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Publication date
2020

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Citation for published version (APA):
Nikolopoulou, M. (2020). *Oral appliance therapy in obstructive sleep apnea: Therapeutic effects and side effects*. [Thesis, externally prepared, Universiteit van Amsterdam].

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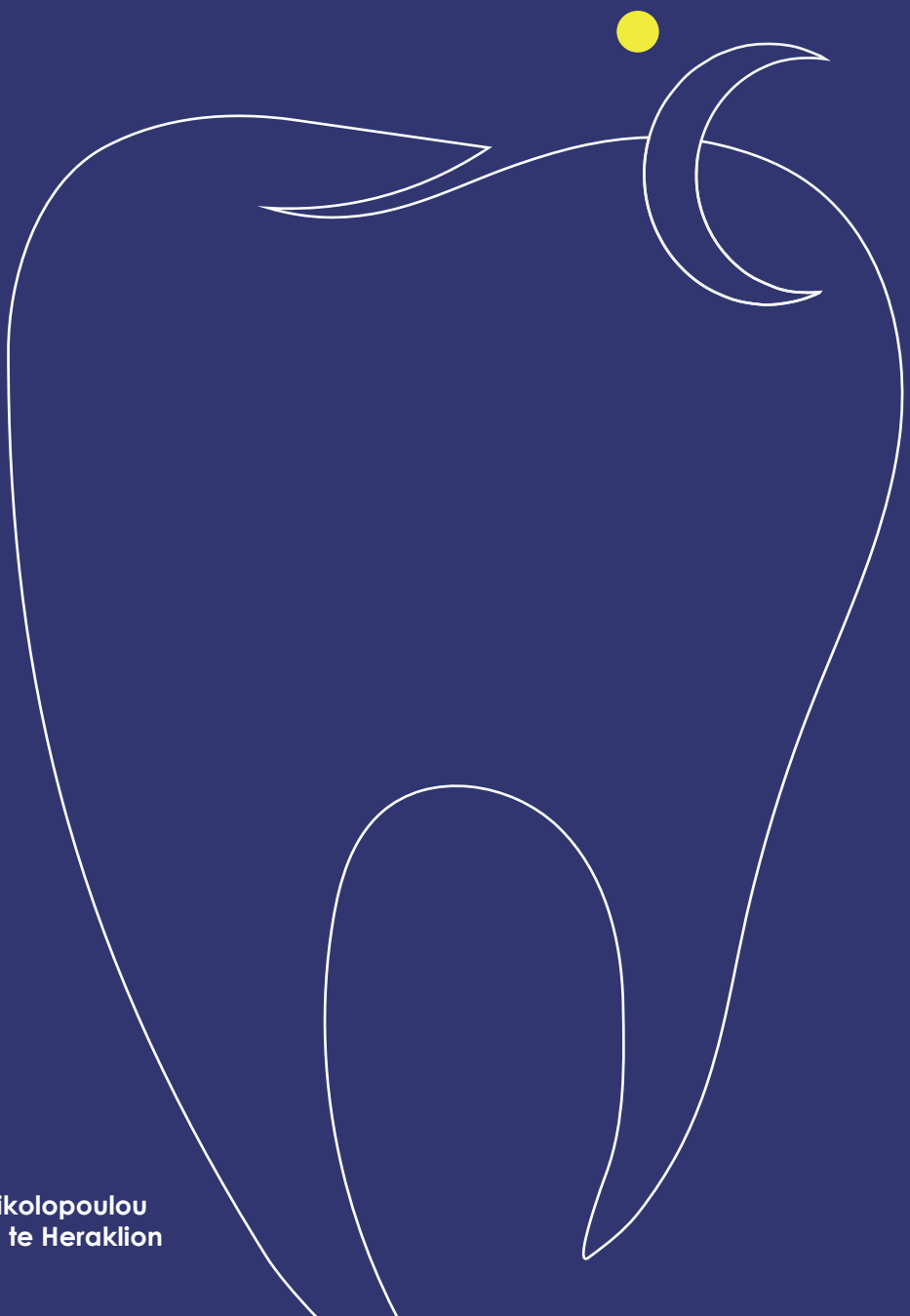

Maria Nikolopoulou
geboren te Heraklion

Oral appliance therapy in obstructive sleep apnea: therapeutic effects and side effects

Maria Nikolopoulou

Στα παιδιά μου, Φίλιππο κι Ευαγγελία

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Layout, cover illustration, and design by Vicky Katsamaka

Printed by: ProefschriftMaken|| www.proefschriftmaken.nl

ISBN/EAN: 978-94-6380-968-9

Oral appliance therapy in obstructive sleep apnea: therapeutic effects and side effects

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Agnietenkapel

op vrijdag 27 november 2020, te 13:00 uur

door Maria Nikolopoulou

geboren te Heraklion

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1

General Introduction

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is characterized by partial (i.e., hypopnea) or complete (i.e., apnea) repetitive obstructions of the upper airway, often resulting in oxygen desaturations and arousals from sleep (1). Current estimates of the prevalence of OSA in male and female adults aged 30–70 years are 14% and 5%, respectively, with prevalence rates increasing over the past decades due to increasing rates of obesity and ageing of the population (2). More recently, it was estimated that up to 49% of middle-aged men in the United States and Europe have clinically significant OSA (3). Of important notice is the finding of Simpson et al (4) that in the general population, approximately 80-90% of patients meeting the criteria of at least moderate OSA remain undiagnosed.

Hypoxemia/hypercapnia, fragmented sleep, as well as exaggerated fluctuations in heart rhythm, blood pressure, and intrathoracic pressure are some of the acute physiological effects of untreated OSA (5). In the long-term, these acute effects result in hypertension and other cardiovascular comorbidities (6, 2) decrements in cognitive function (7, 8), poor mood, reduced quality of life (9,10), and even premature death (11,12). Additionally, in the year 2000, more than 800,000 drivers were involved OSA-related motor-vehicle collisions, of which more than 1,400 fatalities occurred (13).

Diagnosis

For the objective assessment of OSA, polysomnography (PSG) is the current gold-standard approach. This technique requires, amongst others, physiologic measurements of brain activity during sleep (viz., electroencephalography, EEG) and measurements of the amount of airflow reductions and oxygen desaturations during sleep (14). PSG can be performed in a hospital-bound sleep laboratory or at the patient's own home, using ambulatory equipment. Based on this comprehensive diagnostic approach, OSA is diagnosed when the so called apnea-hypopnea index (AHI) has a value of at least 5 events/hour of sleep determined. The severity of this sleep-disordered breathing condition is classified as mild (AHI 5-15), moderate (AHI 15-30), and severe (AHI >30) (1).

Treatment options

Most common treatment strategies for OSA are behavioral therapies, such as weight loss, exercise, and alternation of sleeping position (15, 16), as well as alcohol avoidance and smoking cessation (17). Unfortunately, in most cases these conservative measures are not sufficiently effective to reduce OSA to clinically acceptable levels, let alone to cure the condition (e.g., 18).

Nowadays, positional therapy is widely used in adults with OSA (19). An average of 56 % of OSA patients have position-dependent OSA (POSA), commonly defined as supine to non-supine AHI ratio of ≥ 2 (20). During the past centuries, various techniques have been described to prevent patients from assuming the supine position, such as an upright sleep posture, positional alarms, verbal instructions, tennis balls sewed into the backside of a night suit, or special pillows (21). Most studies show that positional therapy is effective in reducing the AHI during short-term follow-up (22). Devices used in positional therapy are simple to use and usually affordable, for both patients and clinicians, and the strategy is reversible. However, their long-term compliance has been shown to be poor (23). Moreover, it has been shown that the patients who respond to positional therapy tend to be younger, have a milder form of OSA, and a lower BMI (24, 25). Surgery, as a treatment option for OSA, has been extensively reviewed and included in meta-analyses (26-33). Relevant surgical techniques include tongue suspension (28), maxillomandibular advancement (MMA) (30), pharyngeal surgeries (e.g., uvulopharyngopalatoplasty [UPPP]) (29), laser-assisted uvulopalatoplasty (LAUP) (29), radiofrequency ablation (RFA) (26), tracheostomy (27), nasal surgery (28), and glossectomy (32), as well as multi-level and multi-phased procedures. Hypoglossal nerve stimulation (HNS) is a relatively new method that works by electrically stimulating the hypoglossal nerve, a motor nerve innervating the protrusor and retractor muscle of the tongue (34). In obese patients, bariatric surgery is used for OSA treatment. The weight loss achieved by bariatric surgery is associated with significant long-term improvements in obstructive respiratory events and oxygenation (35). Unfortunately, surgery can be followed by severe complications in the peri- and post-operative period, including morbidity, bleedings, infections, and even difficulty in swallowing, including nasal regurgitation (36, 37). Moreover, there is a lack of clear benefit from surgery in the long-term (38). Front-line treatment of OSA relies on mechanically stabilizing the upper airway with a column of air via continuous positive airway pressure (CPAP) treatment. The air is generated by a pump and enters the upper airway via a hose and either a full-face mask or a nasal mask. The latter option is denoted as nasal CPAP (nCPAP). Although CPAP is the "gold standard" treatment for OSA, with proven efficacy and potential cost savings via decreases in health comorbidities and/or motor-vehicle crashes (13, 39), it is unfortunately not very well-tolerated by patients due to various side effects that severely hamper patients' compliance, such as air leakage, skin abrasions, dermatitis, dryness of the mouth and nose mucosa, pressure intolerance, and aerophagia (40, 41).

During the past decades, oral appliances have become a very popular treatment option for OSA. They enlarge the pharyngeal airway, directly by retaining the tongue, or indirectly by advancing the mandible. Another possible working mechanism is that the appliances may cause stretch-induced activation of the pharyngeal motor system, thereby reducing soft tissue laxity and airway collapse (42-44). The most frequently used oral appliances are the mandibular advancement devices (MADs), which protrude the

lower jaw and increase the vertical opening during sleep in order to reduce the airway obstruction. In the short-term, MAD therapy can cause excessive salivation, mouth dryness, tooth pain, gum irritation, headaches, temporomandibular joint discomfort, and morning-after occlusal changes (45). MAD therapy also produces long-term dental and skeletal side effects. Such are a reduction in overjet and overbite, a change in the upper incisor inclination, and a change in lower incisor inclination (46). Therefore, patients who receive MADs need to be monitored over time continuously. Despite these possible short-term and long-term side effects, compliance by OSA patients to MAD treatment is found to be higher as compared to CPAP (44, 47). Mandibular advancement devices are therefore recommended as a primary treatment in mild to moderate OSA patients (48-50).

Psychological distress symptoms

Depression has been reported to be the most common mood disorder associated with OSA. So far, it is unclear if depression in OSA is a consequence of OSA itself (i.e., due to the associated oxygen desaturations and/or arousals) or if it occurs secondary to OSA-related symptoms (e.g., sleepiness, sleep problems, irritability, social withdrawal) or to other factors related to OSA, such as obesity and hypertension. Interestingly, in support of the notion that depression occurs secondary to OSA-related symptoms rather than it being a primary consequence of OSA, the severity of depression and anxiety seems to correlate more with excessive daytime sleepiness than with hypoxemia (51). Specific attention should be paid to the evaluation of mood disorders in OSA, because some of the methods used (e.g., the Beck depression inventory (BDI), hospital anxiety and depression scale (HADS)) may in fact reflect sleep quality and daytime sleepiness rather than mood state (52, 53).

It has been suggested that both intermittent hypoxia and sleep disruption in OSA patients induce dysfunction of the prefrontal regions of the brain cortex, which may predispose to psychological distress (54). Therefore, the aim of the study in **Chapter 2** was to compare the effects of an objectively titrated MAD with those of nCPAP on symptoms of psychological distress in a randomized placebo-controlled trial, the primary outcomes of which have been published previously (49, 50). The hypothesis was that there is no significant difference between objectively titrated MAD and nCPAP therapies in improving psychological distress symptoms in mild/ moderate OSA patients.

Sleep-related complaints

OSA is associated with several other sleep disorders (e.g., insomnia, periodic limb movement disorder, sleep bruxism, and narcolepsy) and sleep-related problems (e.g.,

excessive daytime sleepiness) (55-57). When these disorders coexist, not only is there an increase in cumulative morbidity, but it has also been reported that they have a negative, deteriorating influence on each other (58). The presence of arousals during sleep and a reduced sleep efficiency may, at least in part, explain the overlap between OSA symptoms and symptoms of other common sleep-related disorders (58). Hence, it is important to encourage clinicians to look beyond the medical status of the OSA patient, thereby promoting earlier consideration and detection of other sleep disorders and sleep-related problems, when making treatment decisions. Likewise, it is important to get a deeper knowledge of the effects of MADs and nCPAP on sleep-related problems and other sleep disorders that are part of OSA's comorbidity network than only on the disorder for which these treatment options are intended, viz., OSA. Therefore, the aim of the study in **Chapter 3** was to compare the effects of MAD with those of nCPAP on self-reported symptoms of common sleep disorders and sleep-related problems in mild and moderate OSA patients in a randomized placebo-controlled trial, the primary outcomes of which have been published previously (49, 50).

TMD-related complaints

MAD therapy is sometimes associated with increased pain in the temporomandibular complex (59). Temporomandibular disorders (TMDs) is a collective term that embraces a number of clinical problems that involve the masticatory muscles, the TMJ, and the associated structures (60). TMDs have been identified as a major cause of non-dental pain in the orofacial region and are considered a subclassification of musculoskeletal disorders (61). Both a decrease (62) and an increase in signs and symptoms of TMD have been reported in association with the usage of an MAD (63-65), hence contradictory findings. Therefore, the aim of the study in **Chapter 4** was to compare the temporomandibular side effects of an MAD with those of nCPAP in mild to moderate OSA patients in a randomized, placebo-controlled trial, the primary outcomes of which have been published previously (49-50).

Raising the bite without protrusion

Occlusal stabilization splints (viz., hard acrylic resin dental appliances that cover the occlusal surfaces of the maxillary or mandibular dentition) cause a bite rise without a protrusive component. A previous open-label study suggested that a stabilization splint may decrease the airway patency during sleep in OSA patients (66). It is important to know if a bite raise without protrusion would change the respiratory disturbance. The aim of the study in **Chapter 5** of this thesis was to assess the influence of raising the bite without mandibular protrusion on respiratory variables in OSA patients, using

a placebo-controlled study design. It was hypothesized that raising the bite without mandibular protrusion in OSA patients is associated with an aggravation of the respiratory disturbance.

Occlusal stabilization splints

Everyday dental practice includes several procedures that raise the bite. Full-mouth dental rehabilitations and occlusal stabilization splints are examples of such procedures. Occlusal stabilization splints are commonly used to protect the teeth against the possible detrimental effects of sleep bruxism (notably tooth wear and dental restoration fracture/failure) and/or to manage TMD (67, 68). Sleep bruxism, which has recently been defined as a masticatory muscle activity during sleep that is characterized as rhythmic (phasic) or non-rhythmic (tonic) and is not a movement disorder or a sleep disorder in otherwise healthy individuals (69), has been shown to be part of complex arousal response of the central nervous system, which occurs during changes in sleep depth and is accompanied by, among others, body movements, increased heart rate, respiratory changes, and muscle activities (70). Despite the fact that occlusal stabilization splints are widely used, their mechanism of action in the management of sleep bruxism remains controversial (68), and so is their effectiveness in the management of TMDs (67).

Since dental practitioners need to be aware of all effects and side effects of the management strategies of their choice, it is of importance to know whether insertion of a stabilization splint can increase the AHI in OSA patients. Based on the previous work of Gagnon et al (66), such side effect could be expected to occur not only in patients with an OSA diagnosis, but also in those who have an undetected OSA (4). Therefore, the aim of the study in **Chapter 6** of this thesis was to determine the influence of occlusal stabilization splints on sleep-related respiratory variables in OSA patients. The hypothesis was that inserting an occlusal stabilization splint would increase the vertical dimension, rotate the mandible, cause a reduction of the tongue space, and by that means yield a significant worsening in the OSA condition.

Synopsis

The topic of this thesis is the therapeutic effects and side effects of mandibular advancement devices in OSA. The objectives of this thesis were:

1. To compare the effects of an MAD with those of nCPAP and an intra-oral placebo device on symptoms of psychological distress in mild to moderate OSA patients in a randomized placebo-controlled trial (**Chapter 2**).
2. To compare the effects of an MAD with those of nCPAP on self-reported symptoms of common sleep disorders and sleep-related problems in mild to moderate OSA patients in a randomized placebo-controlled trial (**Chapter 3**).
3. To compare the temporomandibular side effects of an MAD with those of nCPAP in mild to moderate OSA patients in a randomized placebo-controlled trial (**Chapter 4**).
4. To assess the influence of raising the bite without mandibular protrusion on respiratory variables in OSA patients (**Chapter 5**).
5. To assess the influence of occlusal stabilization splints on respiratory variables in OSA patients (**Chapter 6**).

References

1. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667-689.
2. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177:1006–1014.
3. Garvey JF, Pengo MF, Drakatos P, Kent BD. Epidemiological aspects of obstructive sleep apnea. J Thoracic Dis. 2015;7:920-929.
4. Simpson L, Hillman DR, Cooper MN, Ward KL, Hunter M, Cullen S, James A, Palmer LJ, Mukherjee S, Eastwood P. High prevalence of undiagnosed obstructive sleep apnoea in the general population and methods for screening for representative controls. Sleep Breath. 2013;17:967-973.
5. Somers VK, White DP, Amin R Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health) Circulation. 2008;118:1080–2011.
6. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA. 2003;290:1906–1914.
7. Kim HC, Young T, Matthews CG, Weber SM, Woodward AR, Palta M. Sleep-disordered breathing and neuropsychological deficits. A population-based study. Am J Respir Crit Care Med. 1997;156:1813–1819.
8. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, Ancoli-Israel S, Stone KL. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA. 2011;306:613–619.
9. Baldwin CM, Griffith KA, Nieto FJ, O'Connor GT, Walsleben JA, Redline S. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. Sleep. 2001;24:96–105.

10. Peppard PE, Szklo-Coxe M, Hla KM, Young T. Longitudinal association of sleep-related breathing disorder and depression. Arch Intern Med. 2006;166:1709–1715.
11. Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. Sleep. 2008;31: 1079–1085.
12. Young T, Finn L, Peppard PE Szklo-Coxe M, Austin D, Nieto FJ, Stubbs R, Hla KM. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep. 2008;31:1071–1078.
13. Sassani A, Findley LJ, Kryger M, Goldlust E, George C, Davidson TM. Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. Sleep. 2004;27:453–458.
14. Iber C, Ancoli-Israel S, Chesson AL. Jr, Quan SF for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 1st ed. Westchester, IL: American Academy of Sleep Medicine, 2007.
15. Hemmingsson E. Does medically induced weight loss improve obstructive sleep apnoea in the obese: review of randomized trials. Clin Obes. 2011;1:26–30.
16. Kulkas A, Leppanen T, Sahlman J, Tiihonen P, Mervaala E, Kokkarinen J, Randell J, Seppä J, Töyräs J, Tuomilehto H. Weight loss alters severity of individual nocturnal respiratory events depending on sleeping position. Physiol Meas. 2014;35:2037–2052.
17. Trenchea M, Deleanu O, Suta M, Arghir OC. Smoking, snoring and obstructive sleep apnea. Pneumologia.2013;62:52-55.
18. Barvaux VA, Aubert G, Rodenstein DO. Weight loss as a treatment for obstructive sleep apnoea. Sleep Med Rev. 2000;4:435-452.
19. Omobomi O, Quan SF. Positional therapy in the management of positional obstructive sleep apnea-a review of the current literature. Sleep Breath. 2018;22:297-304.
20. Raversloot MJL, van Maanen JP, Dun L, de Vries N. The undervalued potential of positional therapy in position-dependent snoring and obstructive sleep-apnoea- a review of the literature. Sleep Breath. 2013;17:39-49.
21. Randerath WJ, Verbraecken J, Andreas S, Bettega G, Boudewyns A, Hamans E, Jalbert F, Paoli JR, Sanner B, Smith I, Stuck BA, Lacassagne L, Marklund M, Maurer

JT, Pepin JL, Valipour A, Verse T, Fietze I. European Respiratory Society task force on non-CPAP therapies in sleep apnoea. Non-CPAP therapies in obstructive sleep apnoea. Eur Respir J. 2011;37:1000–1028.

22. de Vries GE, Hoekema A, Doff MHJ, Kerstjens HAM, Meijer PM, van der Hoeven JH, Wijkstra PJ. Usage of Positional Therapy in Adults with Obstructive Sleep Apnea. J Clin Sleep Med.2015.15; 11:131–137.
23. Loord H, Hultcrantz E. Positioner–a method for preventing sleep apnea. Acta Otolaryngol. 2007;127:861–868.
24. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. Chest. 1997;112:629–639.
25. Zuberi NA, Rekab K, Nguyen HV. Sleep apnea avoidance pillow effects on obstructive sleep apnea syndrome and snoring. Sleep Breath. 2004;8:201–217.
26. Caples SM, Rowley JA, Prinsell JR, Pallanch JF, Elamin MB, Katz SG, Harwick JD. Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis. Sleep. 2010;33:1396–1407.
27. Camacho M, Certal V, Brietzke SE, Holty JE, Guilleminault C, Capasso R. Tracheostomy as treatment for adult obstructive sleep apnea: a systematic review and meta-analysis. Laryngoscope. 2014;124:803–811.
28. Handler E, Hamans E, Goldberg AN, Mickelson S. Tongue suspension: an evidence-based review and comparison to hypopharyngeal surgery for OSA. Laryngoscope. 2014; 124:329–336.
29. Bostanci A, Turhan M. A systematic review of tongue base suspension techniques as an isolated procedure or combined with uvulopalatopharyngoplasty in obstructive sleep apnea. Eur Arch Otorhinolaryngol. 2016;273:2895-2901.
30. Camacho M, Teixeira J, Abdullatif J, Acevedo JL, Certal V, Capasso R, Powell NB. Maxillomandibular advancement and tracheostomy for morbidly obese obstructive sleep apnea: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2015;152:619–630.
31. Ishii L, Roxbury C, Godoy A, Ishman S, Ishii M. Does nasal surgery improve osa in patients with nasal obstruction and OSA? a meta-analysis. Otolaryngol Head Neck Surg. 2015; 153: 326–333.

