



Mandibular Advancement Device vs CPAP in the Treatment of Obstructive Sleep Apnea: Are they Equally Effective in Short Term Health Outcomes?

Commentary on Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med* 2013;187:879-887.

David P. White, M.D., F.A.A.S.M.¹; Shirin Shafazand, M.D., M.S., F.A.A.S.M.²

¹Harvard Medical School, Boston, MA; ²University of Miami, Miami, FL

ARTICLE SUMMARY

Question: Is the treatment of obstructive sleep apnea (OSA) with mandibular advancement device (MAD) similar in health outcomes to continuous positive airway pressure (CPAP) in the short term (one month health outcomes)?

Design: Randomized, open labeled, cross over, non-inferiority trial; Clinical trial registered with <https://www.anzctr.org.au> (ACTRN 12607000289415).

Allocation: Patients randomized to both the treatment acclimatization and treatment arm orders, resulting in 4 randomized sequences for MAD (M) and CPAP (C): MCMC, MCCM, CMMC and CMCM. Each sequence was generated by a computer program using random permuted blocks. The acclimatization periods for each treatment were generally between 4-6 weeks. Treatment periods were for 1 month each.

Blinding: The investigators and participants were not blinded to study arm assignment.

Follow-up period: 1 month.

Setting: The study was conducted at three sleep centers in Sydney, Australia.

Subjects: 126 adults, mean age 49.5 years, 81% male, mean AHI 25.6 events/h, were randomized. **Inclusion Criteria:** patients with newly diagnosed OSA, AHI > 10 events/h, age ≥ 20 years, ≥ 2 symptoms of OSA (snoring, fragmented sleep, witnessed apneas, or daytime sleepiness), and a willingness to use both treatments. **Exclusion Criteria:** previous OSA treatment or a need for immediate treatment, central sleep apnea, a coexisting sleep disorder, regular use of sedatives or narcotics, preexisting lung or psychiatric disease, and any contraindication for oral appliance therapy (e.g., periodontal disease or insufficient dentition).

Intervention: Patients meeting eligibility criteria were randomized to a 4-6 week each, acclimatization to CPAP and MAD. A 2 week wash out period was then followed by initial assignment to CPAP or MAD treatment and subsequent cross over. During each of the 4-6 weeks of acclimatization with each device, all patients were asked to use their device for as long as they could tolerate it on a nightly basis.

Outcomes: The primary outcome was the difference in 24-hour mean arterial pressure (24MAP) between CPAP and MAD determined by 24-hour ambulatory blood pressure (BP) monitoring. Secondary outcome measures were central BP and arterial stiffness measurements, neurobehavioral function, and quality of life (QOL) using the Functional Outcomes of Sleep Questionnaire (FOSQ), the Short Form-36 (SF-36), the Epworth Sleepiness Score (ESS), and the AusEd driving simulator. Daily diaries were also used to monitor treatment side effects and determine subjective compliance.

The sample size was calculated to show the non-inferiority of MAD

relative to CPAP in the 24MAP after 1 month of therapy, using an a priori determined non-inferiority margin of 1.6 mmHg, assuming 90% power and a true difference between treatment means of zero. The primary hypothesis was tested by comparing the upper limit of the 95% confidence interval for the MAD-CPAP difference in 24MAP with the a priori non-inferiority margin using the paired t-test.

Patient Follow-Up: 18 patients (14%) withdrew after randomization, leaving 108 (86%) who completed the study. Two patients withdrew because of treatment intolerance (one CPAP and one both CPAP and MAD). Analyses were limited to the 108 subjects who completed the trial, regardless of compliance with their assigned treatment.

Main Results: There was no statistically significant difference between the groups in the primary outcome. MAD was non-inferior to CPAP with a CPAP-MAD 24MAP difference, 0.2 mmHg (95% confidence interval, -0.7 to 1.1 mmHg). However, ultimately neither treatment lowered BP from baseline in the entire group, after 1 month of therapy. In the subgroup of patients with baseline hypertension (n = 45), there were consistent treatment-related 24MAP improvements (p < 0.05) of 2.5 mmHg (CPAP) and 2.2 mmHg (MAD), with neither treatment having a superior effect. There were no differences in secondary outcome measures between groups, except MAD performed better than CPAP in improving four of eight SF-36 general QOL domains, and the overall mental component score (p < 0.05). Subjective reports of nightly compliance were less for CPAP compared with MAD (mean compliance 5.2 ± 2.0 vs. 6.5 ± 1.3 h/night, p < 0.0001). Treatment preference results showed that 55 patients (51%) preferred MAD, 25 (23%) preferred CPAP, 23 (21%) preferred either, and 5 (4.6%) preferred neither.

Conclusion: In adults with predominately moderate to severe OSA, the short term (one month) use of an adjustable MAD was not inferior to CPAP in its impact on 24 hour mean ambulatory blood pressure, daytime sleepiness, disease specific and general quality of life.

