

Combination Therapy for Obstructive Sleep Apnea in Order to Achieve Complete Disease Alleviation: from Taboo to New Standard of Care?

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Obstructive sleep apnea (OSA) is a highly prevalent disease with a complex pathophysiology.^{1,2} When undiagnosed or untreated OSA leads to subsequent morbidity and significant long-term mortality, also in patients with mild to moderate disease.³ Treatment with continuous positive airway pressure (CPAP) and oral appliance therapy with mandibular advancement devices (OAm) are the two treatments for OSA whose effects on cardiovascular endpoints have been assessed in randomized controlled trials (RCT).⁴⁻⁷ However, both therapeutic options have their possible limitations as CPAP treatment often comes with low patients' acceptance, poor tolerance and suboptimal compliance, whereas OAm therapy generally has an inferior efficacy as compared to CPAP.^{4,8-10} Indeed, according to the mean disease alleviation (MDA) concept, the risk that the greater efficacy of CPAP is being offset by its inferior compliance relative to OAm therapy is not imaginary, resulting in a similar overall effectiveness for both therapeutic modalities.^{4,9} In other words, treatment of OSA with CPAP, OAm or other non-CPAP modalities, as a single treatment, will commonly be associated with an incomplete elimination of the disease with mean values of the MDA index, as a marker of real clinical effectiveness, ranging from 40 to 59 %.^{8,11,12}

Supporting data from the literature on the role and impact of adjunct therapy that can be used as needed in order to improve the MDA index of the primary treatment options are scarce.¹³ Case series have been published on the combination of CPAP with OAm therapy for the treatment of OSA.^{14,15} It has been demonstrated that when mandibular protrusion is limited in case of OAm therapy, a combined approach utilizing both mandibular protrusion and tongue retention is able to provide an effective treatment for moderate-to-severe OSA as the addition of a tongue bulb to the OAm provides further therapeutic effectiveness.¹⁶ Furthermore, adjunct OAm therapy has been shown to be an effective mode of combination therapy to control OSA after failure of upper airway surgery.^{2,17} Multilevel surgery, being the combination of more than one surgical technique, can also be considered as combination therapy for OSA.¹⁸⁻²³ In obese patients with severe OSA, CPAP requirements might be decreased after bariatric surgery and these lower CPAP pressures may yet lead to an increased CPAP tolerance and an improved overall compliance with CPAP.²³ The effectiveness of other conceivable and convenient combinations in specific patients needs to be put into perspective and requires further investigation in ongoing studies or future trials.

Interestingly, in addition, at least half of OSA patients are reported to suffer from supine-dependent or positional OSA (POSA), commonly defined as an apnea/hypopnea-index (AHI)

being at least twice as high in the supine sleeping position as compared to the AHI in the non-supine positions.^{24,25} While newer methods to treat POSA with higher compliance rates are emerging, the relevance of this finding of POSA being that common is highly relevant.²⁶⁻²⁸ Recently, it has been reported that about 1 out of 3 patients still suffer from residual POSA while undergoing OAm therapy.²⁹ The results of a recently published RCT indicate that in these patients with residual POSA under OAm therapy the combination of OAm and a sleep position trainer leads to a significant improvement of the therapeutic effectiveness with an increase of the MDA index changing from 42% with OAm alone to 70% with the combination treatment of OAm and sleep position trainer, respectively.³⁰ Similarly, positional treatment might also be an adjunct treatment in patients on CPAP who require higher pressure levels in the supine sleeping position than in the non-supine positions in order to improve CPAP compliance.³¹ From a theoretical and conceptual perspective, the combination of positional therapy and surgical upper airway modifications could also result in a significant decrease in OSA severity in patients with POSA.^{32,33}

In summary, the combination of different treatment options for the alleviation of OSA is clearly underestimated, undervalued and underinvestigated in the field of sleep medicine. In order to reach the target, preferably an alleviation of the disease, it might indeed be necessary to prescribe two or more therapies with adjunctive therapies used as needed to supplement the primary treatment options.¹³ In order to avoid incomplete alleviation of OSA, our field needs to think out of the box and try to get rid of the taboo of combining different treatment options in the individual patients in order to reach a well-defined target correlating with long-term elimination of disease. Further research on the clinical effectiveness of the possible combinations to completely eliminate the patient's OSA is highly needed.

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