32. Murphey AW, Kandl JA, Nguyen SA, Weber AC, Gillespie MB. The effect of glossectomy for obstructive sleep apnea: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2015; 153:334–342.
33. Smith DF, Cohen AP, Ishman SL. Surgical management of OSA in adults. Chest. 2015;147:1681-1690.
34. Eastwood PR, Barnes M, Walsh JH, Maddison KJ, Hee G, Schwartz AR, Smith PL, Malhotra A, McEvoy RD, Wheatley JR, O'Donoghue FJ, Rochford PD, Churchward T, Campbell MC, Palme CE, Robinson S, Goding GS, Eckert DJ, Jordan AS, Catcheside PG, Tyler L, Antic NA, Worsnop CJ, Kezirian EJ, Hillman DR. Treating obstructive sleep apnea with hypoglossal nerve stimulation. Sleep. 2011;34:1479–1486.
35. Fritscher, L.G., Canani, S., Mottin, C.C. et al, Bariatric surgery in the treatment of obstructive sleep apnea in morbidly obese patients. Respiration. 2007;74:647–652 .
36. Grøntved AM, Karup P. Complaints and satisfaction after uvulopalatopharyngoplasty. Acta Oto-laryngologica. 2000;543:190–192.
37. Kezirian EJ, Weaver EM, Yueh B, et al. Incidence of serious complications after uvulopalatopharyngoplasty. Laryngoscope. 2004;114:450–453.
38. Sundaram S, Lim J, Lasserson TJ. Surgery for obstructive sleep apnoea in adults. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD001004.
39. Weaver TE, Calik MW, Farabi SS, Fink AM, Galang-Boquiren MT, Kapella MC, Prasad B, Carley DW. Innovative treatments for adults with obstructive sleep apnea. Nat Sci Sleep. 2014;6:137–147.
40. Brostrom A, Arestedt KF, Nilsen P, Strömberg A, Ulander M, Svanborg E. The side effects to CPAP treatment inventory: the development and initial validation of a new tool for the measurement of side effects to CPAP treatment. J Sleep Res. 2010;19:603–611.
41. Weiss P, Kryger M. Positive Airway Pressure Therapy for Obstructive Sleep Apnea. Otolaryngol Clin North Am. 2016;49:1331-1341.
42. Tsuiki, S., Lowe, A. A., Almelda, F. R. and Fleetham, J. A. Effects of an anteriorly titrated mandibular position on awake airway and obstructive sleep apnea severity. Am. J. Orthod. Dentofacial. Orthop.2004,125:548–555.
43. Chan, A.S., Sutherland, K., Schwab, R.J. et al, The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. Thorax. 2010;65:726–732

44. Zhu Y, Long H, Jian F, Lin J, Zhu J, Gao M, Lai W. The effectiveness of oral appliances for obstructive sleep apnea syndrome: A meta-analysis. J Dent. 2015;43:1394–1402.
45. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. Sleep. 2006;29:244–262.
46. Alessandri-Bonetti G., D'Antò V, Stipa C, Rongo R, Incerti-Parenti S, Michelotti A. Dentoskeletal effects of oral appliance wear in obstructive sleep apnoea and snoring patients, *European Journal of Orthodontics*. 2017;39:482-488.
47. Sutherland K, Vanderveken OM, Tsuda H, Marklund M, Gagnadoux F, Kushida CA, Cistulli PA. Oral Appliance Treatment for Obstructive Sleep Apnea: An Update. J Clin Sleep Med. 2014;10:215-227.
48. Gagnadoux F, Fleury B, Vielle B, Petelle B, Meslier N, N'Guyen XL, Trzepizur W, Racineux JL. Titrated mandibular advancement versus positive airway pressure for sleep apnoea. Eur Respir J 2009;34:914-920.
49. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial. Respiration. 2011;81:411-419.
50. Aarab G, Lobbezoo F, Heymans MW, Hamburger HL, Naeije M. Long-term follow-up of a randomized controlled trial of oral appliance therapy in obstructive sleep apnea. Respiration. 2011;82:162-168.
51. Macey PA, Woo MA, Kumar R, Cross RL, Harper RM. Relationship between Obstructive Sleep Apnea Severity and Sleep, Depression and Anxiety Symptoms in Newly-Diagnosed Patients. PLoS One. 2010; 5:e10211.
52. Borak, J.K. Cieslicki, M. Koziej, A. Matuszewski, J. Zielinski. Effects of CPAP treatment on psychological status in patients with severe obstructive sleep apnoea J Sleep Res. 1996;5:123-127.
53. Ejaz SM, Khawaja IS, Bhatia S, Hurwitz TD. Obstructive sleep apnea and depression: a review. Innov Clin Neurosci. 2011;8:17–25.
54. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res. 2002;11:1-16.
55. Carelli G, Krieger J, Calvi-Gries F and Macher JP. Periodic limb movements and

obstructive sleep apneas before and after continuous airway pressure treatment. J Sleep Res. 1999;8:211-216.

56. Sansa G, Iranzo A and Santamaria J. Obstructive sleep apnea in narcolepsy. Sleep Med. 2010;11:93-95.
57. Al-Jawder Se and Bahammam AS. Comorbid insomnia in sleep-related breathing disorders: an under-recognized association. Sleep Breath. 2012;16:295-304.
58. Björnsdóttir E, Janson C, Sigurdsson JF, Gehrman P, Perlis M, Juliusson S, Arnardottir ES, Kuna ST, Pack AI, Gislason T, Benediktsdóttir B. Symptoms of insomnia among patients with obstructive sleep apnea before and after two years of positive airway treatment. Sleep. 2013;36:1901-1909.
59. Martinez-Gomis J, Willaert E, Nogues L, Pascual M, Somoza M, Monasterio C. Five years of sleep apnea treatment with a mandibular advancement device. Side effects and technical complications. Angle Orthod 2010;80:30–36.
60. de Leeuw R/ Klasser Gary D. (ed).Orofacial pain: guidelines for assessment, diagnosis and management. Quintessence, 6th edition.Chicago 2018.
61. Okeson JP. Bell's Orofacial Pain, ed 5. Chicago: Quintessence, 2005.
62. Giannasi LC, Almeida FR, Magini M, Costa MS, de Oliveira CS, de Oliveira JC. Systematic assessment of the impact of oral appliance therapy on the temporomandibular joint during treatment of obstructive sleep apnea: long-term evaluation. Sleep Breath 2009; 13:375–381.
63. Petit FX, Pépin JL, Bettega G, Sadek H, Raphaël B, Lévy P. Mandibular advancement devices: Rate of contraindications in 100 consecutive obstructive sleep apnea patients. Am J Respir Crit Care Med. 2002; 166:274–278.
64. Fransson AM, Tegelberg A, Leissner L, Wenneberg B, Isacsson G. Effects of a mandibular protruding device on the sleep of patients with obstructive sleep apnea and snoring problems: a 2-year follow-up. Sleep Breath. 2003;7:131-141.
65. Doff MH, Veldhuis SK, Hoekema A, Slater JJ, Wijkstra PJ, de Bont LG, Stegenga B. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on temporomandibular side effects. Clin Oral Investig. 2012; 16:689–697.
66. Gagnon Y, Mayer P, Morisson F, Rompre PH, Lavigne GJ. Aggravation of respiratory disturbances by the use of an occlusal splint in apneic patients: A pilot study. Int J Prosthodont. 2004;17:447-453.

67. Al-Ani Z, Gray RJ, Davies SJ, Sloan P, Glenny AM. Stabilization splint therapy for the treatment of temporomandibular myofascial pain: A systematic review. J Dent Educ 2005; 69:1242-1250.
68. Klasser GD, Greene CS, Lavigne GJ. Oral appliances and the management of sleep bruxism in adults: a century of clinical applications and search for mechanisms. Int J Prosthodont. 2010;23:453-462.
69. Lobbezoo F, Ahlberg J, Raphael KG, Wetselaar P, Glaros AG, Kato T, Santiago V, Winocur E, De Laat A, De Leeuw R, Koyano K, Lavigne GJ, Svensson P, Manfredini D. International consensus on the assessment of bruxism: Report of a work in progress. J Oral Rehabil. 2018;45:837-844.
70. Ahlberg J, Lobbezoo F, Ahlberg K, Manfredini D, Hublin C, Sinisalo J, Könönen M, Savolainen A. Self-reported bruxism mirrors anxiety and stress in adults.Med Oral Patol Oral Cir Bucal. 2013 1;18:e7-11.

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Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial on psychological distress

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Clin Oral Investig. 2017 Sep;21(7):2371-2378

Abstract

Background: To our best knowledge, no randomized placebo-controlled trials have been performed comparing the effects of an objectively titrated mandibular advancement device (MAD) and of nasal continuous positive airway pressure (nCPAP) on symptoms of psychological distress in obstructive sleep apnea (OSA) patients. **Objectives**: The aim of this randomized placebo-controlled trail was to compare the effects of an objectively titrated MAD with those of nCPAP and an intra-oral placebo device on symptoms of psychological distress in OSA patien-ts. **Methods**: In a parallel design, sixty-four mild/moderate OSA patients (52.0 ± 9.6 years) were randomly assigned to an objectively titrated MAD, nCPAP or an intra-oral placebo appliance. All patients filled out the Symptom Checklist-90-Revised twice: one before treatment and one after six months of treatment. The Symptom Checklist-90-Revised is a multidimensional symptom inventory designed to measure symptomatic psychological distress over the past week. Linear mixed model analyses were performed to study differences between the therapy groups for the different dimensions of the Symptom Checklist-90-Revised over time. **Results**: The MAD group showed significant improvements over time in the dimensions "somatization", "insufficiency of thinking and acting", "agoraphobia", "anxiety", "sleeping problems", and "global severity index" ($F = 4.14–16.73$, $P = 0.048–0.000$). These improvements in symptoms of psychological distress were, however, not significantly different from those observed in the nCPAP and placebo groups ($P = 0.374–0.953$). **Conclusion**: There is no significant difference between MAD, nCPAP, and an intra-oral placebo appliance in their beneficial effects on symptoms of psychological distress.

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent obstruction of the upper airway, often resulting in oxygen desaturation and arousal from sleep (1). Excessive daytime sleepiness, snoring, and reduction in cognitive functions are common symptoms of this condition (1). OSA patients may also report symptoms of psychological distress, such as depression and anxiety (2). Beebe and Gozal (3) suggested that both intermittent hypoxia and sleep disruption induce dysfunction of the prefrontal regions of the brain cortex, which may predispose to psychological distress.

Although continuous positive airway pressure (CPAP) has been proposed as the most effective treatment for severe OSA patients, nowadays mandibular advancement devices (MADs) are considered as a primary treatment option in mild and moderate OSA patients and in patients who do not tolerate CPAP (4). The rationale behind the efficacy of MADs is that advancement of the mandible and tongue improves upper airway patency during sleep by enlarging the upper airway and by decreasing upper airway collapsibility (5, 6).

Barnes et al. (7) compared the effects of MAD treatment with CPAP on mood disorders and depression in a randomized placebo-controlled crossover trial, and found no significant differences between these two therapies in their improvement of these disorders. Similar results were found by Engleman et al (8) in a randomized crossover trial in which the effects of CPAP and MAD treatment on anxiety and depression symptoms were compared. To our best knowledge, no randomized placebo-controlled trials have been performed comparing the effects of an objectively titrated MAD and CPAP on symptoms of psychological distress. To enable an unbiased comparison between those treatment modalities, both treatments should be titrated objectively. Further, the crossover design of previous studies may have a risk of carry-over effects. The primary aim of this randomized placebo-controlled trial was, therefore, to compare the effects of an objectively titrated MAD with those of nasal CPAP (nCPAP) and an intra-oral placebo appliance on symptoms of psychological distress in a parallel design. The hypothesis was that there is no significant difference between objectively titrated MAD and nCPAP therapies in improving psychological distress symptoms in mild/ moderate OSA patients. To control for possible placebo effects, an intra-oral placebo device served as passive control condition for both active treatment modalities. It was hypothesized that the intra-oral placebo appliance would not significantly improve psychological distress symptoms in mild/ moderate OSA patients. Following the hypothesis of Beebe and Gozal (3), we also hypothesized that a significant correlation between the amount of psychological distress and the apnea-hypopnea index (AHI) values in the three therapy groups would occur. Therefore, the secondary aims of this trial were: (1) to determine the relation between the amount of psychological distress and the AHI values at baseline

in the three therapy groups; and (2) to determine the relation between the amount of psychological distress at baseline and the change of AHI over time in the three therapy groups.

Patients and Methods

Setting and Participants

This study is part of a randomized controlled trial (RCT), in which three therapy groups (viz., MAD, nCPAP, and placebo) were compared (9). Eligible OSA patients, living in the greater Amsterdam area, were referred to the Slotervaart Medical Center by their family physician. All patients underwent a thorough medical examination, including a full polysomnographic (PSG) recording, at the departments of Neurology, Pulmonary Medicine, and ENT, as well as a thorough dental examination at the Department of Oral Kinesiology of the Academic Centre for Dentistry Amsterdam (ACTA). OSA patients were invited for participation in the study when they fulfilled the following inclusion criteria: age > 18 years, an apnea-hypopnea index (AHI) between 5 and 45 events per hour, and an Epworth Sleepiness Score(ESS) ≥ 10 or at least two of the symptoms suggested by the American Academy of Sleep Medicine Task Force, e.g., unrefreshing sleep and daytime fatigue (1, 10). The medical and dental exclusion criteria are shown in Table 1 (9). Exclusion of temporomandibular disorders was based on a functional examination of the masticatory system (11, 12).

The baseline characteristics of the patients at the time of therapy allocation are presented in Table 2. This study was approved by the Slotervaart Medical Center's Ethics Committee (# U/1731/0326, U/2679/0326). This study has been registered at *www.clinicaltrials.gov* (# NCT00950495).

Table 1. Number of patients excluded based on the medical and dental exclusion criteria used in this study.

Exclusion criteria	Number of patients excluded
Medical	
Respiratory /sleep disorder other than OSA	23
Body Mass Index > 40	3
Medication usage that could influence respiration or sleep	2
Periodic Limb Movement Disorder	21
Previous treatment with CPAP or MAD	-
Reversible morphological upper airway abnormalities (e.g., enlarged tonsils)	17
Other medical conditions (e.g., psychiatric disorder)	7
Dental	
Temporomandibular disorders	-
Untreated periodontal problems	1
Dental pain	-
Lack of retention possibilities for an oral appliance	28

Table 2. Patient characteristics (mean ± SD) at baseline of the mandibular advancement device (MAD) group, nasal continuous positive airway pressure (nCPAP) group, placebo group, and drop-outs group and the normal values in the healthy Dutch population for the various dimensions of the Symptom Checklist-90-Revised (SCL-90-R).

	MAD (n = 21)	nCPAP (n = 22)	Placebo (n = 21)	Drop-outs (n = 7)	Normal values of Dutch healthy population (n = 1004)
Age (years)	50.4 ± 8.9	54.0 ± 10.1	51.3 ± 9.6	49.3 ± 7.3	–
Number of man/ woman	17/ 4	15/ 7	15/ 6	5/2	–
Apnea-hypopnea index	21.4 ± 11.0	20.1 ± 9.0	19.5 ± 8.4	14.8 ± 3.8	–
Epworth sleepiness score	12.0 ± 5.7	10.7 ± 4.4	10.8 ± 4.0	13.7 ± 1.9	–
Body mass index (kg/m2)a SCL-90-R	27.1 ± 3.2	30.7 ± 3.7	31.1 ± 4.7	27.8 ± 4.1	–
Somatization	22.0 ± 10.3	24.6 ± 11.9	21.9 ± 10.8	24.3 ± 10.3	16.7 ± 5.3***
Insufficiency of thinking and acting	18.3 ± 7.6	18.7 ± 9.6	19.9 ± 9.5	19.0 ± 6.7	12.6 ± 4.3***
Interpersonal sensitivity	27.6 ± 10.4	26.9 ± 14.5	28.5 ± 17.7	26.3 ± 8.5	24.1 ± 7.6
Depression	26.3 ± 11.8	28.5 ± 15.3	30.5 ± 17.5	30.3 ± 15.8	21.6 ± 7.6***
Anxiety	14.9 ± 6.5	16.9 ± 9.6	15.6 ± 9.7	14.8 ± 5.6	12.8 ± 4.4*
Hostility	8.8 ± 3.7	9.2 ± 3.8	8.6 ± 4.6	8.8 ± 1.9	7.2 ± 2.1**
Agoraphobia	8.7 ± 3.0	9.3 ± 5.1	9.2 ± 6.7	7.5 ± 1.0	7.9 ± 2.3
Sleeping problems	7.6 ± 3.6	7.2 ± 3.8	8.4 ± 4.3	10.4 ± 4.6	4.5 ± 2.2***
Global severity index	149.3 ± 60.3	144.9 ± 68.1	162.0 ± 90.7	118.0 ± 38.2	118.3 ± 32.4*

P values as result of the one-sample *t* tests comparing the three therapy groups and the normal values in Dutch healthy population for the various dimensions of the SCL-90-R: ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$

[a]MAD patients had a significantly lower BMI than placebo and nCPAP patients ($P = 0.002$ and 0.006, respectively)

Randomization and Interventions

At the start of this RCT, consenting patients were allocated to the interventions using block randomization. The allocation sequence was automatically generated and concealed by an independent co-worker. Three types of interventions were used in this parallel-group study. First, an individually fabricated MAD with an adjustable mandibular protrusion position at a constant vertical dimension was used (13, 14). Second, nCPAP of the REMstar Pro system was used (Respironics, Herrsching, Germany). Third, a thin (< 1 mm), hard acrylic-resin palatal splint with only a partial palatal coverage was used as a placebo (15).

Both MAD and nCPAP were titrated before the start of the treatment (9). For the titration of the MAD, four ambulatory polysomnographic (PSG) recordings were performed at regular time intervals of approx. 3 weeks. The total titration period was approx. 10 weeks. The most effective protrusion position of the MAD (i.e., the mandibular position that yielded the lowest AHI value) was chosen from among four randomly offered positions (viz., 0%, 25%, 50%, and 75% of the maximum protrusion). The MAD was set at 25% of the maximum protrusion in one patient, at 50% in 7 patients, and at 75% in 12 patients (9). For the placebo group, four ambulatory PSG recordings were performed at regular time intervals similar to the MAD group (16). The titration of nCPAP was performed during a PSG recording at the Slotervaart Medical Center. The pressure was increased in steps of 1 cm H2O/h, until the AHI and respiration-related arousals were reduced to ≤ 5/h, and snoring was minimized. The average value of the pressure was 7.3 (SD, 1.9; range, 4-11) cm H2O (9).

Procedure

During the titration period of approx. 10 weeks, all patients visited ACTA four times at regular intervals, during which the BMI (kg/m2) was determined and the Epworth Sleepiness Scale (ESS) (10) was completed. The participants were also interviewed 1. about their compliance (% of nights per week of wearing), 2. about possible side effects (nature and number; determined in an open question) of the MAD during the study period, and 3. about the change (increased, unchanged, or decreased) in snoring intensity, based on information they obtained from their bed partner. These outcomes have been described in detail in Aarab *et al*. (13) and Aarab *et al*. (9).

From all patients, two PSG recordings were obtained in the sleep laboratory of the Slotervaart Medical Center: the first one before treatment and the second one after 6 ± 2 months (mean ± SD) for the therapy evaluation. The outcomes of these PSG recordings are also described in detail in Aarab *et al*. (9).

All patients filled out the Dutch version of the Symptom Checklist-90-Revised (SCL-90-R) twice: the first one before treatment and the second one at therapy evaluation. The

SCL-90-R is a multidimensional symptom inventory designed to measure symptomatic psychological distress over the past week (e.g., depression, anxiety, and somatization). Its reliability and validity proved to be good for both the original and the Dutch version (17, 18). Moreover, norm scores are available for the Dutch general population (17).

Data Analysis

The patient characteristics of the three therapy groups at baseline, including the different dimensions of the SCL-90-R, were compared using one-way analyses of variance, followed by least-significant difference (LSD) pair-wise comparisons. One-way analyses of variance was also used to detect differences in compliance between the three therapy groups (9). For the different dimensions of the SCL-90-R, one sample t-tests were used to analyse differences between outcomes related to the therapy groups and the normal values of the Dutch population, and model assumptions were checked. For both the per-protocol analysis and the intention-to-treat analysis, linear mixed models were used to study the differences between the groups for the different dimensions of the SCL-90-R over time. In these models, the treatment group variable was introduced as a dummy variable with the MAD group as reference group. The difference between treatment groups over time was studied by an interaction term of treatment times the time variable. Pearson correlation was used to test the relation between AHI values and the different dimensions of the SCL-90-R.

All statistical tests were performed with the SPSS 21.0 (SPSS Inc., Chicago, IL) and SAS 9.3 (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA) software packages.

Results

A total of 64 patients were enrolled in the study, and were randomized at the start of the RCT as shown in Fig. 1 (9). Three patients in the nCPAP group terminated the treatment before evaluation, because they experienced more side effects than benefits out of their treatment. One patient in the placebo group terminated the treatment, because of private reasons unrelated to the study. Another patient in the placebo group did not receive the placebo treatment, because of an urgent medical condition that occurred after the allocation. Two other patients, one in the nCPAP group and another in the MAD group could not be reached after the at random allocation, and could thus not be evaluated. Hence, 57 patients completed the entire study protocol.

