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THE CHALLENGES OF ADVANCING THE EVIDENCE FOR THE LONG-TERM EFFECTIVENESS OF ORAL APPLIANCE THERAPY FOR SLEEP APNEA

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Commentary on:

A custom-made mandibular repositioning device for obstructive sleep apnoea-hypopnoea syndrome: the ORCADES study.

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Continuous positive airway pressure (CPAP) treatment and oral appliance therapy with mandibular repositioning devices (MRDs), aiming to reduce upper airway collapse by advancing the mandible during sleep, are the two treatments for obstructive sleep apnea (OSA) of which the effects on cardiovascular endpoints have been assessed in randomized trials [1, 2]. There is strong evidence in literature demonstrating that therapy with MRDs improves OSA severity in the majority of patients, including patients with more severe OSA [3]. The most recent joint recommendations of the American Academy of Sleep Medicine (AASM) and the American Academy of Dental Sleep Medicine (AADSM) suggest a qualified dentist to use a custom or bespoke, titratable MRD when a sleep physician prescribes oral appliance therapy for the treatment of OSA [4, 5]. Indeed, the custom or bespoke, titratable oral appliances are the most commonly prescribed and the recommended type of oral appliances for the treatment of OSA [6-9].

A recent randomized controlled trial comparing therapy for OSA using a custom, titratable MRD with CPAP treatment indicated that both have similar health effects and a comparable effect on blood pressure [10]. Several authors have been suggesting that these findings of equal effectiveness might be explained by the fact that the greater efficacy of CPAP treatment, as compared to the efficacy of MRD therapy, is being offset by its inferior compliance relative to MRDs [10-13].

In this issue of *Sleep Medicine*, Professor Vecchierini and her colleagues present and discuss the interim results of a prospective, multicenter, observational trial (ORCADES) determining the efficacy of two custom, titratable MRDs in real-life conditions in a large cohort of 369 CPAP intolerant OSA patients with follow-up up to six months [14]. As a consequence, the study aimed at evaluating MRD therapy as a second-line, non-surgical alternative for CPAP.

The authors have to be congratulated for this well-designed study recruiting eligible OSA patients from 28 sleep centers across France. The intervention included a titration period where, in the absence of a golden standard titration protocol, the degree of mandibular protrusion was decided upon the best achievable benefit-risk ratio between tolerability and resolution of symptoms [14, 15].

In 2015, there are indeed many challenges of adding evidence to the long-term effectiveness of MRD therapy for OSA and the reported study clearly adds to many, but not all, key issues that currently limit this evidence in literature.

First, in contrast to the practice parameters of AASM [5, 6] and AADSM [4], that restrict the indications for oral appliance therapy as a first-line treatment to patients with mild to moderate OSA, the authors of the ORCADES study, as in other recent studies [10], did clearly and purposely include a large subgroup of patients with severe OSA (n=158 out of 369 being 43% of the included patients). This methodology resulted in a relatively high baseline apnea/hypopnea-index (AHI) on average for the whole study group being 30 per hour sleep. In the subgroup with severe OSA a significant decrease in OSA severity was noted with a mean drop in AHI from 43/h at baseline to 18/h with MRD. As such, the data of the reported study add to the current insight that custom, titratable MRDs are effective for patients with mild up to severe OSA, and that future indications could potentially include the prescription of custom, titratable MRDs for the first-line treatment of severe OSA in well-selected patients. The proper “up-front” selection of the good candidates for MRD therapy, however, has not been part of the inclusion process within the reported study. Recent findings on the role of more advanced imaging modalities and specific endoscopy techniques are suggesting that a robust selection protocol might lead to a higher efficacy of MRD therapy, thereby improving the overall clinical effectiveness of this therapeutic option [16-19]. As a consequence, there clearly is a continuous need to further explore both the effectiveness and the related costs of these clinical strategies to predict individual patients' responses to MRD therapy [2].

Second, concerning the health benefits of oral appliance therapy using custom, titratable MRDs, the results of the reported study, once again, confirm that sleepiness, symptoms and quality of life are clearly improved with this therapy in OSA patients [3, 10, 14]. In the long-run the ORCADES project aims at a five-year follow-up of their large cohort of patients treated with MRD. Hence, this project will try to clarify whether the observed effects at 3-6 months interim follow-up translate into a sustained resolution of OSA-related symptoms and morbidity after five years of MRD usage.

Third, the authors conclude that the results of the interim analysis of the ORCADES data indicate that the long-term compliance with custom MRD therapy is excellent unless the fact that their reported discontinuation rate is relatively high being about eight percent at a follow-up up to six months [14]. In addition, the adherence data reported in this study are based solely on self-report whereas the objective measurement of adherence during MRD therapy has been validated recently [17, 20]. Since the easy access to this objective measurement of MRD usage in routine clinical and dental practice, it is highly recommended that the actual MRD use would be objectively assessed in all OSA patients undergoing MRD therapy [17].

