of both treatment on sleep-disordered breathing severity and sleep structure.

Methods

Eligibility criteria

Eligible trials had to include patients with severe OSA defined as an AHI greater than 30 per hour and aged 18 years or older. Trials were required to compare the effect of CPAP versus MAD on AHI in randomly allocated groups (parallel or crossover design). The MAD used in the trials had to be a custom-made titratable duo bloc device with progressive titration, as described in the study methods.

Search strategy and selection process

We conducted an electronic search of the following databases: MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials. We used keywords and free-text words related to "Continuous Positive Airway Pressure" / "CPAP" and "Mandibular Advancement Device" / "MAD" (including "mandibular advancement splints," "oral appliance," "mandibular repositioning appliance" and "mandibular repositioning splints").

Titles and abstracts were screened to ascertain whether each study met the eligibility criteria and to avoid duplicates. The full texts of the eligible articles identified were then evaluated to determine whether or not they should be included in the analysis. Studies rejected at this or subsequent stages were recorded along with reasons for exclusion (Figure 1).

Data collection

We contacted the principal investigator of each eligible trial to request anonymized electronic datasets of individual patient data. We reviewed the individual study protocols, template case report forms, and database dictionaries to ensure homogeneous study databases. Each database was updated with unified coding across trials and were then merged into a single database.

Each trial had been approved by a medical ethics committee according to the respective country's legislation, and all patients or their representatives were informed about the study at the time of inclusion.

Outcomes

Sleepiness: the primary outcome was sleepiness measured by the Epworth sleepiness scale (ESS). ESS is a self-administered questionnaire assessing a person's level of daytime sleepiness and average sleep propensity in eight typical daytime scenarios [8].

Quality of life: Another outcome was the patient's QoL, as measured by the 36-Item Short Form Survey (SF-36) and

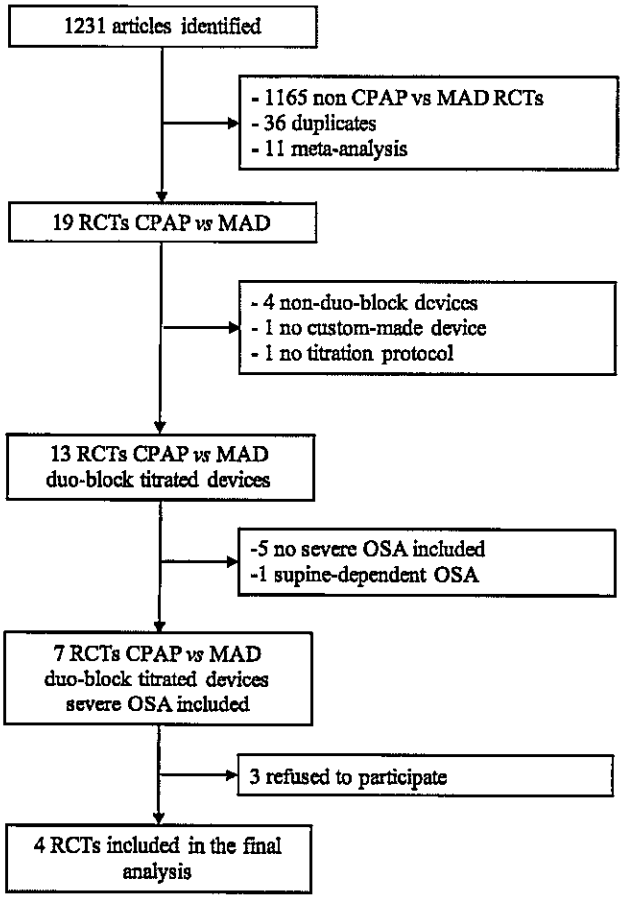

Figure 1. Study selection. RCT, randomized controlled trial; CPAP, continuous positive airway pressure; MAD, mandibular advancement device; OSA, obstructive sleep apnea.

the Functional Outcomes of Sleep Questionnaire (FOSQ). The SF-36 was designed for use in clinical practice and research, health policy evaluations, and general population surveys [9]. The SF-36 questions, assesses eight health concepts, including limitations in physical and social activities, pain, mental and emotional problems, as well as vitality and health perceptions. FOSQ is a self-reported measure designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living [10]. FOSQ is used to determine how disorders of excessive sleepiness, including OSA affect the patient's abilities to conduct normal activities and the extent to which these abilities are improved by effective treatment.