Sources of Funding: The study was supported by Project Grant 457557, Practitioner Fellowship 202916 (R.R.G.), Health Professional Fellowship 571179, and CIRUS Postdoctoral Fellowship (C.L.P.) from the Australian National Health and Medical Research Council. ResMed Inc. donated all continuous positive airway pressure equipment for the trial. SomnoMed Ltd. donated all oral appliances for the trial and an unrestricted grant of A\$60,000 to support the study.

For Correspondence: Craig L. Phillips, Ph.D., Department of Respiratory and Sleep Medicine, Royal North Shore Hospital, St Leonards, NSW 2065 Australia. E-mail: craig.phillips@sydney.edu.au

In this commentary, we address two topics related to this paper:

Are there methodological concerns?

This study is basically sound with a number of important strengths. These include the number of subjects studied, the randomization scheme (for both acclimatization and treatment), the diverse outcome variables assessed, and the comparative effectiveness approach taken. That being said, there are some minor concerns:

- The study was powered to a change in blood pressure (BP) with therapy. Previous reports indicate that the effect of CPAP on BP is small at best and can be variable with the largest changes seen in patients who are hypertensive at initiation of therapy.¹ Thus another outcome variable might have been a better choice although we doubt this weakened the observations.
- The time interval of treatment for both CPAP and the mandibular advancing device (MAD) was only one month. This is understandable based on the complexity of the protocol, but could miss outcome differences between the two therapies that would only become apparent after longer duration treatment.
- Compliance with the MAD was only assessed subjectively. Again, this is understandable because no reasonable method was available to assess MAD use at the time this study was begun. However, this approach still weakens one of the main observations of the study (differences in device adherence between CPAP and MAD) as subjective report is notoriously inaccurate.
- The acclimatization time for both devices was quite long (4 to 6 weeks) which could have led to the withdrawal of subjects who could not tolerate either or both the therapies prior to the actual start of the treatment phase (despite arguments by the authors to the contrary). This could make therapy acceptance and adherence appear to be better than would have otherwise been the case.

In our opinion, none of these potential problems importantly affected the outcome of this study which is clearly the best to date addressing the question raised (outcomes of CPAP versus MAD therapy in obstructive sleep apnea).

Should the guideline regarding the use of MADs in the therapy of severe OSA be changed?

The most recent guideline from the AASM addressing OSA therapy² suggests that MAD devices should primarily be used in patients with mild to moderate OSA. The study by Phillips et al. included 32% severe OSA patients (AHI > 30) or 34 patients. Thus the question is how well did these patients fare on the MAD device? The mean AHI for this group was 42 off therapy

and on the MAD device was about 16-17 (per Figure 2). Although individual data are a bit difficult to ascertain from the paper, Figure 2 suggests the following results for this severe group. On MAD therapy:

- 7 patients (21.2%) had an AHI > 30
- 13 patients (39.4%) had an AHI > 20 (including the 7 with an AHI > 30)
- 8 patients (24.2%) had an AHI of 10-20
- 12 patients (36.4%) had an AHI < 10

The authors report that these severe patients had a similar improvement in sleepiness (based on the Epworth Sleepiness Scale [ESS]) on the MAD as they did on CPAP although the numbers are obviously small. This outcome and the AHI numbers above indicate that not all severe OSA patients respond well to a MAD, although a sizable minority probably does, depending on where one sets the success threshold for AHI, ESS, or any other viable criteria. Thus, the conclusion that a MAD is not an appropriate therapy for a patient with severe OSA may be incorrect. Although MADs may not be first line therapy for patients with severe OSA, the take-home message here is simply that a follow-up sleep study (lab or home) is probably needed for severe OSA patients to assess efficacy; not that MAD is not a good choice for these patients. Thus, for a severe OSA patient struggling with other therapies (particularly CPAP), a MAD is probably the best second line therapy available. As this study is the most comprehensive assessment to date comparing MADs to CPAP, it may be wise to reconsider current recommendations.

CITATION

White DP; Shafazand S. Mandibular advancement device vs CPAP in the treatment of obstructive sleep apnea: are they equally effective in short term health outcomes? *J Clin Sleep Med* 2013;9(9):971-972.

REFERENCES

1. Rao M, Rajda G, Uppuluri S, Beck GR, Liu L, Bisognano JD. The role of continuous positive airway pressure in the treatment of hypertension in patients with obstructive sleep apnea-hypopnea syndrome: a review of randomized trials. *Rev Recent Clin Trials* 2010;5:35-42.
2. Epstein LJ, Kristo D, Strollo PJ Jr, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2009;5:263-76.

CORRESPONDENCE INFORMATION

Address correspondence to: Shirin Shafazand, M.D., M.S., University of Miami, Division of Pulmonary, Critical Care and Sleep Medicine, PO Box 016960 (D60), Miami, FL, 33101; Tel: (305) 243-7838; E-mail: sshafazand@med.miami.edu

DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.