The patient characteristics at baseline are presented in Table 2. BMI was the only baseline characteristic that differed between the three therapy groups ($F = 5.170$; $P = 0.008$). LSD analyses revealed that the MAD group had a significantly lower BMI than the placebo and nCPAP groups ($P = 0.002$ and 0.006, respectively) (9). The mean ($\pm$ SD) baseline values

of the different dimensions of the SCL-90-R of the three therapy groups, of the drop-outs, and of the normal values of the Dutch healthy population are also shown in Table 2. The baseline values of the different dimensions did not differ significantly between the three therapy groups ($P = 0.305 – 0.987$; Table 2). Further, the baseline values of the SCL-90-R of the drop-outs were not different from those of the therapy groups either ($P = 0.348$-0.997). The three groups showed higher average values of psychological distress at baseline than the reported normal values for the Dutch population in the dimensions "somatization", "insufficiency of thinking and acting", "anxiety", "hostility", "depression", "sleeping problems", and "global severity index" ($T = 6,357$- 2.566; $P = 0.000$-0.013; Table 2).

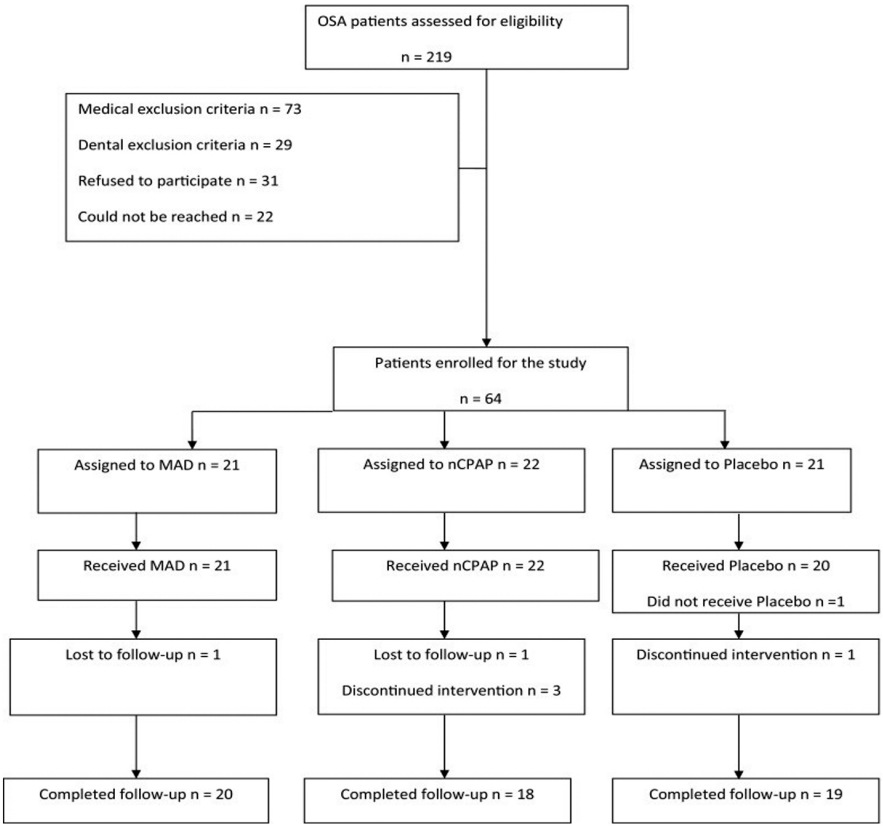

Fig. 1. Flow-chart of the patients through each stage of the trial. MAD = mandibular advancement device; nCPAP = nasal continuous positive airway pressure.

The mean (± SD) baseline values of the different dimensions of the SCL-90-R of the three therapy groups who completed the entire study protocol as well as the changes in these variables from baseline to therapy evaluation are shown in Table 3. As a result of missing values in the different dimensions of the SCL-90-R per therapy group, the number of observations used in the per-protocol analyses varied per dimension (see Table 3). The MAD group showed significant improvements over time in the dimensions "somatization", "insufficiency of thinking and acting", "agoraphobia", "anxiety", "sleeping problems", and the "global severity index" (F = 4.01–15.47, *P* = 0.048–0.000, Table 3). These improvements in symptoms were, however, not significantly different from the improvements in symptoms observed in the nCPAP and placebo groups (*P* = 0.374–0.953). The intention-to-treat analysis showed similar results as the per-protocol analyses: the MAD group showed significant improvements over time in the dimensions "somatization", "insufficiency of thinking and acting", "agoraphobia", "anxiety", "sleeping problems", and the "global severity index" as well (F = 4.01–16.34, *P* = 0.025–0.000), while these improvements were not significantly different from those observed in the nCPAP and placebo groups (*P* = 0.175–0.950).

The MAD group had used their appliance 90.6% (SD, 13.3) of the nights; the nCPAP group 82.9% (SD, 27.2) of the nights; and the placebo group 93.9% (SD, 15.7) of the nights. No significant group differences in compliance were found (F= 1.518, *P* = 0.228) (9).

There was no significant correlation between the baseline AHI value and the baseline values of the different dimensions of the SCL-90-R in the three groups (*P* = 0.121-0.888). A significant correlation was found between the baseline values of the "global severity index" and the changes in AHI values (ΔAHI) between baseline and therapy evaluation in both the MAD and nCPAP group (*P* = 0.025). Patients with higher values of the "global severity index" at baseline showed less reduction in the AHI than patients with lower values of this index at baseline (Fig. 2). In the placebo group, there was no significant correlation between "ΔAHI" and the baseline values of "global severity index" (*P* = 0.615).

Table 3. The mean (±SD) baseline and therapy evaluation values of the different dimensions of the Symptom Checklist-90-Revised (SCL-90-R) of the mandibular advancement device (MAD) group, nasal continuous positive airway pressure (nCPAP) group, and placebo group in the per-protocol analyses.

Dimension (number of observations used)	MAD (n = 20)		P*	nCPAP (n = 18)		Placebo (n = 19)		P*
	Baseline	Therapy		Baseline	Therapy	Baseline	Therapy	
Somatization (*n* = 107)	22.0 ± 10.3	17.7 ± 5.5	0.000**	24.6 ± 11.9	21.3 ± 11.5	21.9 ± 10.8	17.9 ± 7.9	0.374
Insufficiency of thinking and acting* (*n* = 104)	18.3 ± 7.6	15.8 ± 5.7	0.003**	18.7 ± 9.6	17.7 ± 10.0	19.9 ± 9.5	16.3 ± 8.1	0.646
Interpersonal sensitivity (*n* = 102)	27.6 ± 10.4	25.3 ± 8.4	0.206	26.9 ± 14.5	27.3 ± 14.8	28.5 ± 17.7	25.4 ± 15.4	0.953
Depression (*n* = 96)	26.3 ± 11.8	24.0 ± 7.1	0.056	28.5 ± 15.3	25.4 ± 16.4	30.5 ± 17.5	23.8 ± 6.5	0.445
Anxiety (*n* = 104)	14.9 ± 6.5	12.9 ± 4.2	0.033**	16.9 ± 9.6	15.2 ± 9.1	15.6 ± 9.7	14.1 ± 6.8	0.573
Hostility (*n* = 106)	8.8 ± 3.7	8.7 ± 3.3	0.437	9.2 ± 3.8	8.9 ± 3.8	8.6 ± 4.6	7.5 ± 2.6	0.521
Agoraphobia (*n* = 103)	8.7 ± 3.0	7.7 ± 1.1	0.028**	9.3 ± 5.1	7.8 ± 1.9	9.2 ± 6.7	8.9 ± 5.5	0.479
Sleeping problems (*n* = 106)	7.6 ± 3.6	6.3 ± 3.0	0.048**	7.2 ± 3.8	6.1 ± 2.5	8.4 ± 4.3	7.4 ± 3.3	0.792
Global severity index (*n* = 85)	149.3 ± 60.3	132.9 ± 38.2	0.018**	144.9 ± 68.1	137.7 ± 66.2	162.0 ± 90.7	124.1 ± 24.0	0.387

**P* value as result of the linear mixed model analyses for the time effect within the MAD group

***Statistically significant at the 0.05 probability level

****P* value as result of the linear mixed model analyses comparing the three groups over time

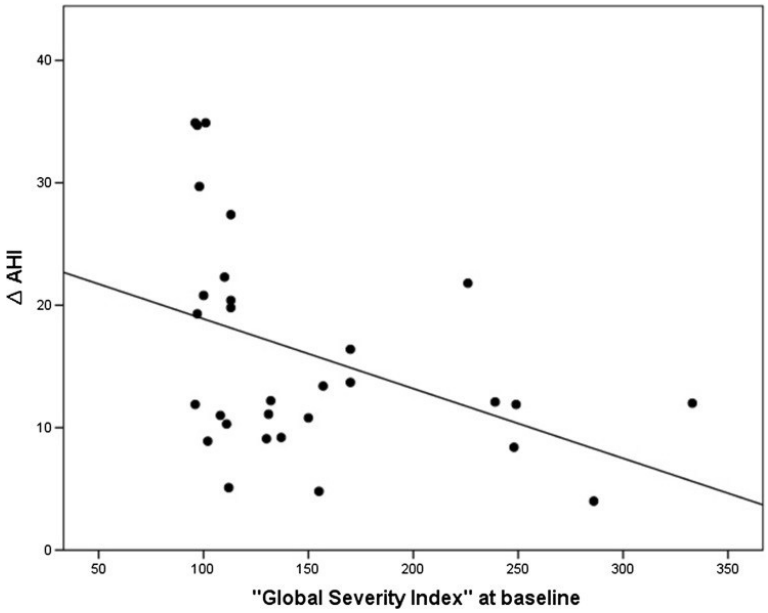

Fig. 2. Scatterplot of the correlation between the baseline values of the "global severity index" and the changes in AHI values between baseline and therapy evaluation (ΔAHI) in both the MAD and nCPAP groups.

Discussion

Both MAD and nCPAP showed significant improvements of symptoms of psychological distress after 6 months of treatment. However, these significant improvements were not different from those observed in the placebo group.

In randomized clinical trials, there are often problems of noncompliance, where the patient does not adhere to the assigned treatment or does not complete questionnaires as we also observed in this study. Typically, this leads to estimates that can potentially be biased when the probability of a missing value is related to the characteristics of the patients. Further, missing data can also lead to a reduction of statistical power (19). To overcome this problem, linear mixed model analysis can be used. The major strengths of mixed models are their ability to accommodate missing data points often encountered in longitudinal datasets and to generate valid study results (20). Therefore, we used linear mixed model analyses in this study.

The population in the present study showed higher average values of psychological distress at baseline than the reported normal values for the Dutch population. The relationship between OSA and psychiatric disorders, especially depression, has already been studied for decades (21). Pillar and Lavie (22) reported in their male population that neither the presence nor the severity of OSA was associated with depression or anxiety.

On the other hand, recent evidence has confirmed important connections between OSA and psychiatric disorders. Psychiatric co-morbidity in OSA patients was examined in a large retrospective chart review of more than 100,000 Veterans. A significantly higher prevalence of numerous psychiatric disorders, including depression and anxiety, was found in OSA patients as compared to non-OSA patients (23). Others reported depression symptoms in 17-41% of OSA patients (24, 25). Harris et al. (2) suggested that direct treatment of depression in OSA patients might improve acceptance of therapy, reduce sleepiness and fatigue, and improve quality of life, but that intervention trials are needed to answer this question. Although the causal relationship between symptoms of psychological distress and OSA has not been determined yet, a higher prevalence of these symptoms in OSA patient seems to be a consistent finding, which corresponds with our results.

All patients who completed the trial showed relatively high compliance rates of approx. 90% (i.e., the percentage of nights per week usage). This relatively high compliance may be explained by the fact that during the study period the patients frequently visited ACTA to be interviewed about the frequency of wearing. This regular contact with the examiner could have motivated the patients to use their appliances frequently (9). Although self-reported compliance has been suggested to overestimate the actual use of MADs, covert compliance monitoring has shown excellent agreement between subjective and objective compliance (26, 27).

The MAD effects on the OSA condition have been compared with those of CPAP in several randomized clinical trials (4). Although in most previous cross-over studies MADs were considered less effective in reducing the AHI value than CPAP in mild-to -moderate OSA patients, similar improvements in subjective outcomes, such as excessive daytime sleepiness and quality of life, were found (8, 28-30). Further, it should be noted that these studies also indicated that, in general, patients find MADs a more acceptable treatment compared to CPAP. In recent RCTs with a parallel design, no significant differences between MAD and nCPAP were reported, neither in the respiratory outcomes, nor in the subjective outcomes (9, 31). Further, a recent cross-over study by Phillips et al. (32) showed that important health outcomes were similar after one month of optimal MAD and CPAP treatment in patients with moderate to severe OSA. Thus, the outcomes of our study are in line with previous studies wherein both MAD and nCPAP show comparable treatment results in a group of mild-to-moderate OSA patients. Beebe and Gozal (3) suggested that both intermittent hypoxia and sleep disruption induce dysfunction of the prefrontal regions of the brain cortex, which may predispose to mood disorders. Following this hypothesis, at baseline, we suspected a significant correlation between the amount of psychological distress and the AHI values. However, we did not find this correlation. On the other hand, OSA patients with higher values of the psychological distress at baseline showed less reduction in the AHI than patients with lower values of

this index at baseline. The nature of this association is unclear, but this finding suggests that the level of psychological distress at the start of the treatment may play a significant role in the treatment outcome.

In this study, the significant improvements in symptoms of psychological distress in the MAD and nCPAP groups were not better than those observed in the placebo group. This is in line with our previous findings wherein we reported significant improvements in the Epworth Sleepiness Scale (ESS) and the Short-Form General Health Survey (SF-36) in all three groups without any differences in effects between the three therapy groups (9). Power calculation was performed for the primary outcome variable of this randomized placebo-controlled trial, viz., the AHI (9). No power calculations were performed for the secondary outcome variables (viz., ESS, SF-36, and SCL-90-R). Therefore, our sample size per therapy group may have not been sufficient to find a significant difference between the therapy groups in the change of the different dimensions of SCL-90-R. However, our findings correspond with many previous, well-designed studies (7, 28, 33, 34) in which it was also reported that most of their OSA patients obtained a significant benefit in neuropsychological function and mood from their placebo treatment compared to MAD and CPAP treatments. These observed improvements in symptoms of psychological distress may be due to extensive attention given to the patients during the entire protocol, to a change in life style as a result of the information given to the patients at baseline, and/or to a placebo response. Further, the high initial values of the SLC-90-R scores at baseline result in a higher possibility of decreases in these scores over time. The tendency of high values to return towards an individual's more typical average state is known as "regression to the mean". Stepnowsky et al. (35) reported in a recent study that baseline emotional distress predicted the drop in AHI in response to placebo treatment. Highly distressed patients showed a greater placebo response with a 34% drop in AHI. Although we could not confirm this in our study, all these findings together support the importance of including a placebo treatment in a randomized controlled trial design to determine unbiased treatment effects.

Within the limits of this study, it can be concluded that there is no significant difference between MAD, nCPAP, and an intraoral placebo appliance in their beneficial effects on symptoms of psychological distress in mild to moderate OSA patients. Further, this study suggests that the level of psychological distress at the start of the treatment may play a significant role in the treatment outcome of MAD and nCPAP in a group of mild to moderate OSA patients.

References

1. American Academy of Sleep Medicine Task Force: Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667-689.
2. Harris M, Glozier N, Ratnavadivel R, Grunstein RR: Obstructive sleep apnea and depression. Sleep Med Rev 2009;13:437-444.
3. Beebe DW, Gozal D: Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res 2002;11:1-16.
4. Marklund M, Verbraecken J, Randerath W: Non-CPAP therapies in obstructive sleep apnoea: mandibular advancement device therapy. Eur Respir J 2012;39:1241-1247.
5. Schmidt-Nowara WW, Meade TE, Hays MB: Treatment of snoring and obstructive sleep apnea with a dental orthosis. Chest 1991:99:1378-1385.
6. Ng AT, Gotsopoulos H, Qian J, Cistulli PA: Effect of oral appliance therapy on upper airway collapsibility in obstructive sleep apnea. Am J Respir Crit Care Med 2003; 168:238-241.
7. Barnes M, Houston D, Worsnop CJ, Neill AM, Mykytyn IJ, Kay A, Trinder J, Saunders NA, Douglas McEvoy R, Pierce RJ: A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. Am J Respir Crit Care Med 2002;165:773-780.
8. Engleman HM, McDonald JP, Graham D, Lello GE, Kingshott RN, Coleman EL, Mackay TW, Douglas NJ: Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. Am J Respir Crit Care Med 2002;166:855-859.
9. Aarab G, Lobbezoo F, Hamburger HL, Naeije M: Oral appliance therapy in obstructive sleep apnea: a randomized, placebo-controlled trail. Respiration 2011;81:411-419.
10. Johns MW. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep 1991;14:540-545.
11. Dworkin SF, LeResche L: Research diagnostic criteria for temporomandibular dis-

orders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301-355.

12. Lobbezoo F, van Selms MK, John MT, Huggins K, Ohrbach R, Visscher CM, van der Zaag J, van der Meulen MJ, Naeije M, Dworkin SF: Use of the Research Diagnostic Criteria for Temporomandibular Disorders for multinational research: translation efforts and reliability assessments in The Netherlands. J Orofac Pain 2005;19:301-308.
13. Aarab G, Lobbezoo F, Hamburger HL, Naeije M: Effects of an oral appliance with different mandibular protrusion positions at a constant vertical dimension on obstructive sleep apnoea. Clin Oral Invest 2010;14:339-345.
14. Aarab G, Lobbezoo F, Wicks DJ, Hamburger HL, Naeije M: Short-term effects of a mandibular advancement device on obstructive sleep apnoea: an open-label pilot trial. J Oral Rehabil 2005;32:564-570.
15. van der Zaag J, Lobbezoo F, Wicks DJ, Visscher CM, Hamburger HL, Naeije M: Controlled assessment of the efficacy of occlusal stabilization splints on sleep bruxism. J Orofac Pain 2005;19:151-158.
16. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Variability in the apnea-hypopnea index and its consequences for diagnosis and therapy evaluation. Respiration 2009;77:32-37.
17. Arrindell, W.A.and Ettema: J.H.M. Handleiding van de SCL-90. Lisse: Swets & Zeitlinger, 1986.
18. Derogatis LR: SCL-90: administration, scoring and procedures manual-I for the (revised) version. Baltimore, MD: Clinical Psychometrics Research, 1977.
19. Schafer JI: Analysis of Incomplete Multivariate Data. London: Chapman and Hall, 1997.
20. Twisk J, de Boer M, de Vente W, Heymans M:Multiple imputation of missing values was not necessary before performing a longitudinal mixed-model analysis. J Clin Epidemiol 2013;66:1022-1028.
21. Sateia MJ: Update on sleep and psychiatric disorders. Chest, 2009, 135: 1370-1379.
22. Pillar G, Lavie P: Psychiatric symptoms in sleep apnea syndrome: effects of gender and respiratory disturbance index. Chest 1998;114:697-703.

23. Sharafkhaneh A, Giray N, Richardson P, Young T, Hirshkowitz M: Association of psychiatric disorders and sleep apnea in a large cohort. Sleep 2005;28:1405-1411.
24. Ohayon MM: The effects of breathing-related sleep disorders on mood disturbances in the general population. J Clin Psychiatry 2003;64:1195-2000.
25. Vandeputte M, de Weerd A: Sleep disorders and depressive feelings: a global survey with the Beck depression scale. Sleep Med 2003;4:343-345.
26. Lowe AA, Sjöholm TT, Ryan CF, Fleetham JA, Ferguson KA, Remmers JE: Treatment, airway and compliance effects of a titratable oral appliance. Sleep 2000; 23: Suppl 4:S172-8.
27. Dieltjens M, Braem MJ, Vroegop AV, Wouters K, Verbraecken JA, De Backer WA, Van de Heyning PH, Vanderveken OM: Objectively measured vs self-reported compliance during oral appliance therapy for sleep-disordered breathing. Chest 2013;144:1495-1502.
28. Barnes M, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, Pierce RJ: Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med 2004;170:656-664.
29. Randerath WJ, Heise M, Hinz R, Ruehle KH: An individually adjustable oral appliance vs continuous positive airway pressure in mild-to-moderate obstructive sleep apnea syndrome. Chest 2002;122:569-575.
30. Clark GT, Arand D, Chung E, Tong D: Effect of anterior mandibular positioning on obstructive sleep apnea. Am Rev Respir Dis 1993;147:624-629.
31. Doff MH, Hoekema A, Wijkstra PJ, van der Hoeven JH, Huddleston Slater JJ, de Bont LG, Stegenga B: Oral appliance versus continuous positive airway pressure in obstructive sleep apnea syndrome: a 2-year follow-up. Sleep 2013;36:1289-1296.
32. Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, Marks GB, Cistulli PA: 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.
33. Naismith SL, Winter VR, Hickie IB, Cistulli PA: Effect of oral appliance therapy on neurobehavioral functioning in obstructive sleep apnea: a randomized controlled trial. J Clin Sleep Med 2005;1:374-380.
34. Marshall NS, Neill AM, Campbell AJ, Sheppard DS: Randomised controlled cross-

over trial of humidified continuous positive airway pressure in mild obstructive sleep apnoea. Thorax 2005;60:427-432.

35. Stepnowsky CJ, Mao WC, Bardwell WA, Loredo JS, Dimsdale JE: Mood Predicts Response to Placebo CPAP. Sleep Disord DOI: 10.1155/2012/404196.