OSA severity markers and sleep architecture outcomes: OSA severity markers recorded in the analysis included AHI, but also 3% oxygen desaturation index (ODI), a marker of nocturnal hypoxia. The impact of the two treatments on sleep architecture was investigated in terms of the following sleep indices: sleep efficiency (SE), arousal index, total sleep time (TST), Stage N1, N2, N3, and Stage REM (rapid eye movement) duration (minutes), wake after sleep onset (WASO) duration (minutes).

Treatment adherence and patient's preference: Self-reported adherence with the two treatments were recorded when available. In studies with a crossover design, patient preference was recorded at the end of the trials.

Statistical analysis

The individual data from RCTs comparing CPAP to MAD intervention, and reporting similar outcomes, were pooled in the meta-analysis. Only patients with a baseline AHI ≥ 30/hour were included in the analysis. Trial authors were contacted to retrieve missing data when necessary. The analyses only included available data (ignoring missing data). As the meta-analysis included both crossover and parallel-group RCTs, changes in the measured outcome from baseline to post-treatment was considered to be the effect measure and unpaired tests were used to compare treatment effects.

Similar analyses, but based solely on data from crossover RCTs using paired tests and comparing post-treatment values were also performed and gave very similar results to baseline to post-treatment changes in the whole population (Supplementary Data 1).

Baseline descriptive data are expressed as percentages, mean and SD, and treatment effects are expressed as mean and 95% confidence interval (95% CI). Statistical comparisons were performed using the Chi-square test for categorical variables and the unpaired t-test for continuous variables. All statistical analyses were performed with software GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, CA).

Results

Figure 1 shows the details of study identification and inclusion and exclusion criteria. Out of the 1,231 articles identified, 13 RCTs comparing titratable duo bloc MAD and CPAP therapy were selected. Five of these 13 RCTs did not include patients with severe OSA and one study was exclusively devoted to supine-dependent OSA patients [11]. Finally, seven studies met the inclusion criteria. The corresponding authors of these seven studies were contacted and four of them agreed to participate in the meta-analysis. Among the four studies included in the meta-analysis, three trials had a crossover design [12–14] and one had a parallel-group design [15]. The main characteristics of the studies included in the meta-analysis are shown in Table 1. The four studies proposed various CPAP titration protocols (nap or one-night manual titration, autotitrating method based on the 95th percentile pressure) and all the patients were treated with a fixed CPAP during the protocol.

The final sample size comprised 151 severe OSA patients corresponding to 249 observations including 125 CPAP treatment periods and 124 MAD treatment periods. Baseline characteristics of these patients are presented in Table 2. As expected, the study samples included a large proportion of men, ranging from 71.4% to 84.9% (mean 83.0%). The reported mean age ranged from 46.0 to 52.2 years. Most patients included in these trials were overweight or obese, with a mean body mass index (BMI) ranging from 28.5 kg/m² to 35.3 kg/m². Three of the four studies reported a mean ESS close to the upper limit of the normal range (10/24). More than half of the patients with severe OSA (58.9%) included in these studies presented significant sleepiness (defined as an ESS > 10).

Baseline and treatment ESS were reported in three of the four studies included. Data from individual studies as well as pooled estimates demonstrated the absence of any significant difference between treatments (mean difference: 0.4; 95% CI = −0.9 to 1.77; $p = 0.53$) (Figure 2). Similar results were found when only patients