Finally, keeping in mind the superior adherence during MRD therapy as compared to CPAP treatment [10, 21], the overall effectiveness of MRDs for OSA therapy can mainly be improved by attempts to improve its efficacy [17]. Apart from the exploration of more effective titration procedures and an enhanced upfront prediction of individual patients' responses to MRD therapy, this efficacy might also be improved by a more accurate documentation of the reasons for any residual OSA under MRD therapy. Among others, there is recent evidence that a residual positional OSA is common as a reason for an incomplete elimination of OSA during MRD therapy [22]. In part, these findings can be explained by the fact that positional or supine-dependent OSA is much more common in patients with mild disease as compared to patients with a higher OSA severity at baseline [23]. If the positional component turns out to be the main reason for the residual OSA during MRD therapy after careful investigation, adding a therapy that is able to avoid the supine sleeping position, is highly probable to lead to a significant improvement of the clinical efficacy [24]. Alternatively, additional upper airway surgery, if indicated, , can lead to a better result of MRD therapy for OSA after careful selection of the patients [25]. The above examples clearly illustrate that the value of combination therapy is undoubtedly underestimated and needs to be further investigated in order to aim at a higher overall clinical effectiveness when prescribing MRDs for the treatment of OSA [26].

When aiming at advancing the evidence for the long-term effectiveness of MRD therapy for OSA, the challenges are clearly multifactorial and also include the continuing exploration of the cost-benefit and potential cost-effectiveness of this therapeutic option for OSA in all its aspects [27-29]. Prospective studies with large numbers of patients and long follow-up periods, such as the ORCADES project, are indeed required to assess the evolution of the results with MRD therapy in OSA patients over time [14, 17]. In future studies that assess the long-term effectiveness of oral appliance therapy for OSA, the use of an objective instrument to measure adherence should be implemented [17]. Both the ORCADES trial and the Oral Appliance Network on Global Effectiveness (ORANGE) network, a multinational observational cohort study, seek to determine the effectiveness of MRDs in real-life conditions [14, 30]. In summary, it can be argued that, based on the interim results of the reported study [14] and also taking into account the recent data on equal effectiveness [10], the authors are probably right in concluding that custom, titratable MRDs are a valid non-CPAP option for the treatment of well-selected OSA patients. As described above, the many challenges that come with determining the long-term overall effectiveness of oral appliance therapy for sleep-disordered breathing should be taken into account when designing future projects that carry these ambitious goals.

References

1. Vanderveken OM, Boudewyns A, Ni Q, et al. Cardiovascular implications in the treatment of obstructive sleep apnea. *Journal of cardiovascular translational research* 2011; **4**(1): 53-60.
2. Sharples LD, Clutterbuck-James AL, Glover MJ, et al. Meta-analysis of randomised controlled trials of oral mandibular advancement devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea. *Sleep medicine reviews* 2015.
3. Sutherland K, Vanderveken OM, Tsuda H, et al. Oral appliance treatment for obstructive sleep apnea: an update. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2014; **10**(2): 215-27.
4. Ramar KD, L.C.; Katz, S.G.; Lettieri, C.J.; Harrod, C.G.; Thomas, S.H.; Chervin, R.D. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. *Journal of Dental Sleep Medicine* 2015; **2**(3): 71-125.
5. Ramar K, Dort LC, Katz SG, et al. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2015.
6. Kushida CA, Morgenthaler TI, Littner MR, et al. Practice parameters for the treatment of snoring and Obstructive Sleep Apnea with oral appliances: an update for 2005. *Sleep* 2006; **29**(2): 240-3.
7. Marklund M, Verbraecken J, Randerath W. Non-CPAP therapies in obstructive sleep apnoea: mandibular advancement device therapy. *The European respiratory journal* 2012; **39**(5): 1241-7.
8. Vanderveken OM, Devolder A, Marklund M, et al. Comparison of a custom-made and a thermoplastic oral appliance for the treatment of mild sleep apnea. *American journal of respiratory and critical care medicine* 2008; **178**(2): 197-202.
9. Lettieri CJ, Paolino N, Eliasson AH, Shah AA, Holley AB. Comparison of adjustable and fixed oral appliances for the treatment of obstructive sleep apnea. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2011; **7**(5): 439-45.
10. 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. *American journal of respiratory and critical care medicine* 2013; **187**(8): 879-87.
11. Vanderveken OM, Braem MJ, Dieltjens M, De Backer WA, Van de Heyning PH. Objective measurement of the therapeutic effectiveness of continuous positive airway pressure versus oral appliance therapy for the treatment of obstructive sleep apnea. *American journal of respiratory and critical care medicine* 2013; **188**(9): 1162.
12. White DP. Reply: Objective measurement of the therapeutic effectiveness of continuous positive airway pressure versus oral appliance therapy for the treatment of obstructive sleep apnea. *American journal of respiratory and critical care medicine* 2013; **188**(9): 1163-4.
13. White DP. Continuous positive airway pressure versus the mandibular advancing splint: are they equally effective in obstructive sleep apnea management? *American journal of respiratory and critical care medicine* 2013; **187**(8): 795-7.
14. Vecchierini MFA, V. ; Collet, J.M.; d'Ortho, M.P.; El Chater, P.; Kerbrat, J.B.; Leger, D.; Monaca, C.; Monteyrol, P.J.; Morin, L.; Mullens, E.; Pigearias, B.; Meurice J.C. A custom-made mandibular repositioning device for obstructive sleep apnoea-hypopnoea syndrome: the ORCADES study. *Sleep medicine* 2015.
15. Dieltjens M, Vanderveken OM, Heyning PH, Braem MJ. Current opinions and clinical practice in the titration of oral appliances in the treatment of sleep-disordered breathing. *Sleep medicine reviews* 2012; **16**(2): 177-85.
16. Vroegop AV, Vanderveken OM, Dieltjens M, et al. Sleep endoscopy with simulation bite for prediction of oral appliance treatment outcome. *Journal of sleep research* 2013; **22**(3): 348-55.
17. Vanderveken OM, Dieltjens M, Wouters K, De Backer WA, Van de Heyning PH, Braem MJ. Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. *Thorax* 2013; **68**(1): 91-6.