3

Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial on self-reported symptoms of common sleep disorders and sleep-related problems

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J Oral Rehabil. 2017 Jun;44(6):452-460

Abstract

Background: Obstructive sleep apnea (OSA) is associated with several common sleep disorders and sleep-related problems. The aim of this study was to compare the effects of a mandibular advancement device (MAD) with those of nasal continuous positive airway pressure (nCPAP) on self- reported symptoms of common sleep disorders and sleep-related problems in mild and moderate OSA patients. **Methods**: This study is part of a randomized placebo-controlled trial in which different treatment effects of an objectively titrated MAD are compared with those of nCPAP and an intra-oral placebo appliance in a parallel design. Sixty-four mild/moderate OSA patients (52.0± 9.6 years) were randomly assigned to these three groups. All participants filled out the validated Dutch Sleep Disorders Questionnaire (SDQ) twice: one before treatment and one after six months of treatment. With 88 questions, thirteen scales were constructed, representing common sleep disorders and sleep-related problems. Linear mixed model analyses were performed to study differences between the groups for the different SDQ scales over time. **Results**: The MAD group showed significant improvements over time in symptoms corresponding with "insomnia", "excessive daytime sleepiness", "psychiatric sleep disorder", "periodic limb movements", "sleep apnea", "sleep paralysis", "daytime dysfunction", "hypnagogic hallucinations/dreaming", "restless sleep", "negative conditioning", and "automatic behaviour" ($F = 31.34\text{-}6.50$, $P = 0.000\text{-}0.014$). These improvements in symptoms were, however, not significantly different from the improvements in symptoms observed in the nCPAP and placebo groups ($P = 0.090\text{-}0.897$). **Conclusion**: Within the limits of this study, it can be concluded that there is no significant difference between MAD, and nCPAP in their positive effects on self-reported symptoms of common sleep disorders and sleep-related problems in mild and moderate OSA patients. These beneficial effects may be a result of the time course and/or of placebo effects.

Background

Obstructive sleep apnea (OSA) is characterized by recurrent obstructions of the upper airway, often resulting in oxygen desaturations and arousals from sleep (1). These sleep-related events lead to poor sleep quality, excessive daytime sleepiness, and reduced quality of life. Further, OSA patients without effective treatment have an increased risk of hypertension, stroke, heart failure, and atrial fibrillation (2, 3). There are many predisposing risk factors for OSA, including obesity, male gender, and ageing (4). OSA is a common sleep-related breathing disorder, affecting 10-17% of middle aged men and 3-9% of middle- aged women (5). The gold standard therapy for especially severe OSA is nasal continuous positive airway pressure (nCPAP; 6). In mild to moderate OSA patients, a mandibular advancement device (MAD) therapy is often recommended as a primary treatment option (7, 8). This oral appliance holds the mandible and tongue in a protruded position. This results in an upper respiratory tract widening and/or a reduced collapsibility of the upper airway (9).

OSA is associated with several other sleep disorders (e.g., insomnia, periodic limb movement disorder, and narcolepsy) and sleep-related problems (e.g., excessive daytime sleepiness) (10-12). When these disorders coexist, not only is there an increase in cumulative morbidity, but it is likely that they influence each other in negative ways (13). Further, the co-occurrence of OSA and other sleep disorders may complicate OSA treatment and reduce treatment adherence (13). The presence of arousals during sleep and a reduced sleep efficiency may explain the overlap between OSA symptoms and symptoms of other common sleep-related disorders (13).

A few studies showed that nCPAP had a positive effect on middle insomnia and on periodic limb movement disorder in OSA patients (13-15). In a randomized controlled trial, Marklund et al. (16) found no improvement in insomnia symptoms in OSA patients under MAD treatment. However, they found a significant improvement in periodic limb movements with MAD is situ. To our best knowledge, no randomized placebo-controlled trials have been conducted comparing the effects of an objectively titrated MAD with those of nCPAP on self-reported symptoms of common sleep disorders and sleep-related problems in OSA patients. To enable an unbiased comparison between those treatment modalities, both treatments should be titrated objectively. The aim of this randomized placebo-controlled trial was, therefore, to compare the effects of an objectively titrated MAD with those of nasal CPAP (nCPAP) and an intra-oral placebo appliance on self-reported symptoms of common sleep disorders and sleep-related problems in OSA patients. The hypothesis for this study was that both an objectively titrated MAD and nCPAP improve symptoms of common sleep disorders and sleep-related problems in mild/moderate OSA patients. To control for possible placebo effects, an intra-oral placebo device served as a passive control condition for both active treatment modalities.

Methods

Participants

This study is part of a randomized placebo-controlled trial in which different treatment effects of an MAD were compared with those of nCPAP and an intra-oral placebo appliance in a parallel design (7, 17). Potential participants were recruited from the Center for Sleep-Wake Disorders of the Slotervaart Medical Center in Amsterdam, the Netherlands. The multidisciplinary team of this center consisted of a neurologist, ENT specialists, pulmonologists, a dentist, psychologists, and sleep medicine technicians. All participants were at least 18 years old with an apnea-hypopnea index (AHI) of 5-45 events/hour. They all reported excessive daytime sleepiness (Epworth sleepiness score ≥ 10), or at least two OSA symptoms presented by the American Academy of Sleep Medicine Task Force (1) (e.g., excessive daytime sleepiness and daytime fatigue). The exclusion criteria were: the existence of sleep disorders other than OSA based on polysomnography, a body mass index (BMI) of more than 40, usage of medication that affects sleep/respiration, reversible morphological upper airway abnormalities, and previous treatment with nCPAP or an intraoral appliance. Patients with temporomandibular disorders (diagnosis based on a functional examination of the masticatory system (18, 19), an unhealthy periodontium, dental pain, and/or an inadequate retention for an intra-oral appliance were excluded as well. Two hundred nineteen participants were eligible for the study. Seventy-three of them did not meet the medical inclusion criteria and 29 patients did not meet the dental inclusion criteria. Thirty-one patients refused to participate and 22 patients did not participate for other reasons, e.g., loss of contact. Finally, a total of 64 OSA patients agreed to participate by written informed consent (7). The scientific and ethical aspects of the protocol were reviewed and approved by the Medical Ethics Committee of the Slotervaart Medical Center (# U/1731/0326, U/2679/0326). This study has been registered at *www.clinicaltrials.gov* (# NCT00950495).

Study protocol

All patients were randomly allocated to one of the three therapy groups by using block randomization. The nCPAP group used the REMstar Pro system (Respironics, Herrsching, Germany), the MAD group used an individually adjustable MAD (20), and the placebo group used a thin (<1mm) hard acrylic resin palatal splint with a partial coverage of the hard palate (21).

Both MAD and nCPAP were titrated before the start of the treatment (7, 17). The titration of nCPAP was performed during a PSG recording at the Slotervaart Medical Center. The pressure was increased in steps of 1 cm H_2O/h, until the AHI and respiration-related arousals were reduced to ≤ 5/h, and snoring was minimized. The average value of the pressure was 7.3 (SD, 1.9; range, 4-11) cm H_2O (7). For the titration of the MAD,

four ambulatory polysomnographic (PSG) recordings were performed at regular time intervals of approx. 3 weeks. The total titration period was approx. 10 weeks. The most effective protrusion position of the MAD (i.e., the mandibular position that yielded the lowest AHI value) was chosen from among four randomly offered positions (viz., 0%, 25%, 50%, and 75% of the maximum protrusion). The MAD was set at 25% of the maximum protrusion in one patient, at 50% in 7 patients, and at 75% in 12 patients (7, 17). For the placebo group, four ambulatory PSG recordings were performed at regular time intervals similar to the MAD group (7, 17).

During the titration period of approx. 10 weeks, all patients visited ACTA four times at regular intervals, during which the BMI (kg/m2) was determined and the Epworth Sleepiness Scale (ESS) (22) was completed. The participants were also interviewed 1. about their compliance (% of nights per week of wearing), 2. about possible side effects (nature and number; determined in an open question) of the MAD during the study period, and 3. about the change (increased, unchanged, or decreased) in snoring intensity, based on information they obtained from their bed partner. These outcomes have been described in detail in Aarab et al. (7).

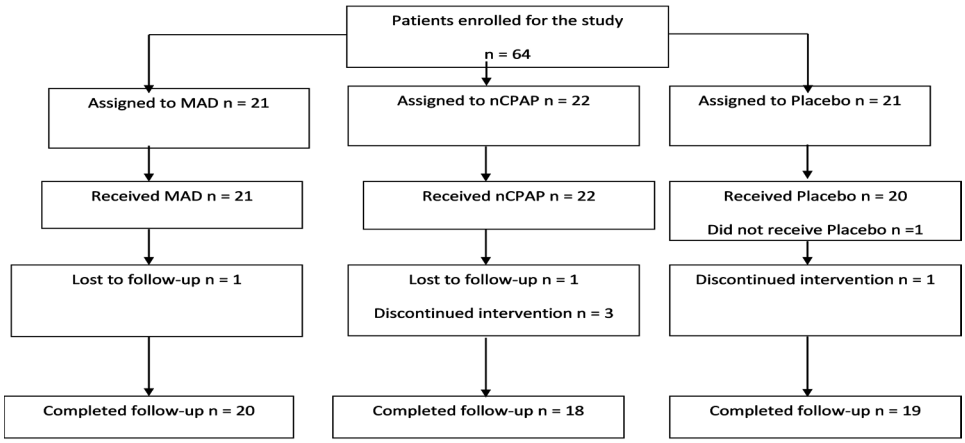

Fig. 1. Flow-chart of the patients through each stage of the trial. MAD = mandibular advancement device; nCPAP = nasal continuous positive airway pressure.

All three groups underwent two full polysomnographic (PSG) recordings in the sleep laboratory of the Slotervaart Medical Center: the first one before treatment and the second one 6 ± 2 months (mean ± SD) after the start of the treatment. The outcomes of the PSG recordings have been published in Aarab et al. (7).

To assess the presence of symptoms of common sleep disorders and sleep-related problems, all patients filled out the validated Dutch Sleep Disorders Questionnaire (SDQ) at the time of the PSG recordings in the sleep laboratory of the Slotervaart Medical Center. The SDQ is the Dutch translation and adaptation of the Sleep Disorders questionnaire, developed by Douglass et al. (23). Sweere et al. (24) tested the SDQ against polysomnography and concluded that the instrument is reliable and reasonably valid for diagnosing common sleep disorders. The SDQ is a self-report questionnaire.

The SDQ consists of 88 questions and includes 13 scales representing the following sleep disorders and sleep-related problems:

- Insomnia (15 questions): inability to fall asleep or to stay asleep as long as desired.
- Excessive daytime sleepiness (6 questions): persistent sleepiness and a general lack of energy, even after apparently adequate or even prolonged night time sleep.
- Psychiatric sleep disorders (13 questions): sleep-related anxiety and depression.
- Periodic limb movements (9 questions): involuntary limb movements during sleep and restless legs syndrome (RLS).
- Sleep apnea (7 questions): cessation of the airflow for at least 10 seconds per event.
- Cataplexy (3 questions): a sudden and transient episode of muscle weakness.
- Sleep paralysis (4 questions): inability to move during sleep-wake transition.
- Daytime dysfunction (7 questions): dysfunction during daytime activities.
- Hypnagogic hallucinations/dreaming (5 questions): experiencing vivid dreams/ nightmares.
- Sexual/social dissatisfaction (4 questions): dissatisfaction about social and sexual life.
- Restless sleep (4 questions): tossing and turning in bed.
- Negative conditioning (2 questions): negative feelings about falling asleep.
- Automatic behavior (4 questions): concentration and memory problems.

Excessive daytime sleepiness, cataplexy, and sleep paralyses are part of the diagnosis "narcolepsy". The answers to all questions were scored on a 5-point ordinal scale (1= never, 2= seldom, 3= sometimes, 4= often, and 5= always). The total scores of each scale of the SDQ were the outcome variables.

Statistical Analysis

The patient characteristics of the three therapy groups at baseline, including the different scales of the SDQ, were compared using one-way analyses of variance, followed by least-significant difference (LSD) pair-wise comparisons. For both the per-protocol and the intention-to-treat analysis, linear mixed models were used to study the differences between the groups for the scales of the SDQ over time. In these models, the treatment group variable was introduced as a dummy variable with the MAD group as reference group. The difference between treatment groups over time was studied by an interaction term of treatment times the time variable. All statistical tests were performed with the SPSS 21.0 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA) and SAS 9.3 (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA) software packages. P <.05 was considered statistically significant.

Results

A total of 64 patients were enrolled in the study, and were randomized at the start of the RCT as shown in Fig. 1. The patient characteristics at baseline are presented in Table 1. Seven patients dropped out of the study for various reasons (see fig. 1). Thus, 57 participants (20 MAD patients, 18 nCPAP patients, and 19 placebo patients) completed the entire study protocol. BMI was the only baseline characteristic that differed between the three therapy groups (F = 5.170; P = 0.008). LSD analyses revealed that the MAD group had a significantly lower BMI than the placebo and nCPAP groups (P = 0.002 and 0.006, respectively; 7) .

	MAD (N=21)	nCPAP (N= 22)	Placebo (N=21)	Drop-outs (N=7)
Age (years)	50.4 ± 8.9	54.0 ± 10.1	51.3 ± 9.6	49.3±7.3
Number of men/women	17/ 4	15/ 7	15/ 6	5/2
Apnea-hypopnea index (AHI)	21.4 ± 11.0	20.1 ± 9.0	19.5 ± 8.4	14.8±3.8
Epworth Sleepiness Scale	12.0 ± 5.7	10.7 ± 4.4	10.8 ± 4.0	13.7±1.9
Body Mass Index* (kg/m2)	27.1 ± 3.2	30.7 ± 3.7	31.1 ± 4.7	27.8 ± 4.1

Table 1. Patient characteristics (mean ± SD) at baseline of the mandibular advancement device (MAD) group, the nasal continuous positive airway pressure (nCPAP) group, the placebo group, and the drop-outs (Aarab et al., 2011a).

The mean (±SD) values of each scale of the SDQ at baseline and at therapy evaluation of the three groups are presented in Table 2. As a result of missing values in the different scales of the SDQ, the number of observations used in the per-protocol analyses varied per scale (see Table 2). At baseline, there were no significant differences between the three therapy groups in the SDQ scales (F = 1.947-0.015; *P* = 0.153-0.985). At therapy evaluation, the MAD group showed significant improvements in symptoms corresponding with "insomnia", "excessive daytime sleepiness", "psychiatric sleep disorder", "periodic limb movements", "sleep apnea", "sleep paralysis", "daytime dysfunction", "hypnagogic hallucinations/dreaming", "restless sleep", "negative conditioning", and "automatic behavior" (F = 31.34-6.50, *P* = 0.000-0.014). These improvements in symptoms were, however, not significantly different from those observed in the nCPAP and placebo groups (*P* = 0.090-0.897).

The intention-to-treat analyses (n = 64) showed similar results as the per-protocol analyses: the MAD group showed significant improvements over time in symptoms corresponding with "insomnia", "excessive daytime sleepiness", "psychiatric sleep disorder", "periodic limb movements", "sleep apnea", "sleep paralysis", "daytime dysfunction", "hypnagogic hallucinations/dreaming", "restless sleep", "negative conditioning", and "automatic behavior" (F = 29.82-6.86, *P* = 0.000-0.011). However, these improvements in symptoms were not significantly different from those observed in the nCPAP and placebo groups (*P* = 0.082-0.949).

Table 2. The mean (± SD) baseline and therapy evaluation values of the different scales of the Dutch Sleep Disorders Questionnaire (SDQ) of the mandibular advancement device (MAD) group, nasal continuous positive airway pressure (nCPAP) group, and placebo group in the per-protocol analyses.

SDQ-scales (number of observations used)	MAD (n = 20)		nCPAP (n=18)		Placebo (n=19)		Within the MAD group over time	Between groups over time
	Baseline	Therapy	Baseline	Therapy	Baseline	Therapy	*P**	*P***
Insomnia (n = 101)	2.6±0.9	2.3±0.8	2.6±0.8	2.1±0.8	2.7±1.0	2.4±1.0	0.000[Ω]	0.619
Excessive daytime sleepiness (n = 98)	2.8±1.0	2.5±1.0	2.3±0.7	1.8±0.7	2.4±0.8	2.1±0.8	0.000[Ω]	0.629
Psychiatric sleep disorders (n = 103)	2.2±0.8	1.8±0.7	2.3±1.0	1.8±1.0	2.1±1.0	1.8±1.0	0.000[Ω]	0.731
Periodic limb movements (n = 105)	2.1±1.0	1.6±0.8	2.3±1.0	1.7±0.8	2.0±1.0	1.8±1.0	0.000[Ω]	0.371

Sleep apnea (n = 86)	3.7±0.6	2.8±1.1	3.3±0.6	2.8±0.9	3.5±0.9	3.1±0.9	0.000Ω	0.090
Cataplexy (n = 107)	1.2±0.4	1.2±0.5	1.4±0.5	1.2±0.6	1.4±0.9	1.2±0.6	0.089	0.258
Sleep paralysis (n= 107)	1.8±0.8	1.4±0.6	2.2±1.1	1.5±0.8	1.9±1.0	1.7±0.8	0.000Ω	0.291
Daytime dysfunction (n=92)	2.7±0.9	2.4±1.0	2.4±1.0	2.2±1.0	2.7±1.0	2.1±0.9	0.006Ω	0.289
Hypnagogic hallucinations/ dreaming (n=105)	2.2±0.9	1.7±0.7	1.8±0.7	1.6±0.7	2.1±1.2	1.7±0.8	0.001Ω	0.196
Sexual/ social dissatisfaction (n=102)	2.5±0.9	2.3±1.2	1.9±0.9	1.9±0.9	2.2±1.1	2.2±1.0	0.896	0.897
Restless sleep (n=106)	2.9±1.0	2.1±0.8	2.6±1.0	2.1±0.8	2.8±1.2	2.3±1.1	0.000Ω	0.336
Negative Conditioning (n=108)	2.1±1.1	1.7±0.9	2.0±1.1	1.8±0.7	2.1±1.1	1.9±1.1	0.014Ω	0.891
Automatic behaviour (n=104)	2.3±0.8	1.9±0.7	2.0±0.7	1.8±0.7	2.0±1.0	1.9±1.0	0.001Ω	0.764

*P-value as result of the linear mixed model analyses for the time effect within the MAD group.

**P-value as result of the linear mixed model analyses comparing the three therapy groups over time.

Ω Statistically significant at the 0.05 probability level.

Discussion

The effects of an MAD and nCPAP on self-reported symptoms of common sleep disorders and sleep-related problems were compared in a group of mild and moderate OSA patients. No significant differences were found between MAD, nCPAP, and placebo in their beneficial effects on symptoms of several sleep disorders and sleep-related problems.

There are some aspects related to this study that should be discussed. First, the dropouts in this study and the missing values in the questionnaires reduced the power of this study. Missing values may lead to selection bias, because participants who complete the entire study may show better treatment outcomes than dropouts (25). To overcome this problem, an intention-to-treat analysis with linear mixed models was used to assess the differences between the groups. The major strengths of mixed models are their ability to accommodate missing data points often encountered in longitudinal datasets and to generate valid study results (26). Therefore, a linear mixed model analysis was used in this

study to deal with the missing values. Second, as a part of a large randomized placebo-controlled trial in which different treatment effects of an MAD were investigated, this study had strict inclusion criteria and strict exclusion criteria. This reduces the external validity of the study, as the group is not representative of the entire OSA population. On the other hand, however, it reduces the risk of bias in the outcome measures (27). Third, when compared to a cross-over design, the parallel design of our study has the advantage of excluding carry-over effects of the different treatments used (28).

Different sleep disorders may show similar symptoms, such as poor sleep quality and excessive daytime sleepiness (10, 29-30). The consequences of different sleep disorders may also show many similarities, such as motor vehicle accidents due excessive daytime sleepiness as a consequence of sleep apnea or narcolepsy (31, 32). It is therefore difficult to distinguish between different sleep disorders based on oral history. Therefore, the validated SDQ questionnaire was used in this study in addition to a full polysomnographic recording for the diagnosis of OSA.

Patients with other sleep disorders than OSA were excluded from this study. This was based on single PSG recordings. In clinical practice, but also in research, only one PSG recording is commonly made for diagnosis of OSA because these recordings are time-consuming and costly. However, many sleep-related disorders can be missed after a one-night polysomnographic recording (33). The first-night effect in the sleep laboratory may affect many recorded sleep variables. The main characteristics of the first-night effect are a reduced total sleep time and REM sleep time, lower sleep efficiency, longer REM sleep latency, and decreased slow wave sleep. These factors may result in false-negative findings of different sleep disorders (34). Further, there is a natural fluctuation of sleep-related variables in PSG recordings over time (35, 36). Therefore, a single-night recording may not be sufficient to exclude sleep disorders. This would have been valid for also the OSA diagnosis, however, the OSA diagnosis was an inclusion criterion for this study. Consequently, a false negative finding of OSA as a consequence of a first-night effect was excluded. Further, the relatively low ordinal scale values of the symptoms of the other common sleep disorders in this OSA group of approx. “2= seldom” and “3= sometimes” at baseline (see table 2) raise the question if the symptoms of these sleep disorders were severe enough for a valid diagnosis, and if the small significant improvements in these symptoms are actually clinically relevant, especially because these improvements were also observed in the placebo group. The relatively high ordinal scale values of approx. “4= often” for the sleep apnea diagnosis at baseline (see table 2) confirm that the patients in our study had mainly OSA symptoms.