Table 1. Summary of the studies included

	Study design. intervention, sample size (severe OSA *n*; %)	Inclusion criteria	Treatment duration	Outcomes reported	CPAP titration process	MAD titration process
Hoekema *et al.* 2008	Parallel groups CPAP *n* = 52 (27; 52%) MAD *n* = 51 (26; 51%)	AHI > 5/hour	8 ± 4 weeks	ESS PSG SF 36 FOSQ	CPAP: no details Titration: abolishing SRD during afternoon nap	Thornton® (Airway Management) Titration: self-titrated symptom-based progressive mandibular protrusion
Phillips et al. 2013	Crossover *n* = 108 (49; 45%)	AHI > 10/hour	4 weeks	ESS PSG SF 36 FOSQ Compliance Preference	ResMed Autoset S8 (ResMed) Titration: auto-titration first; fix pressure second	SomnoDent® (Somnomed) Titration: self-titrated symptom-based progressive mandibular protrusion
Glos et al. 2016	Crossover *n* = 40 (14; 35%)	AHI > 5/hours	12 weeks	PSG	REMstar Pro ® (Philips Respironics) Titration: overnight PSG	SomnoDent® (Somnomed) Titration: mandibular protrusion during PSGs
Gagnadoux et al. 2009	Crossover *n* = 59 (35; 59%)	AHI > 10/hour	8 weeks	Overnight polysomnography ESS Compliance Preference	Sullivan S6 Elite ® (Resmed) Titration: overnight PSG	AMC® (Artech Médical): remote progressive mandibular advancement during overnight PSG

AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; MAD, mandibular advancement device; OSA, obstructive sleep apnea; ESS, Epworth sleepiness scale; FOSQ, Functional Outcomes of Sleep Questionnaire; SF-36, 36-Item Short Form Survey; PSG, polysomnography.

Table 2. Baseline characteristics of patients with severe OSA

	All patients	Hoekema et al. 2008	Gagnadoux et al. 2009	Phillips et al. 2013	Glos et al. 2016
N	151	53	35	49	14
Age, *n*	50.3 (11.1)	48.7 (9.4)	52.2 (9.5)	51.9 (12.4)	46.0 (14.6)
Sex (M)	83%	84.9%	80.0%	83.7%	71.4%
BMI	31.1 (5.9)	35.3 (5.6)	27.3 (3.7)	30.1 (4.7)	28.5 (6.0)
Baseline ESS	11.4 (5.2)	14.8 (5.1)	10.2 (4.0)	9.1 (4.9)	9.6 (3.6)
AHI	50.0 (18.3)	63.2 (21.6)	42.2 (10.3)	42.6 (9.1)	45.2 (16.9)
Sleep Efficiency	83.1 (13.7)	88.6 (11.3)	83.8 (9.4)	75.0 (16.1)	88.2 (7.5)

AHI, apnea-hypopnea index; ESS, Epworth sleepiness scale; BMI, body mass index.

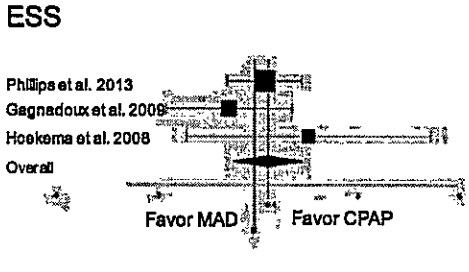

Figure 2. Effect of CPAP and MAD on ESS in patients with severe OSA. CPAP: continuous positive airway pressure; MAD: mandibular advancement device; OSA: obstructive sleep apnea; ESS: Epworth sleepiness scale.

with significant baseline sleepiness (ESS > 10) were included in the analysis (mean difference: 0.7; 95% CI = −1.1 to 2.5; $p = 0.46$).

Two of the four studies reported the impact of treatment on QoL using the same tools (SF-36 and FOSQ), corresponding to 74 observations in the CPAP treatment arm and 72 in the MAD treatment arm. As shown in Table 3, both CPAP and MAD improved most of the domains investigated compared to baseline (except for "intimacy" for the FOSQ and "bodily pain" for the SF-36), with no other differences between treatment arms.

All studies reported AHI values and three of the four studies reported ODI values. Impacts of treatments on AHI in individual studies and in pooled estimates are presented in Figure 3. Overall, subjects treated by MAD had a significantly less reduction of AHI and ODI compared to subjects treated by CPAP (mean difference: 11.1; 95% CI = 6.6 to 15.7; $p < 0.0001$ and 4.8; 95% CI = 0.4 to 9.3; $p = 0.03$, respectively).