18. De Vito A, Carrasco Llatas M, Vanni A, et al. European position paper on drug-induced sedation endoscopy (DISE). *Sleep & breathing = Schlaf & Atmung* 2014; **18**(3): 453-65.
19. Chan AS, Sutherland K, Schwab RJ, et al. The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. *Thorax* 2010; **65**(8): 726-32.
20. Dieltjens M, Braem MJ, Vroegop AV, et al. Objectively measured vs self-reported compliance during oral appliance therapy for sleep-disordered breathing. *Chest* 2013; **144**(5): 1495-502.
21. Grote L, Hedner J, Grunstein R, Kraiczi H. Therapy with nCPAP: incomplete elimination of Sleep Related Breathing Disorder. *The European respiratory journal* 2000; **16**(5): 921-7.
22. Dieltjens M, Braem MJ, Van de Heyning PH, Wouters K, Vanderveken OM. Prevalence and clinical significance of supine-dependent obstructive sleep apnea in patients using oral appliance therapy. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2014; **10**(9): 959-64.
23. Joosten SA, Hamza K, Sands S, Turton A, Berger P, Hamilton G. Phenotypes of patients with mild to moderate obstructive sleep apnoea as confirmed by cluster analysis. *Respirology* 2012; **17**(1): 99-107.
24. Dieltjens M, Vroegop AV, Verbruggen AE, et al. A promising concept of combination therapy for positional obstructive sleep apnea. *Sleep & breathing = Schlaf & Atmung* 2014.
25. Millman RP, Rosenberg CL, Carlisle CC, Kramer NR, Kahn DM, Bonitati AE. The efficacy of oral appliances in the treatment of persistent sleep apnea after uvulopalatopharyngoplasty. *Chest* 1998; **113**(4): 992-6.
26. Vanderveken OM. Combination Therapy for Obstructive Sleep Apnea in Order to Achieve Complete Disease Alleviation: from Taboo to New Standard of Care? *Journal of Dental Sleep Medicine* 2015; **2**: 7-8.
27. Trenaman L, Sadatsafavi M, Almeida F, et al. Exploring the Potential Cost-Effectiveness of Patient Decision Aids for Use in Adults with Obstructive Sleep Apnea: A Case Study. *Medical decision making : an international journal of the Society for Medical Decision Making* 2015; **35**(5): 671-82.
28. Sharples L, Glover M, Clutterbuck-James A, et al. Clinical effectiveness and cost-effectiveness results from the randomised controlled Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea-hypopnoea (TOMADO) and long-term economic analysis of oral devices and continuous positive airway pressure. *Health technology assessment* 2014; **18**(67): 1-296.
29. Quinnell TG, Bennett M, Jordan J, et al. A crossover randomised controlled trial of oral mandibular advancement devices for obstructive sleep apnoea-hypopnoea (TOMADO). *Thorax* 2014; **69**(10): 938-45.
30. Almeida F, Vanderveken OM, Cistulli P, et al. ORal Appliance Network on Global Effectiveness (ORANGE) : start-up and design description. *Journal of dental sleep medicine* 2014; **1**(1): 1-11.