Björnsdóttir et al. (13) studied the changes in insomnia symptoms based on self-report questionnaires among OSA patient under CPAP treatment over two years. They hypothesized that the reduction of the number of respiratory-related arousals under

CPAP treatment will result in better sleep efficiency in insomnia patients. They found indeed that CPAP treatment significantly reduces symptoms of middle insomnia. On the other hand, Luyster et al. (37) reviewed studies examining the co-occurrence of insomnia and OSA, and concluded that the effect of different OSA treatments (viz., CPAP, oral appliances, and surgery) on insomnia remains unclear. Pataka et al. (15) concluded that the use of nCPAP may be beneficial for some narcoleptics with OSA, and that it can be used as a secondary therapy in this patient group. Marklund et al. (16) found in a randomized controlled trial that both MAD and a placebo appliance had no effect on insomnia symptoms. However, their MAD treatment resulted in a significant improvement of restless legs symptoms when compared to placebo. To our best knowledge, our study is the first one comparing the effects of an objectively titrated MAD with those of nCPAP on self-reported symptoms of common sleep disorders and sleep-related problems in OSA patients. No significant differences were found between MAD and nCPAP and an intra-oral placebo appliance in their beneficial effects on symptoms of common sleep disorders and sleep-related problems in mild and moderate OSA patients. It was expected that an improvement in the symptoms of the other common sleep disorders and sleep-related problems would occur as a consequence of a significant reduction in the number of respiratory-related arousals in both the nCPAP and MAD groups (7, 17). However, the placebo group also showed significant improvements in these symptoms, although elevated respiratory arousal indices with the placebo appliance in situ were present at therapy evaluation (7, 17). Therefore, the positive effects on these symptoms may not be explained by an improvement in sleep quality. These observed improvements in the three groups may be due to changes in life style as a result of sleep hygiene advises and general information about their condition given at baseline (38). Further, the observed improvement in the placebo group may also be a result of the attention given to the patients by the physician/dentist, resulting in a positive effect on self-reports about symptoms of common sleep disorders and sleep-related problems. These possible explanations for the findings in the placebo group underline the importance of including a placebo group in randomized controlled trials to enable a clear distinction between a real treatment effect and a placebo effect.

In conclusion, our results show that there is no significant difference between MAD and nCPAP in their positive effects on symptoms of common sleep disorders and sleep-related problems in a group of mild to moderate OSA patients. Placebo effects may explain these beneficial effects.

References

1. American Academy of Sleep Medicine Task Force: Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667-689.
2. Ayas NT, Hirsch AA, Laher I, Bradley TD, Malhotra A, Polotsky VY, Tasali E. New frontiers in obstructive sleep apnoea. Clin Sci 2014;127:209-216.
3. Lavie L. Oxidative stress in obstructive sleep apnea and intermittent hypoxia - Revisited - The bad ugly and good: Implications to the heart and brain. Sleep Med Rev 2015;20:27-45.
4. Young T, Palta M, Dempsey J, Skatrud J, Weber S and Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-1235.
5. Badran M, Ayas NT and Laher I. Insights into obstructive sleep apnea research. Sleep Med 2014;15:485-495.
6. Rosenberg R, Doghramji P. Optimal treatment of obstructive sleep apnea and excessive sleepiness. Adv Ther. 2009;26:295-312.
7. Aarab G, Lobbezoo F, Heijmans MW, Hamburger HL, Naeije M. Long-term follow up of a randomized controlled trial of oral appliance therapy in obstructive sleep apnea. Respiration 2011;82:162-168.
8. Doff MHJ, Finnema KJ, Hoekema A, Wijkstra PJ, de Bont LGM, Stegenga B. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on dental side effects. Clin Oral Invest. 2013;17:475–482.
9. Kushida CA, Morgenthaler TI, Littner MR, Alessi CA, Bailey D, Coleman J JR, Friedman L, Hirshkowitz M, Kapen S, Kramer M, Lee-Chiong T, Owens J, Pancer JP; American Academy of Sleep. Practice parameters for the treatment of snoring and Obstructive Sleep Apnea with oral appliances: an update for 2005. Sleep 2006;29:240-243.
10. Al- Jawder SE and Bahammam AS. Comorbid insomnia in sleep-related breathing disorders: an under-recognized association. Sleep Breath 2012;16:295-304.
11. Carelli G, Krieger J, Calvi-Gries F and Macher JP. Periodic limb movements and obstructive sleep apneas before and after continuous positive airway pressure treatment. J Sleep Res 1999; 8:211-216.

12. Sansa G, Iranzo A and Santamaria J. Obstructive sleep apnea in narcolepsy. Sleep Med 2010;11:93-95.
13. Björnsdóttir E, Janson, C, Sigurdsson JF, Gehrman P, Perlis M, Juliusson S, Arnardottir ES, Kuna ST, Pack AI, Gislason T, Benediktsdóttir B. Symptoms of insomnia among patients with obstructive sleep apnea before and after two years of positive airway treatment. Sleep 2013;36:1901-1909.
14. Glidewell RN, Renn BN, Roby E, Orr WC. Predictors and patters of insomnia symptons in OSA before and after PAP therapy. Sleep Med 2014;15:899-905.
15. Pataka AD, Frangulyan RR, Mackay TW, Douglas NJ, Riha RL. Narcolepsy and sleep-disordered breathing. Eur J Neurol 2012;19:696-702.
16. Marklund M, Carlberg B, Forsgren L, Olsson T, Stenlund H, Franklin KA. Oral Appliance Therapy in Patients With Daytime Sleepiness and Snoring or Mild to Moderate Sleep Apnea: A Randomized Clinical Trial. JAMA Intern Med. 2015;175:1278-1285.
17. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial. Respiration 2011;81:411-419.
18. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301–355.
19. Lobbezoo F, van Selms MK, John MT, Huggins K, Ohrbach R, Visscher CM,et al. Use of the research diagnostic criteria for temporomandibular disorders for multinational research: translation efforts and reliability assessments in The Netherlands. J Orofac Pain 2005;19:301–308.
20. Aarab G, Lobbezoo F, Wicks DJ, Hamburger HL and Naeije M. Short-term effects of a mandibular advancement device on obstructive sleep apnea: an open-label pilot trial. J Oral Rehabil 2005;32:564-570.
21. Van der Zaag J, Lobbezoo F, Wicks DJ, Visscher CM, Hamburger HL and Naeije M. Controlled assessment of the efficacy of the occlusal stabilization splints on sleep bruxism. J Orofac Pain 2005;19:151-158.
22. Johns M.W. Daytime sleepiness, snoring, and obstructive sleep apnea; The Epworth Sleepiness Scale . Chest.1993;103:30-36.

23. Douglass AB, Bornstein R, Nino-Murcia G, Keenan S. Creation of the "ASDC sleep disorders questionnaire". Sleep Res 1986;15:117.
24. Sweere Y, Kerkhof GA, De Weerd AW, Kamphuisen HA, Kemp B, Schimsheimer RJ. The validity of the Dutch Sleep Disorders Questionnaire (SDQ). J Psychosom Res. 1998; 45:549-555.
25. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: A gentle introduction to imputation of missing values. J Clin Epidemiol. 2006; 59:1087-1091.
26. Twisk J, de Boer M, de Vente W, Heymans M. Multiple imputation of missing values was not necessary before performing a longitudinal mixed-model analysis. J of Clinical Epidemiology. 2013;66:1022-1028.
27. Khorsan R, Crawford C. How to assess the external validity and model validity of therapeutic trials: a conceptual approach to systematic review methodology. Evid Based Complement Alternat Med 2014; doi: 10.1155/2014/694804.
28. Berry CC, Moore P, Dimsdale JE. Assessing the trade-off between crossover and parallel group design in sleep research. J Sleep Res 2006;15:348-357.
29. Slater G and Steier J. Excessive daytime sleepiness in sleep disorders. J Thorac Dis 2012; 4:608-616.
30. Roth T, Dauvilliers Y, Mignot E, Montplaisir J, Paul J, Swick T, Zee P. Disrupted nighttime sleep in narcolepsy. J Clin Sleep Med 2013;9:955-965.
31. Sanna A. Obstructive sleep apnoea, motor vehicle accidents, and work performance. Chron Respir Dis 2013;10:29-33.
32. León-Muñoz L, de la Calzada MD, Guitart M. Accidents prevalence in a group of patients with the narcolepsy- cataplexy syndrome. Rev Neurol 2000;30:596-598.
33. Toussaint M, Luthringer R, Schaltenbrand N, et al. First-night effect in normal subjects and psychiatric-inpatients. Sleep 1995;18:463-469.
34. Gouveris H, Selivanova O, Bausmer U, Goepel B, Mann W. First-night-effect on polysomnographic respiratory sleep parameters in patients with sleep-disordered breathing and upper airway pathology. Eur Arch Otorinolaryngol 2010;267:1449-1453.
35. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Variability in the Apnea-Hypopnea Index and its Consequences for Diagnosis and Therapy Evaluation. Respiration 2009;77:32-37.

36. Van Der Zaag J, Lobbezoo F, Visscher CM, Hamburger HL, Naeije M. Time-variant nature of sleep bruxism outcome variables using ambulatory polysomnography: implications for recognition and therapy evaluation. J Oral Rehabil 2008;35:577-584.
37. Luyster FS, Buysse DJ, Strollo PJ. Comorbid Insomnia and Obstructive Sleep Apnea: Challenges for Clinical Practice and Research. J Clin Sleep Med 2010;6:196–204.
38. Irish LA, Kline CE, Gunn HE, Buysse DJ, Hall MH. The role of sleep hygiene in promoting public health: A review of empirical evidence. Sleep Med Rev 2015;22:23-36.

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Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial on temporomandibular side effects

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Clin Exp Dent Res. 2020 Apr 4. DOI: 10.1002/cre2.288

Abstract

Background: To assess the differences in the frequency of clinical signs of temporomandibular disorder (TMD) pain and in mandibular function impairment between mandibular advancement device (MAD) and nasal continuous positive airway pressure (nCPAP) therapies in obstructive sleep apnea (OSA) patients at baseline and after 6 month of treatment. **Methods:** This study concerns a secondary analysis of a randomized placebo-controlled trial in which different treatment effects of an objectively titrated MAD were compared with those of nCPAP and an intra-oral placebo appliance in a parallel design. Sixty-four mild to severe OSA patients (52.0 ± 9.6 years) were randomly assigned to these three groups. All patients underwent a shortened functional examination of their masticatory system at baseline and after 6 months to establish the presence of clinical signs of TMD pain. Mandibular function impairment was assessed with a questionnaire. **Results:** Clinical signs of TMD pain were only rarely present at baseline and at therapy evaluation. No significant differences were found between the three groups in the (low) frequency of clinical signs of TMD pain at both time points (P = 0.401-0.176). In addition, the (low) scores of mandibular function impairment did not differ between the three groups either, neither at baseline (P = 0.744) nor after 6 months (P = 0.359). **Conclusion:** A low frequency of clinical signs of TMD pain in mild to severe OSA patients was found after 6 months, regardless of treatment with MAD or nCPAP. In addition, no difference in mandibular function impairment was observed between the different treatment modalities.

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent obstructions of the upper airway, often resulting in oxygen desaturations and arousals from sleep (1). OSA is a common sleep-related breathing disorder that affects 10-17% of middle aged men and 3-9% of middle aged women, with a higher prevalence amongst obese patients (2). OSA patients without effective treatment have an increased risk of cardiovascular conditions like hypertension, stroke, heart failure, and atrial fibrillation (3-5).

The treatment of OSA has been undergoing a steady shift over the last years. While (nasal) CPAP ((n)CPAP) was more or less the sole effective treatment for many years, mandibular advancement device (MAD) therapy is increasingly recognized as a viable treatment for OSA (6,7). MADs are currently indicated for the treatment of mild to moderate OSA patients as well as of severe OSA patients who are intolerant to, or refuse CPAP therapy (6,7). MADs protrude the mandible and improve upper airway patency by enlarging the upper airway and/or by reducing its collapsibility (8). During the monitoring phase of this treatment, the mandibular protrusion position of the MAD is often titrated by the dentist or patient to improve its efficacy and to reduce its side effects (9). However, due to their design, MADs exert potentially detrimental forces on the teeth, oral soft tissues, and musculoskeletal structures of the masticatory system. Amongst others, MADs may result in excessive salivation, mouth dryness, and temporomandibular side effects on the short-term (10-14).

Temporomandibular disorders (TMDs) are defined as musculoskeletal disorders that include symptoms like pain and dysfunction of the temporomandibular joint and/or the jaw muscles (15). De Leeuw and Klasser extensively describe various methods for the clinical assessment of TMD pain, all of them based on a combination of self-report and clinical tests that provoke the musculoskeletal system (15). Importantly, the clinical assessment of the impairment of mandibular function associated with TMDs should not only comprise a diagnostic assessment of symptoms and signs but also an assessment of the functional impairment as it is perceived in the patient's value system (16).

Both improvements and deteriorations in signs and symptoms of TMDs have been found during MAD treatment (10, 12, 17-21). Most previous studies, however, were retrospective in design, or did not include a placebo group (10, 12, 17, 18). Moreover, the impact of the TMD on the patient's mandibular function has seldom been determined (10). Therefore, a definitive conclusion about the frequency of TMD side effects and their impact on mandibular function in OSA patients under MAD treatment cannot be drawn.

The aim of this study was to assess the differences in the frequency of clinical signs of TMD pain and in the mandibular function impairment between MAD and nCPAP therapies at baseline and after 6 months in mild to severe OSA patients in a randomized, placebo-

controlled trial design. We hypothesized that an MAD would result in significantly more clinical signs of TMD pain than nCPAP and placebo. Further, this TMD pain was hypothesized to lead to more mandibular function impairment in the MAD group than in the nCPAP and placebo groups.

Materials and methods

This study concerns a secondary analysis of a large randomized placebo-controlled trial in which different treatment effects of an objectively titrated MAD were compared with those of nCPAP and an intra-oral placebo appliance in a parallel design. The short-term and long-term outcomes of this trial have been published previously (6, 9, 22).

Participants

Potential participants were recruited from the Center for Sleep-Wake Disorders of the Slotervaart Medical Center in Amsterdam, The Netherlands. The multidisciplinary team of this center consisted of a neurologist, ENT specialists, pulmonologists, a dentist, psychologists, and sleep medicine technicians. All participants were at least 18 years old, with an apnea-hypopnea index (AHI) of 5-45 events/hour. They all reported excessive daytime sleepiness (Epworth sleepiness score ≥ 10), or at least two OSA symptoms presented by the American Academy of Sleep Medicine Task Force (e.g., daytime sleepiness, fatigue) (1). The exclusion criteria were: the existence of sleep disorders other than OSA based on polysomnography, a body mass index (BMI) of more than 40, usage of medication that affects sleep or respiration, reversible morphological upper airway abnormalities, and previous treatment with nCPAP or an intraoral appliance. Patients with clinical signs of temporomandibular disorders (TMDs; diagnosis based on a functional examination of the masticatory system) (23) who also expressed a desire for treatment of their TMD complaints, an unhealthy periodontium (periodontal pockets > 5mm), dental pain, and/or an inadequate retention possibilities for an intra-oral appliance were excluded as well. Two-hundred-nineteen participants were eligible for the study. Seventy-three of them did not meet the medical inclusion criteria, and 29 patients did not meet the dental inclusion criteria. Thirty-one patients refused to participate and 22 patients did not participate for other reasons, e.g., loss of contact. Finally, a total of 64 OSA patients agreed to participate and provided written informed consent (Fig. 1). The scientific and ethical aspects of the protocol were reviewed and approved by the Medical Ethics Committee of the Slotervaart Medical Center (## U/1731/0326, U/2679/0326). This study has been registered at www.clinicaltrials.gov (# NCT00950495).

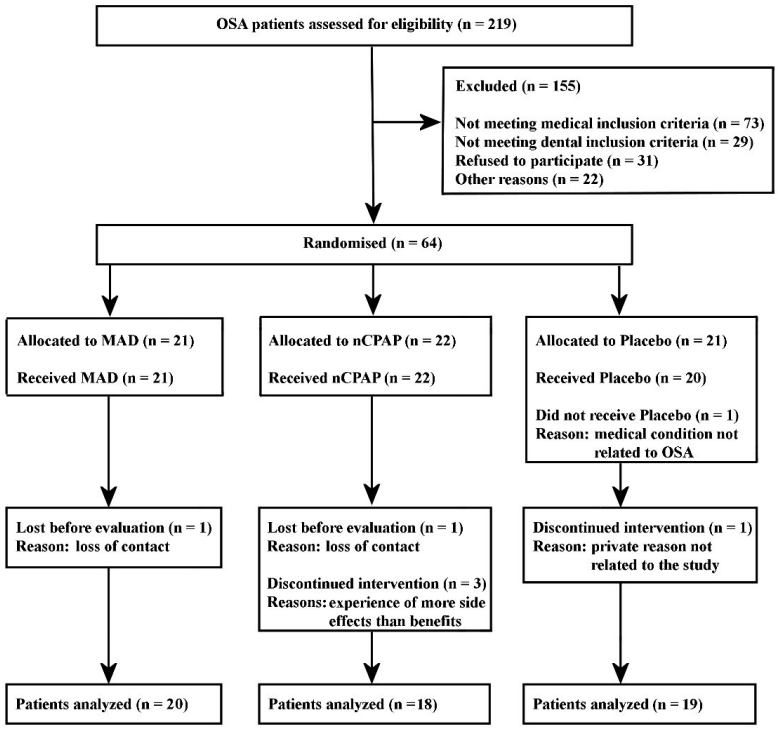

Fig. 1. Flow-chart of the patients through each stage of the trial. OSA = obstructive sleep apnea; MAD = mandibular advancement device; nCPAP = nasal continuous positive airway pressure.

Interventions

The nCPAP group used the REMstar Pro system (Respironics, Herrsching, Germany). The MAD group used a custom-made device with an individually adjustable mandibular protrusion position at a constant vertical dimension, the design of which has been described in detail previously (9). The MAD did not allow vertical opening and lateral movements. The placebo group used a thin (<1mm) hard acrylic resin palatal splint with only a partial coverage of the hard palate and no interference with the dental occlusion (6).

Study protocol

The protocol of this study has been described in detail previously (6). Below, an outline is provided with the protocol's key characteristics, along with pertinent additions that made it possible to answer the current research question.

All patients were randomly allocated to one of the three therapy groups. To ensure that the groups were of approx. the same size, block randomization was used. Block sizes were

6, 12, and 18; sizes were randomly varied. The allocation sequence was automatically generated and subsequently concealed by an independent co-worker, who kept a paper copy in a lockable drawer. Sealed opaque envelopes were used to conceal the allocation from the principal investigator (6). Both MAD and nCPAP were titrated before the start of the treatment (6). For the titration of the MAD, four ambulatory polysomnographic (PSG) recordings were performed at regular time intervals of approx. 3 weeks. The total titration period was approx. 10 weeks. The most effective protrusion position of the MAD (i.e., the mandibular position that yielded the lowest AHI value) was chosen from among four randomly offered positions, viz., 0%, 25%, 50%, and 75% of the maximum protrusion. The MAD was set at 25% of the maximum protrusion in one patient, at 50% in 7 patients, and at 75% in 12 patients (6). The titration of nCPAP was performed during a PSG recording at the Slotervaart Medical Center. The pressure was increased in steps of 1 cm H2O/h, until the AHI and respiration-related arousals were reduced to ≤ 5 events/h, and snoring was minimized. The average value of the pressure was 7.3 (SD, 1.9; range, 4-11) cm H_2O (6). For the placebo group, four ambulatory PSG recordings were performed at regular time intervals similar to the MAD group (6).

During the titration period of approx. 10 weeks, all patients visited ACTA four times at regular intervals, during which the BMI (kg/m2) was determined and the Epworth Sleepiness Scale (ESS) was completed (24). The participants were also interviewed about their compliance (% of nights per week of wearing), and the change (increased, unchanged, or decreased) in snoring intensity, based on information they obtained from their bed partner. These outcomes have been described in detail by Aarab et al. (6). Further, the visits at ACTA were also used to adjust the protrusion position of the MAD according to the random order of the study protocol.

Besides the above-described titration PSGs, all three groups underwent two full PSG recordings in the sleep laboratory of the Slotervaart Medical Center: the first one before treatment and the second one 6.0 ± 2.0 months (mean ± SD) after the start of the treatment. The outcomes of the PSG recordings have been published by Aarab et al. (6).

Clinical signs of TMD pain and mandibular function impairment

During the consultations at baseline and after 6 months of treatment, patients were informed about the mild and transient nature of a possible TMD pain by the clinician. The assessment of TMD pain and mandibular function impairment was performed at both time points. The assessment included, amongst others, an oral history and orthopedic tests, viz., the static and dynamic tests (23). A single, experienced, and well-trained clinician performed all examinations throughout the entire study. This clinician was not blinded for the type of treatment of each patient. Clinical signs of TMD pain was

considered present when patients reported pain on at least one of the static or dynamic tests during opening, closing, and protrusion of the mandible. The presence of clinical signs of TMD pain was scored "1", and their absence was scored "0".

The Mandibular Function Impairment Questionnaire (MFIQ) was completed by all patients at baseline and after 6 months, in order to subjectively assess function impairment of the masticatory system. The MFIQ is a validated questionnaire, which is used to assess the impact of TMDs on mandibular function in daily life (16). The MFIQ scores perceived difficulty of 17 representative mandibular functions in relation to joint or muscle complaints. The answers are scored on five-point Likert-type scales (0 to 4), where 0 represents "no difficulty" and 4 represents "very great difficulty or impossible without help". The sum item score for function impairment ranges from 0 to 68. Using these scores, a Raw Component Score is calculated and a functional impairment rating scale (FIRS) is derived (0-5). A FIRS of 0 or 1 indicates low level of function impairment, a FIRS of 2 or 3 indicates moderate level of function impairment, and a FIRS of 4 or 5 indicates severe level of function impairment.

Statistical analysis

The null hypothesis of this study was that there is no significant difference between the MAD group, the nCPAP group, and the placebo group in the presence of clinical signs of TMD pain at baseline and at therapy evaluation. The chi square (X^2) test was used to examine whether the distributions of TMD pain between the three groups differed. The Wilcoxon Signed rank test (for the within groups comparison) and the Kruskal-Wallis tests (for the between groups comparison) were used to test the difference between the three groups in the change of their FIRS score between baseline and 6 months after the start of the treatment. All statistical analyses were performed using the Statistical Package for the Social Sciences (version 24.0, SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

The patient characteristics at baseline are presented in Table 1. BMI was the only baseline characteristic that differed between the three therapy groups. Seven patients dropped out of the study for various reasons (see Fig. 1). Thus, 57 participants (20 MAD patients, 18 nCPAP patients, and 19 placebo patients) completed the entire study protocol (6).