Three studies reported data from overnight PSG with both MAD and CPAP treatments. Data from individual studies as well as pooled estimates revealed that MAD and CPAP treatment significantly improved SE by about 4%, but with no significant difference between them (mean difference: −0.44; 95% CI = −4.8 to 3.9; $p = 0.84$). Both treatments decreased the arousal index with a trend towards a more marked decrease with CPAP compared to MAD (mean difference: 5.0; 95% CI = −0.6 to 10.7; $p = 0.08$). The impact of MAD and CPAP treatment on sleep architecture is presented in Figure 4. Both treatments had a similar impact on sleep with an increase of N3 and REM stage duration and a decrease of N1 stage and

Table 3. Effect of CPAP and MAD on quality of life in patients with severe OSA

	Baseline	Mean Baseline – CPAP difference	Mean Baseline – MAD difference	Mean MAD-CPAP difference
FOSQ	14.8 (3.3)	2.1 (1.4 to 2.8)***	1.7 (1.0 to 2.5)***	−0.3 (−1.3 to 0.6)
Activity	2.8 (0.7)	0.5 (0.3 to 0.6)***	0.5 (0.3 to 0.6)***	−0.01 (−0.2 to 0.2)
Vigilance	2.7 (0.8)	0.6 (0.4 to 0.8)***	0.4 (0.2 to 0.6)***	−0.2 (−0.5 to 0.1)
Intimacy	3.0 (1.0)	0.17 (−0.1 to 0.4)	0.1 (−0.2 to 0.3)	−0.1 (−0.4 to 0.3)
Productivity	3.1 (0.7)	0.4 (0.3 to 0.6)***	0.4 (0.2 to 0.5)***	0.0 (−0.2 to 0.2)
Social	3.2 (0.7)	0.4 (0.3 to 0.6)***	0.3 (0.1 to 0.5)***	−0.1 (−0.3 to 0.2)
SF-36				
Physical function	75.8 (22.7)	5.7 (1.5 to 9.8)**	5.2 (0.6 to 9.8)*	−0.5 (−6.6 to 5.7)
Role physical	54.95 (40.16)	24.7 (16.2 to 33.2)***	15.3 (6.8 to 23.7)***	−9.4 (−21.2 to 2.5)
Bodily pain	80.0 (22.8)	1.5 (−3.8 to 6.8)	4.6 (−0.2 to 9.3)	3.1 (−4.0 to 10.1)
General health	61.6 (22.1)	3.9 (0.3 to 7.5)*	5.0 (1.8 to 8.2)**	1.1 (−3.7 to 5.9)
Vitality	44.9 (22.0)	16.3 (11.8 to 20.9)***	16.2 (10.7 to 21.7)***	−0.1 (−7.1 to 6.9)
Social function	75.4 (21.8)	6.7 (2.4 to 11.1)***	7.8 (3.7 to 11.8)***	1.0 (−4.9 to 6.9)
Role emotional	71.4 (39.6)	12.9 (4.0 to 21.6)**	9.7 (0.9 to 18.5)*	−3.1 (−15.4 to 9.2)
Mental health	71.6 (16.5)	5.7 (2.4 to 8.9)**	4.1 (1.1 to 7.0)**	−1.6 (−5.9 to 2.7)
Physical component	68.1 (20.7)	8.9 (5.2 to 12.7)***	7.5 (3.7 to 11.4)***	−1.4 (−6.7 to 3.9)
Mental component	65.9 (20.0)	10.4 (6.3 to 14.5)***	9.5 (5.8 to 13.1)***	−1.0 (−6.4 to 4.5)

Presented data correspond to 74 observations in the CPAP treatment arm and 72 observations in the MAD treatment arm extracted from two studies. CPAP, continuous positive airway pressure; MAD, mandibular advancement device; OSA, obstructive sleep apnea; FOSQ, Functional Outcomes of Sleep Questionnaire; SF-36, 36-Item Short Form Survey; PSG, polysomnography.
*$p < 0.5$; **$p < 0.01$; ***$p < 0.001$.