Details of the primary analyses of the RCT have been described previously; see (6). In short, the MAD group had used their appliance 90.6% (SD, 13.3) of the nights; the nCPAP group 82.9% (SD, 27.2) of the nights; and the placebo group 93.9% (SD, 15.7) of the

nights. No significant group differences in compliance were found (F = 1.518, P = 0.228). In addition, BMI did not change significantly from baseline to 6-month follow-up in any of the three therapy groups (paired t tests; P = 0.408-0.752). AHI, on the other hand, showed a significant improvement over time in all three therapy groups. The decrease in AHI from baseline to 6-month follow-up differed significantly between the groups (ANCOVA; F = 14.886, P = 0.000). While this decrease was comparable for MAD and nCPAP (P = 0.092), both treatments showed a significantly larger decrease than the placebo condition (P = 0.000 and 0.0002, respectively). Finally, for excessive daytime sleepiness, the pooled data of the three groups showed a significant decrease over time (paired t test, P = 0.002).

In Table 2, the outcome variables are presented. Clinical signs of TMD pain were only rarely encountered. No significant differences were found between the three treatment groups in the (low) frequency of the clinical signs of TMD pain at baseline and at therapy evaluation after 6 months ($\chi 2$= 1.830 and $\chi 2$= 3.478; *P* = 0.401 and 0.176, respectively). All FIRS scores were qualified as low. There was no significant change in the FIRS score within the groups between baseline and therapy evaluation (Z= -0.632; *P* = 0.527), nor was there a significant difference between the three different treatment groups in their (low) level of mandibular function impairment at baseline (*P* = 0.744) and after 6 months (*P* = 0.359); see Table 2.

Table 1. Patient characteristics (mean ± SD) at baseline of the mandibular advancement device (MAD) group, the nasal continuous positive airway pressure (nCPAP) group, the placebo group, and the dropouts; see [6] for more details.

	MAD (N=21)	nCPAP (N= 22)	Placebo (N=21)	Dropouts (N=7)
Age (years)	50.4 ± 8.9	54.0 ± 10.1	51.3 ± 9.6	49.3±7.3
Number of men/women	17/ 4	15/ 7	15/ 6	5/2
Apnea-hypopnea index (AHI)	21.4 ± 11.0	20.1 ± 9.0	19.5 ± 8.4	14.8±3.8
Epworth Sleepiness Scale	12.0 ± 5.7	10.7 ± 4.4	10.8 ± 4.0	13.7±1.9
Body Mass Index[1] (kg/ m2)	27.1 ± 3.2	30.7 ± 3.7	31.1 ± 4.7	27.8 ± 4.1

[1]MAD patients had a significantly lower BMI than placebo and nCPAP patients (P = 0.002 and 0.006, respectively; one-way ANOVA, followed by least-significant difference pairwise comparisons.

Table 2. Presence of clinical signs of TMD pain and the Function Impairment Rating Scale (FIRS) score at baseline and 6 months after the start of the therapy for the mandibular advancement device (MAD) group, the nasal continuous positive airway pressure (nCPAP) group, and the placebo group.

Outcome measures	MAD (n=20)		nCPAP (n=18)		Placebo (n=19)	
	Baseline	6 months	Baseline	6 months	baseline	6 months
Presence of clinical signs of TMD pain (n)[1]	0	0	2	2	1	0
FIRS score (25%|median|75%)[2]	0|0|1	0|0|0.50	0|0|0.25	0|0|1	0|0|0	0|0|0

[1]Number of complete data sets per group: MAD (n=18); nCPAP (n=17); placebo (n=14)

[2]Number of complete data sets per group: MAD (n=17); nCPAP (n=13); placebo (n=18)

Discussion

The aim of this study was to assess the differences in the frequency of clinical signs of TMD pain and in mandibular function impairment after 6 months of treatment between MAD and nCPAP therapies in mild to severe OSA patients in a randomized, placebo-controlled trial design. No significant differences were found between the three treatment groups in the frequency of clinical signs of TMD pain at baseline and at therapy evaluation after 6 months. Further, there was no significant difference between the three different treatment groups in their (low) level of mandibular function impairment in daily life either.

A study of Sanders et al. tested the hypothesis that signs and symptoms of OSA are associated with the occurrence of TMD, and precede first-onset TMD (25). Their data was based on a prospective study (n=2,604) and a case-control study (n= 1,716). Both studies supported a significant association between OSA symptoms and TMD, and they found evidence that OSA symptoms preceded first-onset TMD. One of their explanations for OSA preceding TMD was that OSA patient show more sleep bruxism (SB) activity and therefore more TMD. However, there is no solid evidence for the cause-effect relationship between OSA and SB on one hand, and between SB and TMD on the other hand (26, 27). Further, OSA was not determined objectively (i.e., by means of PSG) in the study of Sanders et al. (25). Therefore, their hypothesis should be tested further in future

studies. Nevertheless, Kato et al. found self-reported jaw symptoms (viz., morning jaw discomfort, morning jaw pain, daytime jaw pain, and jaw opening difficulties) in 19% of 511 OSA patients (28). Further, Perez et al. showed that TMD pain was present in approximately 10% of their OSA patients at baseline, based on a clinical examination (29), which corresponds with the TMD-pain prevalence rate of 10% in the general population (30). Based on these studies, we may conclude that TMD is associated with OSA. However, TMD pain may be equally prevalent in OSA patients and the general population.

The present study concerns a secondary analysis of a large randomized placebo-controlled trial, the short-term and long-term outcomes of which have been published previously (6, 9, 22). This means that the data that were analyzed to answer the present research questions were originally collected for other purposes. While the advantages of using secondary data are clear (e.g., time-saving, cost-efficient), its use is also associated with potential disadvantages, such as the application outdated or inaccurate methods that may jeopardize the validity of the results. In the present study, however, both TMD pain and mandibular function impairment were assessed with up-to-date and validated tools, viz., static and dynamic tests (23) and Mandibular Function Impairment Questionnaire (16), respectively. Hence, we are confident that in the present study, the use of secondary data has yielded accurate outcomes.

The experienced and well-trained clinician who performed all examinations throughout the entire study was not blinded for the type of treatment of each patient. Since this approach is associated with a risk of observer bias, this could be considered as a potential limitation of the present study. Further, not all patients completed the entire protocol of the present study. Therefore, both our original study sample and the dropouts contributed to a reduced power of this study. Missing values may lead to selection bias, because participants who complete the entire study may show better treatment outcomes than dropouts (31). However, the outcomes of our study are similar to previous ones. Perez et al. determined the prevalence and incidence of TMD pain in 167 OSA patients undergoing MAD treatment (29). They found that after approx. 4 months, TMD pain was present in only a small proportion of their study sample and that this pain was no longer present after 1 year. Similar findings were reported by Doff et al. in their study wherein 51 MAD patients were compared to 52 CPAP patients on the occurrence of TMD and the risk of pain and function impairment in a 2-year follow-up (32). They found that MAD therapy is associated with increased TMD pain in the first 2 months of use, but that this TMD side effect had a transient nature: they found no difference in TMD pain between the MAD group and their CPAP group after one year. Therefore, they concluded from their study that, because of the transient nature of TMD pain, this pain is not a reason to contra-indicate an MAD treatment. Also, Knappe et al. (33) reported a low prevalence rate of jaw-muscle tenderness, viz., 7.1%, and no significant changes in

orofacial function in association with MAD therapy after 6 months. In our study, TMD pain in the MAD group was also evaluated after 6 months. We hypothesize, based on the outcomes of the studies of Perez et al. (29), Doff et al. (32), and Knappe et al. (33), that the TMD pain in our MAD group had already disappeared in the first few months. Therefore, no difference in clinical signs of TMD pain between the MAD, nCPAP, and placebo groups was found in our study.

In conclusion, our study showed a low frequency of clinical signs of TMD pain in mild to severe OSA patients after 6 months, regardless of treatment with MAD or nCPAP. In addition, no difference in mandibular function impairment was observed between the different treatment modalities.

References

1. American Academy of Sleep Medicine. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667-689.
2. Badran M, Ayas N, Laher I. Insights into obstructive sleep apnea research. Sleep Med. 2014;15:485-495.
3. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365:1046-1053.
4. Ayas NT, Owens RL, Kheirandish-Gozal L. Update in Sleep Medicine 2014. Am J Respir Crit Care Med. 2015;192:415-420.
5. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med. 2005;353:2034-2041.
6. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial. Respiration. 2011;81:411-419.
7. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. J Clin Sleep Med. 2015;11:773-827.
8. Schmidt-Nowara W, Lowe A, Wiegand L, Cartwright R, Perez-Guerra F, Menn S. Oral appliances for the treatment of snoring and obstructive sleep apnea: a review. Sleep.1995;18:501-510.
9. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Effects of an oral appliance with different mandibular protrusive positions at a constant vertical dimension on obstructive sleep apnoea. Clin Oral Invest. 2010;14:339-345.
10. Doff MH, Veldhuis SK, Hoekema A, Slater JJ, Wijkstra PJ, de Bont LG, Stegenga B. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on temporomandibular side effects. Clin Oral Investig. 2012;16:689–697.
11. Hammond RJ, Gotsopoulos H, Shen G, Petocz P, Cistulli PA, Darendeliler MA. A fol-

low-up study of dental and skeletal changes associated with mandibular advancement splint use in obstructive sleep apnea. Am J Orthod Dentofacial Orthop. 2007;132:806-814.

12. Martinez-Gomis J, Willaert E, Nogues L, Pascual M, Somoza M, Monasterio C. Five years of sleep apnea treatment with a mandibular advancement device. Side effects and technical complications. Angle Orthod. 2010;80:30–36.
13. Pantin CC, Hillman DR, Tennant M. Dental side effects of an oral device to treat snoring and obstructive sleep apnea. Sleep. 1999;22:237-240.
14. Tegelberg A, Wilhelmsson B, Walker-Engstrom ML, Ringqvist M, Andersson L, Krekmanov L. Effects and adverse events of a dental appliance for treatment of obstructive sleep apnoea. Swed Dent J. 1999;23:117–126.
15. de Leeuw R, Klasser GD (eds).Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management, ed 6. Chicago: Quintessence, 2018.
16. Stegenga B, de Bont LG, de Leeuw R, Boering G. Assessment of mandibular function impairment associated with temporo-mandibular joint osteoarthrosis and internal derangement. J Orofac Pain. 1993;7:183–195.
17. Bondemark L, Lindman R. Craniomandibular status and function in patients with habitual snoring and obstructive sleep apnoea after nocturnal treatment with a mandibular advancement splint: A 2-year follow-up. Eur J Orthod. 2000;22:53–60.
18. Cunali PA, Almeida FR, Santos CD, Valdrighi NY, Nascimento LS, Dal'Fabbro C, Tufik S, Bittencourt LR. Prevalence of temporomandibular disorders in obstructive sleep apnea patients referred for oral appliance therapy. J Orofac Pain. 2009;23:339–344.
19. Fransson AM, Tegelberg A, Leissner L, Wenneberg B, Isacsson G. Effects of a mandibular protruding device on the sleep of patients with obstructive sleep apnea and snoring problems: a 2-year follow-up. Sleep Breath. 2003;7:131-141.
20. Giannasi LC, Almeida FR, Magini M, Costa MS, de Oliveira CS, de Oliveira JC. Systematic assessment of the impact of oral appliance therapy on the temporomandibular joint during treatment of obstructive sleep apnea: long-term evaluation. Sleep Breath. 2009;13:375–381.
21. Petit FX, Pépin JL, Bettega G, Sadek H, Raphaël B, Lévy P. Mandibular advancement devices: Rate of contraindications in 100 consecutive obstructive sleep apnea patients. Am J Respir Crit Care Med. 2002;166:274–278.

22. Aarab G, Lobbezoo F, Heijmans MW, Hamburger HL, Naeije M. Long-tern follow up of a randomized controlled trial of oral appliance therapy in obstructive sleep apnea. Respiration. 2011;82:162-168.
23. Visscher CM, Naeije M, De Laat A, Michelotti A, Nilner M, Craane B, Ekberg EC, Farella M, Lobbezoo F. Diagnostic accuracy of temporomandibular disorder pain tests: a multicenter study. J Orofac Pain. 2009;23:108-114.
24. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14:540–545.
25. Sanders AE, Essick GK, Fillingim R, Knott C, Ohrbach R, Greenspan JD, Diatchenko L, Maixner W, Dubner R, Bair E, Miller VE, Slade GD. Sleep apnea symptoms and risk of temporomandibular disorder: OPPERA cohort. J Dent Res. 2013;92:70S-7S.
26. Manfredini D, Lobbezoo F. Relationship between bruxism and temporomandibular disorders: A systematic review of literature from 1998 to 2008. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109:26-50.
27. Manfredini D, Guarda-Nardini L, Marchese-Ragona R, Lobbezoo F. Theories on possible temporal relationships between sleep bruxism and obstructive sleep apnea events. An expert opinion. Sleep Breath. 2015;19:1459-1465.
28. Kato T, Katase T, Yamashita S, Sugita H, Muraki H, Mikami A, Okura M, Ohi M, Masuda Y, Taniguchi M. Responsiveness of jaw motor activation to arousals during sleep in patients with obstructive sleep apnea syndrome. J Clin Sleep Med. 2013;9:759-765.
29. Perez CV, de Leeuw R, Okeson JP, Carlson CR, Li HF, Bush HM, Falace DA. The incidence and prevalence of temporomandibular disorders and posterior open bite in patients receiving mandibular advancement device therapy for obstructive sleep apnea. Sleep Breath. 2013;17:323-332.
30. LeResche L. Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. Crit Rev Oral Biol Med. 1997;8:291-305.
31. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: A gentle introduction to imputation of missing values. J Clin Epidemiol. 2006;59:1087-1091.
32. Doff MHJ, Finnema KJ, Hoekema A, Wijkstra PJ, de Bont LGM, Stegenga B. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on dental side effects. Clin Oral Invest. 2013;17:475–482.
33. Knappe SW, Bakke M, Svanholt P, Petersson A, Sonnesen L. Long-term side effects

on the temporomandibular joints and oro-facial function in patients with obstructive sleep apnoea treated with a mandibular advancement device. J Oral Rehabil. 2017;44:354-362.

5

The effect of raising the bite without mandibular protrusion on obstructive sleep apnoea

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J Oral Rehabil. 2011 Sep;38(9):643-7

Abstract

Background: It has recently been suggested that wearing a maxillary occlusal splint (i.e. a hard acrylic resin dental appliance that covers the occlusal surfaces of the maxillary dentition and that is being indicated for the treatment of, e.g. temporomandibular pain) may be associated with a risk of aggravating obstructive sleep apnoea (OSA). The present study tested the hypothesis that raising the bite without mandibular protrusion in OSA patients is associated with an increase in the apnoea–hypopnoea index (AHI). **Methods:** Eighteen OSA patients (13 men; 49·5±8·1 years old) received a mandibular advancement device in 0% protrusion of the mandible (0%MAD). The MAD caused a bite rise of 6 mm as measured interincisally. Polysomnographic recordings were obtained at baseline and with the 0%MAD in situ. **Results:** No statistically significant difference in AHI was noted between the baseline night and the 0%MAD night. However, nine patients had an aggravation in AHI during the night they used the 0%MAD. Taking into account the previously established smallest detectable difference of 12·8 in AHI, the AHI increased in only two of the patients. **Conclusion:** The outcomes of this study suggest that an increased jaw gape without mandibular protrusion might be associated with a risk of aggravation of OSA for some, but not for all OSA patients. Dental practitioners should be aware of this possible association when treating patients with oral devices that raise the bite.

Introduction

Obstructive sleep apnoea (OSA) is a sleep disorder that is characterised by recurrent episodes of partial or complete upper airway obstruction during sleep, leading to hypoxaemia and sleep disruption. The consequences of OSA include daytime sleepiness, neurocognitive dysfunction, cardiovascular disorders, metabolic dysfunction and impaired quality of life (1). Obstructive sleep apnoea is a common sleep disorder, especially in obese, middle-aged men, with an estimated prevalence of 4% in men and 2% in women (2). Undiagnosed OSA represents a public health problem, and some suggest that the incidence of OSA may even be higher than estimated (3,4).

Daily dental practice includes several procedures that raise the bite. Full-mouth dental rehabilitations and occlusal splints are examples of such procedures. Occlusal splints are frequently used in the management of temporomandibular disorders and bruxism (i.e. grinding and clenching of the teeth), as a part of rehabilitation procedures in patients with occlusal tooth wear, and as a protection of dental restorations. Occlusal splints modify the space between the dental arches, rotate the mandible and reduce the space for the tongue (5, 6). The possibility that an occlusal splint may alter airway patency in OSA patients during sleep has been investigated previously (7). In that open-label pilot study, it was found that the use of an occlusal splint in OSA patients may be associated with a risk of aggravation of their respiratory disturbance. Given the preliminary nature of this finding, more research is needed to further substantiate this understudied topic. Therefore, the aim of the present study was to test the hypothesis that raising the bite without mandibular protrusion in OSA patients is associated with an aggravation of the respiratory disturbance. This study is part of a large-scale study on the treatment effects of a mandibular advancement device (MAD) on OSA (8, 9).

Materials and methods

Participants

A total of 20 patients were invited to participate in the present study. They were selected from the Center for Sleep-Wake Disorders of the Slotervaart Medical Center. The multidisciplinary team that evaluates the polysomnographic (PSG) recordings and decides for treatment modalities consists of a neurologist, ENT specialists, pulmonologists, a dentist, psychologists and technicians especially trained in sleep medicine. All participants were at least 18 years old, had no orthodontic abnormalities and had an apnoea–hypopnoea index (AHI) between 5 and 45. Exclusion criteria were the following: the existence of sleep disorders other than OSA, a body mass index (BMI) of more than 40 (i.e. BMI values indicating morbid obesity), usage of medication that affects sleep, periodic limb movement disorder and previous treatment with continuous

positive airway pressure or a MAD. Patients with temporomandibular disorders (diagnosis based on a functional examination of the masticatory system) (10,11), an unhealthy periodontium, dental pain and/or an inadequate dentition for good retention of the MAD were excluded as well. The scientific and ethical aspects of the protocol were reviewed and approved by the Medical Ethics Committee of the Slotervaart Medical Center (#U/1731/0326).

Intra-oral device

The 20 patients received a MAD that consisted of two hard acrylic resin splints worn in the upper jaw and in the lower jaw. The two splints were connected with each other with a screw that allowed protrusion of the lower splint, and by that means, of the lower jaw. For the purpose of this study, the MAD was placed at 0% protrusion, i.e. with 0 mm advancement of the mandible. The MAD caused a bite rise of 6 mm as measured interincisally. For a detailed description of the MAD, see Aarab et al. (8, 9). The MADs were fabricated at the Department of Oral Kinesiology of the Academic Centre for Dentistry Amsterdam, The Netherlands. The MAD was constructed in collaboration with a dental laboratory (Amsterdams Tandtechnisch Laboratorium, Amsterdam, The Netherlands).

Study protocol

All patients underwent a full-night baseline PSG recording at the Slotervaart Medical Center without the intra-oral device in situ. Siesta hardware and ProFusion software (Compumedics, Abbotsford, Australia) were used for the recordings. After 3,85 +/- 0,98 weeks of wearing the device every night, all participants underwent a full-night ambulatory PSG recording at home, with their MAD in situ. Monet hardware and Rembrandt software (Medcare Automation BV, Amsterdam, The Netherlands) were used for the recordings. A trained co-worker performed the montage of both the baseline recordings and the ambulatory recordings at the Slotervaart Medical Center. All PSG recordings consisted of two electroencephalographic leads (C3-A2 and O2-A1), two electrooculographic leads, mental surface electromyography, nasal–oral airflow using a thermistor, oximetry, abdominal and thoracic respiratory effort, body position, electrocardiography, leg movements (m. tibialis anterior) and a piezoelectric lead for the detection of snoring. After each PSG recording, BMI and Epworth Sleepiness Scale (ESS) were obtained.

Data analysis

All PSG recordings were coded, randomised and analysed under blind conditions by a specialised technician. Only after the analyses of the data, the recordings were decoded. Sleep stages were scored manually in 30-s epochs according to Rechtschaffen and Kales (12) and standard sleep variables [see Aarab et al. (9)]; none of them differed significantly

between baseline and the 0%MAD night; data not shown) and respiratory variables were calculated. Following the American Academy of Sleep Medicine Task Force (1), an apnoea was defined as a cessation of airflow for at least 10 s; a hypopnoea, as a decrease in nasal–oral air flow of more than 50% for at least 10 s, or less than a 50% decrease if simultaneous arousal and/or an oxygen desaturation of >3% occurred. Subsequently, the AHI was calculated as the number of apnoeas and hypopnoeas per hour of sleep.

Statistical analysis

To enable the use of between-subjects factors, ANOVA for repeated measures was performed to assess possible statistical differences in the AHI and ESS between the two nights. Based on current insights into the aetiology and mechanisms of OSA, BMI (13, 14) was used as between-subjects factors. The number of patients that switched from mild to moderate, from mild to severe and from moderate to severe OSA was also assessed. Patients were categorized as mild if AHI was between 5 and 15; as moderate if AHI was between 15 and 30; and as severe if AHI was >30. For each individual patient that showed a worsening of the AHI, changes in AHI from baseline to the night with the MAD in situ were assessed for their statistical significance. To that end, a smallest detectable difference (SDD) value of 12.8 events per hour was used (15), as to account for the intra-individual variability in the AHI.

All analyses were carried out with SPSS package for windows, version 16.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

Initially, 20 OSA patients (14 men; 50.3 ± 9.1 years old) were included in the study. Two patients (a man and a woman) refused the ambulatory PSG recordings because they felt distressed while using the MAD in 0% protrusion of the mandible (feeling of choking). Thus, 18 patients (13 men; 49.5 ± 8.1 years old) completed the study protocol. The data of the two dropouts were not included in the final data analysis. ANOVA for repeated measures revealed no statistically significant difference in between the baseline night and the MAD night, neither for the AHI ($F = 0.07$, $P = 0.81$, $DF = 1$; Fig. 1) nor for ESS ($F = 0.23$, $P = 0.63$, $DF = 1$; Fig. 2).

When the patients were categorised as mild, moderate or severe OSA, two of them went from mild to moderate OSA, one from moderate to severe OSA and one from mild to severe OSA. Nine individual patients (50% of the participants) showed an aggravation in AHI during the night they used the MAD (Fig. 1). However, using the SDD to account for the intra-individual variability in the AHI, only two individuals showed a statistically significant aggravation of the AHI, viz., from 13,5 to 43,0 events per hour respectively from 41,7 to 55,3 events per hour.

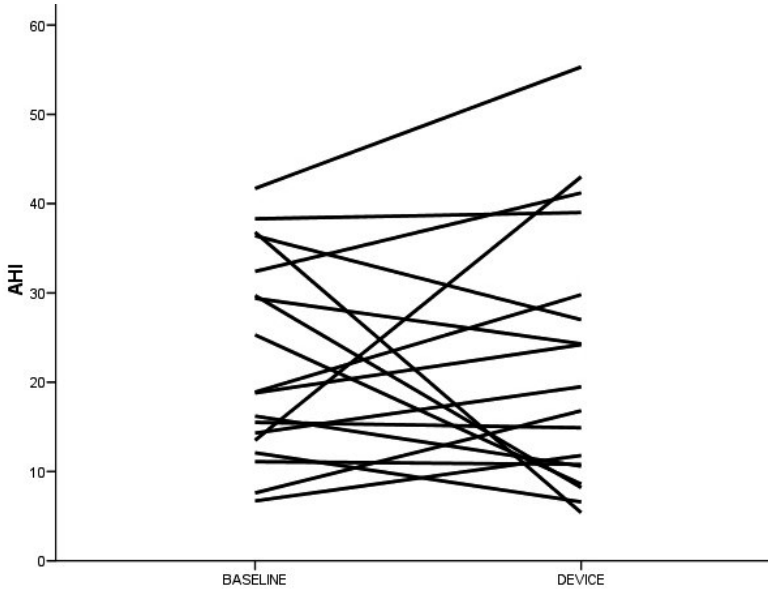

Fig. 1. Distribution of the apnoea–hypopnoea index for baseline and device [viz., with a mandibular advancement device in 0% protrusion of the mandible (0%MAD) in situ].

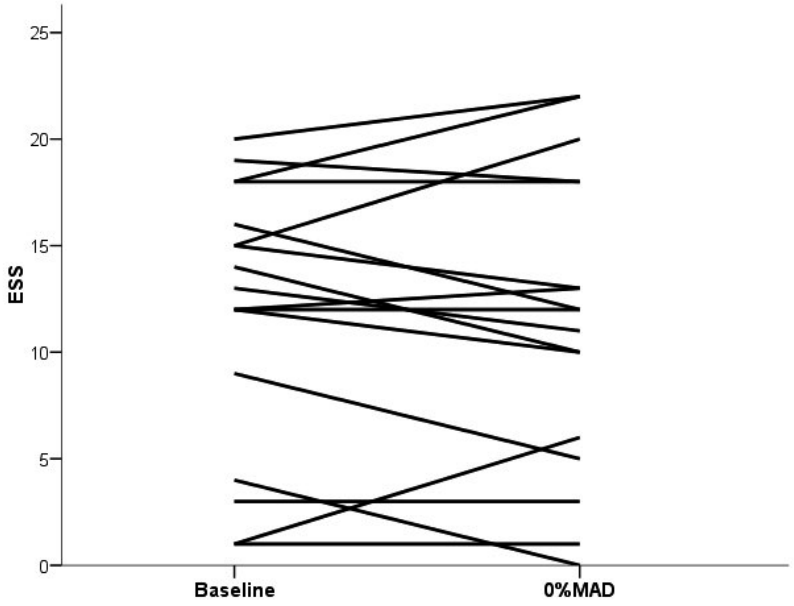

Fig. 2. Distribution of Epworth sleepiness scale for baseline and device. For further explanation, see Fig. 1.

Discussion

In the present study, the hypothesis was tested that an increase in bite rise without mandibular protrusion is associated with aggravating the respiratory disturbance in OSA patients.

Raising the bite with a MAD in 0% protrusion position did not increase the AHI at the group level, but at the individual level, the increased jaw gape was associated with an aggravation of the respiratory disturbance in 50% of our patients. It should be noted that the observed differences between two recordings do not necessarily reflect a true effect of the intervention. Body position can be ruled out as a possible explanation for the observed differences, because the percentage of time spent sleeping in supine position did not differ between baseline and the 0% MAD night. However, the differences may be related to factors like the natural course of the disorder under study and the biological fluctuation of the variables measured. Therefore, the SDD was used to take into account the night to- night variability in the AHI (15). Consequently, only two patients showed a statistically significant worsening of their AHI with the MAD in situ. When the SDD value of 12.8 events per hour is applied to the individual results in the study by Gagnon et al. (7), approximately one-third of their patients would have had a statistically significant increase in the AHI (see their Fig. 1 on p. 450). Even though Gagnon et al. (7) thus found a larger proportion of patients with an increase in their AHI, no significant group effect was observed. Apparently, some individuals are prone to develop a worsening of their OSA condition in response to a bite rise, while others are insensitive for such an effect. From the present study, it remains unclear which patient characteristics can be held responsible for aggravating the OSA condition. Clearly, this requires more research.

On the mechanisms that cause a worsening of the respiratory disturbance in some OSA patients in response to raising the bite, one can only speculate. In an OSA patient, the upper airway patency is reduced during sleep. Especially when the patient sleeps in supine position, the jaw is more open and the tongue and hyoid bone are posteriorly displaced (16, 17). In line with these observations, it could be speculated that a MAD in 0% protrusion position indeed modifies upper airway patency by increasing the vertical dimension, altering the position of the tongue, and rotating the mandible posteriorly. However, this possible mechanism needs to be substantiated in future studies.

The magnitude of the bite rise in the present study differed from that in the study by Gagnon et al. (7). Where Gagnon et al. (7) used an occlusal splint with a thickness of approximately 1,5 mm at the molar level and an interincisal thickness of maximally 4,5 mm, we employed an intra-oral device with a larger bite rise of 6 mm at the incisor level. Nevertheless, the proportion of OSA patients showing a worsening of their condition was smaller than that in the study by Gagnon et al. (7), while the opposite (i.e. more

aggravation with larger bite rises) might have been expected. Apparently, the (so far unknown) patient characteristics that can be held responsible for aggravating the OSA condition are more important than the actual magnitude of the bite rise.

It should also be noted that in the present study, the bite was not only raised but also fixated. This experimental condition does therefore not fully resemble the clinical situation where, as in the study by Gagnon et al. (7), an occlusal splint is inserted as a means to increase the vertical dimension. In the latter case, the mandible has the freedom to move in several directions, thus yielding differential effects on the OSA condition.

The accuracy of the present findings needs to be validated in a prospective randomised controlled trial (RCT), testing the effects of regular occlusal splints, before any clinical recommendations can be given. Such a RCT should contain, amongst others, multiple PSG recordings for each participant, as to take into account the night-to-night variability in AHI that has been described earlier (15, 18, 19).

The outcomes of this study suggest that an increase in bite rise without mandibular protrusion might be associated with a risk of aggravation of OSA for some but not for all OSA patients. Within the limitations of the present study design, in which a relatively large bite rise was tested and the mandible was immobilised during sleep, our results stress the fact that dental practitioners should be aware of the above-mentioned possible association when treating a patient with oral devices that raise the bite, because their patient might have an undiagnosed OSA. Hence, dentists should always focus on a possible OSA in their patients' oral history.

References

1. American Academy of Sleep Medicine Task Force. Sleeprelated breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep. 1999;22:667–689.
2. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Bader S. The occurrence of sleep disordered breathing among middleaged adults. N Engl J Med. 1993;328:1230–1235.
3. Kapur V, Strohl KP, Redline S, Iber C, O'Connor G, Nieto J. Underdiagnosis of sleep apnea syndrome in U.S. communities. Sleep Breath. 2002;6:49–54.
4. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep. 1997;20:705–706.
5. Dao TT, Lavigne GJ. Oral splints: the crutches for temporomandibular disorders and bruxism? Crit Rev Oral Biol Med. 1998;9:345–361.
6. Macedo CR, Silva AB, Machado MA, Saconato H, Prado GF. Occlusal splints for treating sleep bruxism (review). Cochrane Database Syst Rev. 2007;17:CD005514.
7. Gagnon Y, Mayer P, Morisson F, Rompre´ PH, Lavigne GJ. Aggravation of respiratory disturbances by the use of an occlusal splint in apneic patients: A pilot study. Int J Prosthodont. 2004;17:447–453.
8. Aarab G, Lobbezoo F, Wicks DJ, Hamburger HL, Naeije M. Short-term effects of a mandibular advancement device on obstructive sleep apnoea: an open-label pilot trial. J Oral Rehabil. 2005;32:564–570.
9. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Effects of an oral appliance with different mandibular protrusion positions at a constant vertical dimension on obstructive sleep apnea. Clin Oral Invest. 2010;14:339–345.
10. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord. 1992;6:301–355.
11. Lobbezoo F, van Selms MK, John MT, Huggins K, Ohrbach R, Visscher CM et al. Use of the research diagnostic criteria for temporomandibular disorders for multinational research: translation efforts and reliability assessments in The Netherlands. J Orofac Pain. 2005;19:301–308.
12. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and

scoring systems for sleep stages of human subjects. Los Angeles: Brain Information Service/Brain Research Institute, UCLA; 1968.

13. Johns MW. Daytime sleepiness, snoring and obstructive sleep apnea: the Epworth sleepiness scale. Chest. 1993;103:30–36.
14. Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. Thorax. 1991;46:85–90.
15. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Variability in the apnea- hypopnea index and its consequences for diagnosis and therapy evaluation. Respiration. 2009;77:32–37.
16. Cartwright RD. Effect of sleep position on sleep apnea severity. Sleep. 1984;7:110–114.
17. Miyamoto K, Ozbek MM, Lowe AA, Sjo¨holm TT, Fleetham JA, Ryan CF. Mandibular posture during sleep in patients with obstructive sleep apnoea. Archs Oral Biol. 1999;44:657– 664.
18. Bittencourt LRA, Suchecki D, Tufik S. The variability of the apnoea-hypopnoea Index. J Sleep Res. 2001;10:245–251.
19. Mosko SS, Dickel MJ, Ashurst J. Night-to night variability in sleep apnea and sleep-related periodic leg movements in the elderly. Sleep. 1988;11:340–348.

6

Effects of occlusal stabilization splints on obstructive sleep apnea: a randomized controlled trial

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J Orofac Pain. 2013 Summer;27(3):199-205

Abstract

Background: It has been suggested that wearing an occlusal stabilization splint may be associated with a risk of aggravating obstructive sleep apnea (OSA). The aim of the study was to assess the influence of a stabilization splint on OSA in a randomized controlled trial design. **Methods**: Ten OSA patients (47.3 ± 11.7 years) received an occlusal stabilization splint in the upper jaw. All patients underwent three polysomnographic recordings (PSGs) with their splint in situ, and three PSGs without their splint in situ, using a randomized cross-over design. **Results:** There was no statistically significant difference in the Apnea-Hypopnea Index (AHI) or in the Epworth Sleepiness Scale (ESS), neither between the three nights without the stabilization splint (AHI: $F = 2.757$, $p = 0.090$; ESS: $F = 0.153$, $p = 0.860$) nor between the three nights with the splint in situ (AHI: $F = 0.815$, $p = 0.458$; ESS: $F = 0.231$, $p = 0.796$). However, the mean AHI of the three nights with the stabilization splint in situ was significantly higher than that of the three nights without the splint in situ ($F = 7.203$, $p = 0.025$). No difference in ESS was found when both conditions were compared ($F = 2.03$, $p = 0.343$). **Conclusion**: The use of an occlusal stabilization splint is associated with a risk of aggravation of OSA. Dental practitioners should be aware of a possible OSA in their patients' oral history, as to prevent indicating a stabilization splint in patients with an undiagnosed OSA unquestioningly.

Introduction

In dentistry, occlusal stabilization splints (i.e., hard acrylic-resin dental appliances that cover the occlusal surfaces of the maxillary dentition) are commonly used in the management of temporomandibular disorders (a number of clinical problems that involve the masticatory muscles, the temporomandibular joint, and the associated structures) (1) and of sleep bruxism (an oral parafunction characterized by grinding or clenching of the teeth during sleep), (2) . They are also used in dental rehabilitation procedures for patients with occlusal tooth wear, and to protect dental restorations. The possibility that a stabilization splint alters airway patency during sleep in patients with obstructive sleep apnea (OSA; a condition characterized by repetitive complete or partial obstruction of the upper airway during sleep) (3) has been investigated in two previous pilot studies (4, 5). One study found that the use of stabilization splints in OSA patients may be associated with a risk of aggravating these patients' respiratory disturbance. In the other study, a mandibular advancement device, which is a common treatment option for mild and moderate OSA (6), was inserted in the 0% protrusion position (ie without protruding the mandible), thereby only raising the bite of the participating OSA patients (5). In line with the finding of Gagnon et al.(4), the outcome of that study suggested that a bite rise without a protrusive component may be associated with a risk of aggravation of OSA for some, but not for all OSA patients. So far, however, no well-controlled prospective clinical trial has been performed on this topic, thus rendering the suggested association between stabilization splints and aggravation of OSA as inconclusive. The aim of the present study, therefore, was to assess the influence of occlusal stabilization splints on sleep-related respiratory variables in OSA patients was employed. A cross-over, randomized, controlled trial design. The hypothesis was that insertion of a stabilization splint, resulting in an increase of the vertical dimension of occlusion, rotation of the mandible, and reduction of the tongue space would yield a significant worsening of the OSA condition.

Materials and methods

Settings and Participants

Potential participants for the present study were selected from among those being referred to the Center for Sleep-Wake Disorders of the Slotervaart Medical Center in Amsterdam by their family physician because of a possible OSA. All potential participants underwent a thorough medical examination, including a full-night polysomnographic (PSG) recording, using Siesta hardware and ProFusion software (Compumedics). A multidisciplinary OSA team, consisting of neurologists, ear, nose and throat specialists, pulmonologists, dentists, psychologists, and technicians especially trained in sleep medicine, discussed all PSG recordings. All consecutive and eligible OSA patients for

whom a mandibular advancement device was indicated were invited for participation in the study, provided that they also fulfilled the other inclusion and exclusion criteria (see below).

OSA was quantified and classified using the apnea-hypopnea index (AHI) (3), which was used as this study's primary outcome measure. According to the American Academy of Sleep Medicine Task Force (3), an apnea is defined as a cessation of airflow for at least 10 seconds. A hypopnea is defined as a decrease in nasal-oral airflow of more than 50% for at least 10 seconds, or a substantial decrease of less than 50% in nasal-oral airflow if associated with an arousal and/or an oxygen desaturation of greater than 3%. The AHI is the number of apneas and hypopneas per hour of sleep. Based on the report of the American Academy of Sleep Medicine Task Force (3), an AHI of at least 5 events/hour and the presence of excessive daytime sleepiness (measured objectively or subjectively) which is not explained by other factors, are commonly used for an OSA diagnosis. When excessive daytime sleepiness is absent, at least two symptoms, e.g., recurrent complaints of unrefreshing sleep and daytime fatigue, should be present (3).

To be included in this study, participants had to be at least 18 years of age, and their AHI should have a value between 5 and 30 events/hour of sleep (7), combined with an Epworth Sleepiness Scale (ESS) score 6-10 (higher values were excluded for ethical reasons) (8), or with at least two of the symptoms suggested by the American Academy of Sleep Medicine Task Force (3); (see above). Further, the participants had to have adequate retention possibilities in their dentition for an occlusal stabilization splint (i.e., not missing more than two posterior teeth and not wearing a removable dental prosthesis), which was determined during a thorough dental examination at the Department of Oral Kinesiology of the Academic Centre for Dentistry Amsterdam (ACTA). Exclusion criteria were medicine usage that influences sleep (e.g., selective serotonin re-uptake inhibitors, benzodiazepines), a body mass index (BMI) of more than 40, and/or sleep bruxism (i.e., diagnosed by a PSG recording following the criteria of Lavigne et al. (9)). Patients with temporomandibular disorders (diagnosis based on a functional examination of the masticatory system) (10), an unhealthy periodontium (i.e., periodontal diseases), and/or dental pain (e.g., chronic pulpitis) were excluded as well.

Following the above-outlined selection procedure, a total 16 OSA patients were asked to participate in the present study. Six of them (3 men and 3 women) declined participation because of time constraints. Thus, a total of 10 mild/moderate OSA patients with an AHI between 5 and 30 events/ hour participated in the study. There were 3 men and 7 women, with a mean (± SD, range) age of 47.3 (± 11.7, 23-62) years.

The scientific and ethical aspects of the protocol were reviewed and approved by the Medical Ethics Committee of the Slotervaart Medical Center (NL23988.048.08). The protocol was also registered at ClinicalTrials.gov under number NCT01004692.

Randomization and Allocation

The participants were randomly allocated to one of two investive groups (see Study protocol). To ensure that the groups were of approximately the same size, block randomization was used. The allocation sequence was automatically generated and subsequently concealed by an independent co-worker, who kept a paper copy in a lockable drawer. Sealed opaque envelopes were used to conceal the allocation from the principal investigator.

Occlusal Stabilization Splint and Blinding

An occlusal stabilization splint was constructed for each participant. The splint was a hard acrylic-resin appliance with no palatal coverage, to be worn in the maxilla. It caused a bite rise of about 1.0 mm at the level of the first molar (for a detailed description, see van der Zaag et al., (11)). The intermaxillary relationship of choice was the retruded contact position, i.e., the point of initial contact between the mandibular dentition and the splint when the mandibular condyles are guided along the posterior slope of the articular eminence into their most superior position on jaw closure (1). Canine guidance and anterior guidance were built-in so as to enable contralateral and posterior disclusion during articulation movements. The splint did not come into contact with the participant's soft tissues, nor did it act as an orthodontic device. The splints were fabricated at the Department of Oral Kinesiology of ACTA, in collaboration with a dental laboratory (Excent Tandtechniek Amsterdam).

The participants were blinded to the priory hypothesis regarding the effect of the splint on their OSA condition. After using the splint, all the patients were asked if they experienced a change in their sleep apnea symptoms with the splint in situ. Analyst blinding was ascertained by assigning codes to data sets and by analyzing these sets in random blocks.

Study Protocol

After written informed consent was obtained, all participants underwent two sets of three consecutive ambulatory PSG home recordings, with two weeks between both sets, using a cross-over design. In the first randomly composed group (see Randomization and Allocation), the participants (2 men, 4 women) who had a mean (± SD, range) age of 50.2 ± 8.7 39-60) years first underwent the three nights of PSG recordings without the stabilization splint in situ. After the two-week wash-out period, they underwent the three nights of recordings with the splint in situ. In the second group, the participants (1 man, 3 women) with a mean (± SD, range) age 43.0 ± 15.7, 23-62) years first underwent the three PSG recordings with the splint in situ, and two weeks later, they underwent the three PSG recordings without the splint in situ. All participants used the splint in situ ten nights before the recordings as a habituation period.

Monet hardware (Medcare) was used for the ambulatory recordings, and Rembrandt software (Medcare) was used for the analyses. All PSG recordings consisted of two electroencephalographic leads (C3-A2 and O2-A1), two electro-oculographic leads, mental surface electromyography, nasal-oral airflow using a thermistor, oximetry, abdominal and thoracic respiratory effort, body position, electrocardiography, leg movements (m tibialis anterior), and a piezoelectric lead for the detection of snoring. A trained co-worker performed the montage of the recording devices at the Slotervaart Medical Center.

After each PSG recording, values of BMI and ESS were obtained.

Data Analysis

All PSG recordings were coded, randomized, and analyzed under blind conditions by a specialized sleep medicine technician. This examiner's intra-observer reliability of AHI scoring was excellent, with an intraclass correlation coefficient (ICC) of 0.96; that of sleep scoring could be qualified as good to excellent, with ICC values ranging from 0.64 to 0.96. Sleep stages were scored manually in 30-sec epochs according to Rechtschaffen and Kales (12), and standard sleep variables and respiratory variables were obtained. After the completion of the analyses, the recordings were decoded again.

Statistical Analysis

To enable the use of within-subjects factors, analyses of variance (ANOVAs) for repeated measures were performed. Based on current insights into the etiology and mechanisms of OSA (8, 13), BMI was introduced as between-subjects (co-) factor in case of a significant interaction of BMI with the variable of interest (i.e., AHI or ESS). Repeated measures ANOVA was used to assess possible statistical differences in the AHI (the primary outcome measure) and ESS between the consecutive nights. Second, the AHI and ESS values of the three non-splint nights and of the three splint nights were averaged, followed by independent ANOVA to check if there was a statistically significant difference in AHI and in ESS between the mean values of the non-splint nights and the mean values of the splint nights. Finally, the standard sleep variables, averaged over the three nights for each condition, were compared between the splint and non-splint conditions by using two-independent-samples t tests and Bonferroni adjustment for multiple comparisons.

All analyses were performed with the SPSS package for windows, version 16.0 (SPSS Inc). $P < .05$ was considered statistically significant.

Results

All but one participants, completed the entire study protocol, even though two of them felt that the stabilization splint caused dry lips and increased their snoring. The patient who did not complete the entire protocol, failed to do the last recording of the splint condition because of severe allergy to the glue and stickers used for the recordings. All PSG recordings were judged to have normal structures by the medically responsible sleep medicine specialist (HLH). The standard sleep variables are shown in Table 1. None of them differed significantly between the splint and non-splint conditions after Bonferroni adjustment (i.e., statistically significant when $P < .0083$).