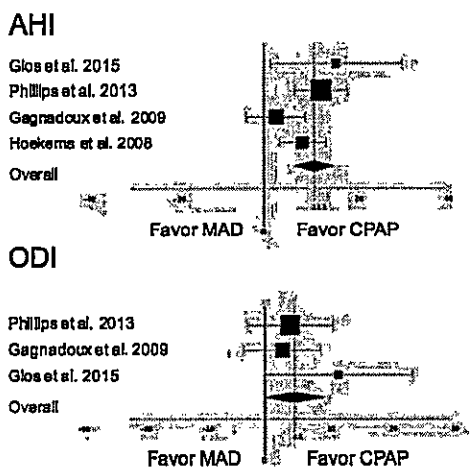

Figure 3. Effect of CPAP and MAD on AHI and ODI in patients with severe OSA. AHI: apnea-hypopnea index; CPAP: continuous positive airway pressure; MAD: mandibular advancement device; OSA: obstructive sleep apnea; ODI: oxygen desaturation index

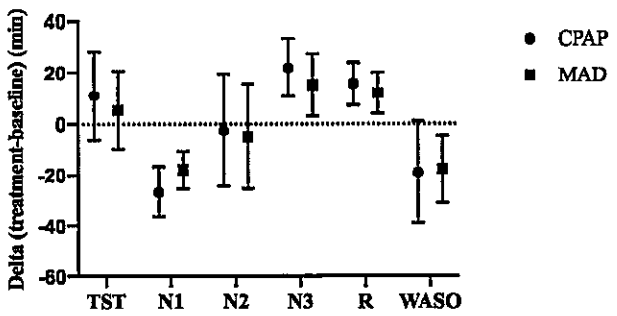

Figure 4. Effect of CPAP and MAD on sleep in patients with severe OSA. Presented data correspond to 75 observations in the CPAP treatment arm and 71 observations in the MAD treatment arm extracted from three studies. CPAP: continuous positive airway pressure; MAD: mandibular advancement device; OSA: obstructive sleep apnea; TST: total sleep time; N1: N1 stage sleep; N2: N2 stage sleep; N3: N3 stage sleep; R: rapid eye movement sleep; WASO: wake after sleep onset.

WASO duration (CPAP treatment as trend: mean −19 min; 95% CI = −39.0 to 1.0; $p = 0.06$) with no significant differences between treatment arms.

Three studies reported subjective adherence data for the two treatments. Patients reported higher adherence with MAD than with CPAP (mean difference: 1.1 hour; 95% CI = 0.7 to 1.6; $p < 0.0001$). Treatment preference results showed that 48 patients (60.8%) preferred MAD, 14 (17.7%) preferred CPAP, and 17 (21.5%) had no preference.

Discussion

To the best of our knowledge, this is the first study directly comparing the impact of CPAP and MAD in severe OSA. In summary, no statistically significant differences in terms of sleepiness and sleep architecture were observed between CPAP and MAD. Although CPAP was more effective in reducing AHI and ODI values, a majority of patients preferred MAD to CPAP and MAD was associated with higher subjective treatment adherence. Finally, no clear difference emerged in terms of the impact of the two treatments on QoL.

Recent meta-analyses have already compared MAD and CPAP in terms of major clinical outcomes and major sleep recording data. These meta-analyses included all available studies comparing CPAP and MAD independently of MAD design. Some evidence suggests that titratable duo bloc MADs are associated with a higher treatment success rate compared to monobloc devices, as a retrospective analysis of 805 patients using either an adjustable MAD ($n = 602$) or a fixed MAD found a higher treatment response rate for the adjustable device (56.8% vs. 47.0%) [16]. Furthermore, maximizing mandibular advancement seems to be more important in patients with severe disease. In a study of mild-to-moderate OSA patients randomized to either 50% or 75% of maximum advancement, there was no

difference between these levels in terms of treatment AHI or proportion of patients successfully treated (79% vs. 73%) [17]. In contrast, in severe OSA, more patients achieved treatment success with 75% compared to 50% maximum advancement (52% vs. 31%) [18], which is why the use of custom-made titratable appliances is recommended by European and American guidelines [6, 7]. It can be hypothesized that previous meta-analyses pooling data concerning monobloc and duobloc MADs may have underestimated the efficacy of MAD compared to CPAP, especially in patients with severe OSA.

To the best of our knowledge, no published or ongoing trial has been designed to compare CPAP and MAD in severe OSA. A subgroup analysis for severe OSA was proposed in the meta-analysis by Sharples et al. [3]. However, only mean baseline AHI was considered to allocate all patients from the study to an OSA severity category. As mean AHI in the studies were regularly close to the moderate and severe cut-off value (30/hour), a large percentage of the patients were wrongly allocated to severity categories, making it difficult to draw any definitive conclusions. Therefore, this individual patient meta-analysis provides first evidence of comparative effects of these two treatments on actual patient-centered outcomes in severe OSA.

In addition to the results indicating a similar effect of the two treatment modalities on patient-centered outcomes (sleepiness and QoL), this study also provides interesting data regarding the impact of the two treatments on sleep structure: a decrease of N1 stage and an increase of N3, REM, and SE. Similar effects were observed for the effect of CPAP versus placebo in RCTs [19–21]. Limited data are available based on direct comparison of MAD and CPAP on sleep structure. El-Solh *et al.* recently reported sleep recording data on both treatments, but only the titration night was reported and the various sleep stages were grouped into two categories (REM and non-REM) [22]. Studies comprising limited sample sizes and a mix of patients with both moderate and severe OSA have previously suggested a trend towards a similar increase in stage 3 sleep with the two treatments [23, 24]. As the increase in stage 3 duration have already been shown to be strongly associated with improvement of sleepiness [20], it can be hypothesized that the results of the present study could help to explain the similar clinical impact of the two treatments despite the larger effect of CPAP on AHI decrease.

Limitations

There are several limitations that should be considered in relation to our study. Three studies were not included in the analysis due to investigators declining. Among those studies, El-Solh et al. focused on a very specific population and outcomes (Veterans with Posttraumatic Stress Disorder) [22]. The study by Schutz et al. included a limited number of patients in a parallel-group design (nine moderate to severe OSA patients in each treatment arm) [24]. Finally, the study by Dal-Fabbro et al. included 35 moderate to severe OSA patients in a cross-over design and focused on cardiovascular outcomes [23]. Therefore, we acknowledge a limited sample size in our final analyses especially for the evaluation of the effects of treatments on quality of life and sleep structure.

PSG data arise from four different sleep centers with no centralized analyses of the recordings. However, all the four studies used 1999 AASM criteria to score respiratory events. It was recently suggested that 1999 and 2012 AASM criteria have similar sensitivity to identify severe OSA patients [25]. The present results are therefore relevant to current practice.

Due to the use of various tools to access cardiovascular and cognitive outcomes in the studies, those evaluations were not included in the present meta-analysis. Phillips et al. reported the impact of both treatments on 24-hour blood pressure and arterial stiffness and found no changes in the entire group (and similar impact of both treatments in hypertensive participants) [14]. Glos et al. reported daytime blood pressure and heart rate variability and found that both treatments resulted in similar beneficial changes in blood pressure and cardiac autonomic function during daytime [13]. Similarly, various tools were used in two studies to access the impact of treatments on cognitive function (driving stimulation, Trail Making Test) and found similar improvements with both treatments.

Included studies did not propose objective measure of MAD compliance. Two studies reported objective and subjective compliance for CPAP and found that patients overestimate actual CPAP use. Novel technology for measuring objective MAD compliance is now available and could allow objective compliance comparison in future studies.

Cross-over and parallel group studies were included in the meta-analysis. Consequently, changes in the measured outcome from baseline to post-treatment was considered to be the effect measure and unpaired tests were used to compare treatment effects. As unpaired tests might underestimate the differences between groups from the cross-over trials, paired analyses were performed on data from the three cross-over studies and showed similar results. As shown in Table 1, the studies had different inclusion criteria and proposed various MAD devices. However, as only patients with an AHI > 30/hour were included in the present analysis, the final study population is relatively homogenous. Various MAD devices were also proposed but all the selected studies proposed a mandibular advancement titration process to ensure optimal efficacy. Finally, when compared to a classical OSA population, patients included in the present meta-analysis were relatively young limiting thereby the extrapolation of the results.

Conclusion

Titratable MAD has a similar impact to CPAP on major patient-centered outcomes (sleepiness and QoL) in severe OSA patients. CPAP was more effective in reducing AHI and ODI, but treatment adherence and patient preference were largely in favor of MAD. Finally, both treatments had a similar impact on detailed sleep structure with an increase of N3 and REM sleep. This meta-analysis suggests that MAD represents an effective alternative treatment option in all OSA patients intolerant to CPAP or who prefer alternate therapy, including those with severe OSA. This work provides impetus for future studies to focus on severe OSA, and to explore a range of additional outcomes, including cardiometabolic comorbidities and cognitive function.

Supplementary material

Supplementary material is available at *SLEEP* online.

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