Since no significant interactions between BMI and any of the outcome measures were present, the ANOVAs for repeated measures were performed without using BMI as a cofactor. There was no statistically significant difference in AHI or in ESS between the three nights without the stabilization splint (AHI: $F = 2.757$, $P = 0.090$; ESS: $F = 0.153$, $P = 0.860$). Similarly, there was no statistically significant difference in AHI or in ESS between the three nights with the splint in situ (AHI: $F = 0.815$, $P = 0.458$; ESS: $F = 0.231$, $P = 0.796$). To illustrate the night-to-night variability in AHI, Fig. 1 shows the results of the six PSG recordings for each individual.

Fig. 2 shows the mean AHI values of the three PSG recordings per experimental condition (ie, without and with the stabilization splint in situ) for all ten participants individually. The mean AHI of the three nights with the stabilization splint in situ was significantly higher than that of the three nights without the splint in situ (with splint: mean $\pm$ SD = 17.4 $\pm$ 7.0 events/hour; without splint: mean $\pm$ SD = 15.9 $\pm$ 6.4 events/hour; $F = 7.203$, $P = .025$). The mean $\pm$ SD increase in AHI with the splint in situ was 1.4 $\pm$ 1.7 events/hour; its 95% confidence interval (1.4 $\pm$ 1.96*1.7=) was -1.9 – 4.7. Even when the patient with the largest effect size (a 62-year-old male; BMI = 20.9; neck circumference = 44.2 cm) was removed from the analyses, the mean increase ($\pm$SD) in AHI (0.9 $\pm$ 0.5) remained statistically significant ($F = 29.033$; $P = .001$). No significant difference in ESS was found when both experimental conditions were compared (with splint: mean $\pm$ SD= 9.5 $\pm$ 5.3; without splint: mean $\pm$ SD = 9.6 $\pm$ 5.2; $F = 1.00$, $P = .343$). An interaction with randomization order was not present for AHI or for ESS (AHI: $F = 2.65$, $P = .142$; ESS: $F = .812$, $P = .394$).

Table 1. Mean values ± SD of the standard sleep variables of the ten participants, averaged over the three nights for both experimental conditions (i.e., without and with the stabilization splint in situ). T = test statistic for two-independent-samples t tests.*

	No splint	Splint	T	P
Total sleep time (min)	428.9 ± 64.9	437.1 ±85.9	-.315	.757
Stage 1 and 2 (%)	67 ± 11.4	60.4 ±14.8	1.990	.065
Stage 3 and 4 (%)	14.7 ± 12.8	17.5 ±7.2	-.994	.330
Stage REM (%)	19.9 ± 6.5	20.3 ±5.2	-.933	.362
Sleep in supine position (%)	51.0 ± 23.9	42.1 ± 22.8	1.120	.279
Sleep Efficiency (%)	83.3 ± 7.3	87.9 ±4.1	-2.61	.042

*For one participant, the mean values of the splint condition were based on two PSG recordings (see Results)

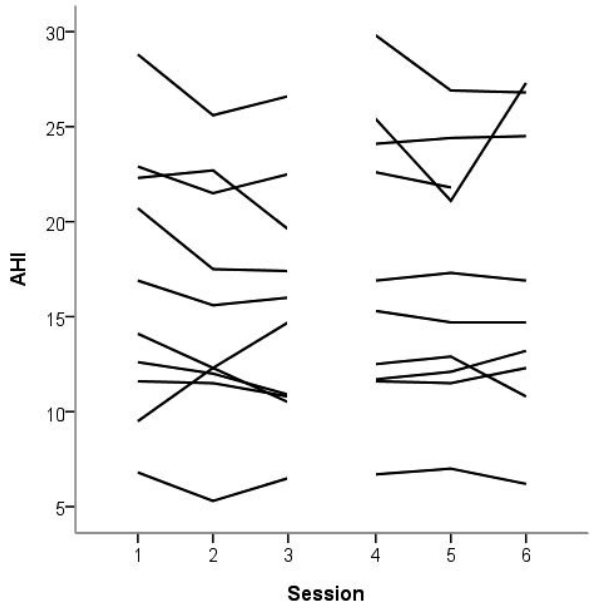

Fig. 1. AHI values obtained with the six PSG recordings per participant. Please note that for one participant, the AHI from the sixth PSG recording is missing (see Results).

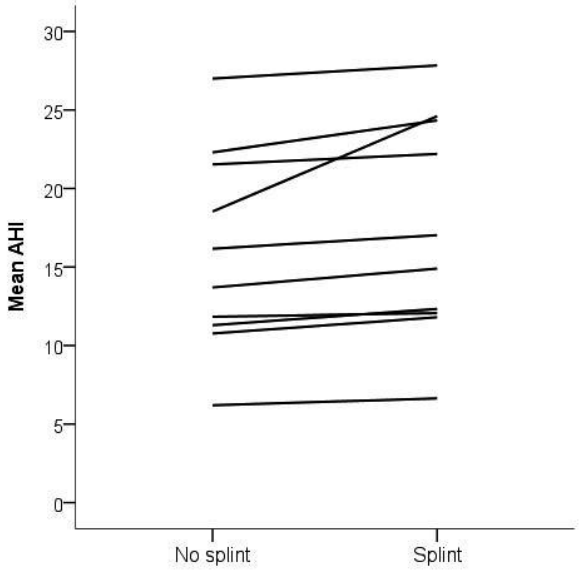

Fig. 2. Mean AHI values of the three PSG recordings per experimental condition (i.e., without and with the stabilization splint in situ) for all ten participants individually. Please note that for one participant, the mean value of the splint condition was based on two PSG recordings (see Results).

Discussion

The hypothesis tested in this study was that an occlusal stabilization splint is associated with aggravating the respiratory disturbance in OSA patients. The use of stabilization splints indeed raised the AHI significantly. The increase in the AHI was small, but it occurred in all 10 OSA patients who participated in the study (see Fig. 2). Even when the patient with the largest effect size was removed from the analyses, the mean increase in AHI remained statistically significant. If one considers the mean difference plus or minus its 95% confidence interval, however, it turns out that zero is included in the interval, suggesting that both experimental conditions could be considered equivalent. Hence, whether the small increase in the AHI is actually clinically relevant, remains to be studied. Also, the long-term effects of stabilization splints on OSA need to be captured in future longitudinal trials, although such studies may be difficult to perform, because most patients will have received treatment for their OSA condition in the meantime.

Previous studies (4, 5) found no significant group change of the AHI when the bite was raised in OSA patients. Increases were observed only at the individual level. In both previous studies, however, it was noted that the observed differences between the two conditions (i.e., no increased jaw gape versus increased vertical dimension) did not necessarily reflect a true effect of the intervention, because these were not randomized

controlled trials (RCTs). In contrast, the present study was a RCT. The employed cross-over design allowed each patient to be his or her own control. The design included a 2 weeks wash-out period between both conditions (ie, no splint versus splint). Furthermore, multiple PSG recordings were obtained for both conditions and for each participant, to take into account the night-to-night variability in AHI (14-16). Hence, the present study yielded conclusive data.

Apart from the dissimilarities in study design, variation in the design of the intraoral devices could have influenced the differences between both previous studies (4, 5) and the present one as well. Indeed, the magnitude of the bite rise in the present study (viz., about 1.0 mm at the level of the first molar) differed from that in the studies by Gagnon et al (4) and Nikolopoulou et al (5). Gagnon et al (4) used an occlusal stabilization splint with a slightly larger thickness of approximately 1.5 mm at the molar level and of maximally 4.5 mm at the incisor level, while Nikolopoulou et al (5) used an intra-oral device (viz., a mandibular advancement device with 0% protrusion) with a bite rise of 6 mm at the incisor level. Where the small difference in thickness of only about 0.5 mm between the splints used in the present study and those used by Gagnon et al (4) is unlikely to have contributed to the different findings between both studies, the considerable difference in thickness between the devices used in the authors' previous study[5] and in the present one may have contributed to the different findings.

The exact mechanism that may have caused the above-discussed effect of increased thickness is as yet unknown. Possibly, it is related to the fact that occlusal stabilization splints not only modify the space between the dental arches, but also reduce the space for the tongue and rotate and anteriorly translate the condyles (17-19), thus compromising the upper airway lumen.

Another aspect related to the design of the intraoral devices used in the various studies so far is the fact that in the study by Nikolopoulou et al (5), the mandible was fixed to the maxilla with the intraoral device in situ, while both in the study by Gagnon et al (4) and in the present study the mandible could move freely in all directions. Hence, the above-discussed lumen-narrowing effect of intraoral devices is likely to have been stronger in the study by Nikolopoulou et al (5), because the mandible was prevented from moving anteriorly, and thus from widening the upper airway lumen.

The 62-year-old male participant who showed the largest increase in the AHI with the occlusal stabilization splint in situ, was also one of the two patients who complained of increased snoring with the splint in situ. Interestingly, when this patient was compared to the other participants, he turned out to have a relatively low BMI but a relatively large neck circumference. Obesity is known to be the main risk factor of OSA (20, 21). However, in this case, the participant was of normal weight, even tending towards underweight. On the other hand, fat deposition around the upper airway, as suggested in this participant

by his neck circumference, may narrow the airway lumen and increase the collapsibility of the pharynx. (22). Furthermore, the older the age (and this was the oldest participant), the more this factor is considered a risk for developing OSA (23). Mechanisms, proposed in the literature for the age-related increase in OSA include increased deposition of fat in the parapharyngeal area and lengthening of the soft palate, which both result in a narrowed upper airway and a worsening of the upper airway neuromuscular reflexes (24, 25)This participant's fat deposition around the neck in combination with his relatively high age could thus explain the considerable rise of the AHI with the splint in situ.

ESS did not differ between the two conditions studied. This was to be expected, because already in the study of Nikolopoulou et al (5), where a much higher bite raise was used in a comparable time frame, there was no change in ESS between both conditions either. Further, a change of lifestyle, which could lead to an improvement in ESS, was not possible within the short time frame of the present study. In a long-term follow-up study, Aarab et al (26) observed a delayed improvement of both continuous positive airway pressure and mandibular advancement devices on ESS as compared to the effects of these interventions on the AHI. Hence, long-term studies are needed to reveal the possible effects of occlusal stabilization splints on ESS.

Conclusions

This study revealed a small but statistically significant increase in the AHI of OSA patients with an occlusal stabilization splint in situ as compared to the condition without occlusal splint. The use of an occlusal stabilization splint may thus be associated with a risk of aggravation of OSA, although the clinical relevance of this finding may be questioned given the small effect size and the fact that the ESS did not change. Nevertheless, as in individual patients a stabilization splint may lead to an apparent increase in the AHI in individual patients, so dental practitioners should be aware of a possible OSA in their patients' oral history.

References

1. American Academy of Orofacial Pain. Orofacial Pain. Guidelines for Assessment, Diagnosis, and Management, Fourth Edition. R De Leeuw (Ed). Chicago: Quintessence Publishing Co, Inc, 2008.
2. American Academy of Sleep Medicine: International Classification of Sleep Disorders. Westchester, IL: American Academy of Sleep Medicine, 2005.
3. American Academy of Sleep Medicine Task Force: Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667-689.
4. Gagnon Y, Mayer P, Morisson F, Rompré PH, Lavigne GJ. Aggravation of respiratory disturbances by the use of an occlusal splint in apneic patients: A pilot study. Int J Prosthodont 2004;17:447-453.
5. Nikolopoulou M, Naeije M, Aarab G, Hamburger HL, Visscher CM, Lobbezoo F. The effect of raising the bite without mandibular protrusion on obstructive sleep apnea. J Oral Rehabil 2011;38:643-647.
6. Kushida CA, Morgenthaler TI, Littner MR, et al. American Academy of Sleep: Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005. Sleep 2006;29:240-243.
7. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Effects of oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: A randomized, placebo-controlled trial. Respiration 2011;81:411-419.
8. Johns MW: A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-545.
9. . Lavigne GJ, Rompré PH, Montplaisir JY. Sleep bruxism: Validity of clinical research diagnostic criteria in a controlled polysomnographic study. J Dent Res 1996;75:546-552.
10. Lobbezoo F, van Selms MK, John MT, et al. Use of the research diagnostic criteria for temporomandibular disorders for multinational research: Translation efforts and reliability assessments in The Netherlands. J Orofac Pain 2005;19:301-308.
11. Van der Zaag, Lobbezoo F, Wicks DJ, Visscher CM, Hamburger HL, Naeije M. Con-

trolled assessment of the efficacy of occlusal stabilization splints on sleep bruxism. J Orofac Pain 2005;19:151-158.

12. Rechtschaffen A, Kales A. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Los Angeles: UCLA Brain Information Service/Brain Research Institute, 1968.
13. Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. Thorax 1991;46:85-90.
14. Mosko SS, Dickel MJ, Ashurst J. Night-to night variability in sleep apnea and sleep-related periodic leg movements in the elderly. Sleep 1988;11:340-348.
15. Bittencourt LRA, Suchecki D, Tufik S. The variability of the apnoea-hypopnoea index. J Sleep Res 2001;10:245-251.
16. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Variability of the apnoea- hypopnoea index and its consequences for diagnosis and therapy evaluation. Respiration 2009;77:32-37.
17. Dao TT, Lavigne GJ. Oral splints: The crutches for temporomandibular disorders and bruxism? Crit Rev Oral Biol Med 1998;9:345-361.
18. Macedo CR, Silva AB, Machado MA, Saconato H, Prado GF. Occlusal splints for treating sleep bruxism (review). Cochrane Database Syst Rev 2007;17: D005514.
19. Ettlin DA, Mang H, Colombo V, Palla S, Gallo LM. Stereometric assessment of TMJ space variation by occlusal splints. J Dent Res 2008;87:877-881.
20. Davies RJ, Stradling JR. The relationship between neck circumference, radiographic pharyngeal anatomy, and the obstructive sleep apnoea syndrome. Eur Respir J 1990;3:509-514.
21. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: A population health perspective. Am J Respir Crit Care Med 2002;165:1217-1239.
22. Strobel RJ, Rosen RC. Obesity and weight loss in obstructive sleep apnea: a critical review. Sleep 1996;19:104-115.
23. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008;5:136-143.
24. Malhotra A, Huang Y, Fogel R, et al. Aging influences on pharyngeal anatomy and physiology: the predisposition to pharyngeal collapse. Am J Med 2006;119:72.e9-14.

25. Eikermann M, Jordan AS, Chamberlin NL, et al. The influence of aging on pharyngeal collapsibility during sleep. Chest 2007;131:1702-1709.
26. Aarab G, Lobbezoo F, Heymans MW, Hamburger HL, Naeije M. Long-term follow-up of a randomized controlled trial of oral appliance therapy in obstructive sleep apnea. Respiration 2011;82:162-168.

7

General Discussion

The studies included in this thesis all aimed at further clarifying the therapeutic effects and side effects of mandibular advancement devices (MADs) in the management of obstructive sleep apnea (OSA). Four out of the five studies were part of a large placebo-controlled randomized clinical trial (RCT) in which the effects of an MAD were compared to those of nasal continuous positive airway pressure (nCPAP) and an intraoral placebo appliance. The primary outcomes of this RCT have been published previously (1, 2). The fifth study was designed separately from the large RCT, in order to examine the effects of an occlusal stabilization splint in OSA patients.

Methodological considerations

All studies in this thesis have an RCT design. Four are part of a larger RCT, the primary outcomes of which have been published previously. One of them was newly designed (3).

RCT's have both advantages and disadvantages. The ability to make causal inferences means that RCT's provide the strongest empirical evidence of a treatment's efficacy. Randomization of participants to the test and control arms and concealment of their allocation ensures that allocation bias and confounding of unknown variables are minimized. Moreover, an RCT study can be tailored to answer a specific research question (4).

Amongst the disadvantages, awareness is increasing that the highly selected study samples almost never yield results that can be extrapolated to the general population. Therefore, a single RCT is not enough for a solid evidence base for a certain treatment. Rather, multiple RCT's are needed to that end, so that the results can be used in meta-analyses, the outcome of which will be more validly applicable to the general population than its constituent RCT's alone (5). One might even argue that large observational trials using propensity score matching and appropriate multivariate regression analyses might better reflect the 'real clinical world' than an RCT performed in a homogenous subgroup of patients (6). Of important notice in this context is the need for standardized methods and large study samples. Hence, internationally accepted data collection protocols are needed that are preferably used in large-scale multicenter or ever international consortia. Only then, results will be found that can be used in evidence-based guidelines that will ultimately be of benefit for our patients.

The larger RCT, on which four of the five studies of this thesis are based, included some specific design elements, viz.: 1. the use of an MAD with a constant vertical dimension at various protrusion positions; 2. the application of a stringent titration protocol, not only for nCPAP but also for MAD treatment; and 3. the inclusion of a placebo condition. The use of an MAD with a constant vertical dimension at various protrusion positions

enabled an unequivocal interpretation of the effects of mandibular protrusion alone, i.e., without the usual hybrid effect of protrusion in combination with vertical opening. Consequently, the findings can be interpreted in a more straightforward way, i.e., in terms of the actual horizontal movement of the mandible. Application of a stringent titration protocol enabled an unbiased comparison between MAD and nCPAP treatment, while enabling an optimal balance between MAD effects and side effects at the same time. Finally, the inclusion of a placebo condition reduced the risk of bias. All in all, the larger RCT fulfills most of the so-called CONSORT [CONsolidated Standards of Reporting Trials; (7)] criteria for parallel-group clinical trials and can thus be considered a high-quality RCT.

Comorbidity network

OSA is not an isolated entity. Rather, it is part of a complex comorbidity network, in which it has direct or indirect associations with many other conditions and disorders. At the same time, these associations are influenced by a variety factors that link two or more conditions or disorders with each other (8, 9). The first three studies of this thesis, described in chapters 2-4, contribute to unravelling part of OSA's comorbidity network by studying the effects of MAD and nCPAP on comorbid conditions like psychological distress, sleep-related problems and sleep disorders other than OSA, and temporomandibular disorder (TMD) pain in a placebo-controlled design.

It was the studies' general hypothesis that by successfully treating the primary condition, in this case OSA, also associated comorbid conditions, but for TMD pain, would show improvement. We concluded that both the MAD group and the nCPAP group showed significant improvements over time in psychological distress, but so did the placebo group. We believe that this may be due to the attention given to the patients during the entire protocol, or even to a possible change in lifestyle that was suggested already at the intake. Similar positive effects on self-reported symptoms of common sleep disorders and sleep-related problems in mild and moderate OSA patients were found for both the MAD group and the nCPAP group. The improvement of these symptoms was similar in the placebo group as well. Therefore, it is unclear if the positive effects on the symptoms was due to a better sleep quality or due to, e.g., a better sleep hygiene followed by the patients. Regarding the TMD pain, we hypothesized that treatment of OSA with MAD would result in ore clinical signs and symptoms of TMD pain, as well as with possible mandibular function impairment. We concluded that this was not the case after 6 months of treatment. This is possibly because of the transient nature of TMD pain as a side effect in OSA treatment.

Interesting byproduct would be that alleviation of comorbid conditions like psychological distress, sleep-related problems and sleep disorders other than OSA would be beneficial for treatment compliance. The social and psychological factors that can influence compliance are knowledge and understanding of the therapeutic regimens, including communication, the patient–provider relationship, patient satisfaction, social isolation, and social support, including the effect of the family, health beliefs and attitudes (10). In addition, factors that are associated with the illness and the treatment itself, including the duration and the complexity of the treatment, influence compliance (11). Following that, patients with higher values of social and psychological distress would show higher AHI reduction values. Interestingly, in our study, OSA patients with higher values of the psychological distress at baseline showed less reduction in the apnea-hypopnea index (AHI) than patients with lower values of this index at baseline. The nature of this association is unclear, but this finding suggests that the level of psychological distress at the start of the treatment may play a significant role in the treatment outcome.

Vertical dimension

Two of the included studies in this thesis (chapters 5 and 6) focused of the effects of vertical dimension on the primary outcome measure of the RCTs, namely the AHI. The first one (chapter 5) used the MAD of the larger RCT, set in the 0% protrusion position and using the intraoral placebo appliance as its control condition, while the second one (chapter 6) used occlusal stabilization splints versus the no-splint condition.

Importantly, it should be noted that a 0%-MAD cannot directly be compared to a stabilization splint; they are totally different appliances with different effects on vertical dimension. While a stabilization splint causes a relatively small vertical opening of approx. 1 mm measured between the first molars, the one caused by an MAD is significantly larger, viz., approx. 6 mm.

Further, while the splint is made with the lower jaw in centric relation, i.e., the most dorsal yet unstrained position of the mandible with respect to the maxilla, the 0%-MAD forces the mandible to its rearmost position. This is not only uncomfortable for many patients, it also represents an extra compromising factor for the upper airway, apart from the already larger backward rotation due to the larger mouth opening. A larger vertical dimension is known to be related to narrowing of the upper airway, because mouth opening is associated with an inferior-posterior movement of the mandible and the tongue, which influences pharyngeal airway patency (12). The vertical dimension during sleep is larger in patients with OSA than in healthy adults, and the mouth opening increases progressively during apneic episodes and decreases at the termination of those episodes (13). Lowe (14) has proposed that advancement of the mandible

displaces the tongue away from the posterior wall of the upper airway, whereas its inferior displacement shifts the tongue away from the soft palate. Hence, mandibular protrusion in combination with an increased vertical dimension may negate pharyngeal closure induced by increased mouth opening alone.

In the 0% protrusion position, a worsening of OSA was observed in some but not all patients, as compared to the placebo condition. Apart from the explanations provided in chapter 5, another possible explanation could be that the MAD was actually successful in reducing sleep bruxism (SB). Indeed, short-term usage of an MAD by SB patients is associated with a significant reduction in SB motor activity (15-17). Nowadays, SB is suggested to be important in maintaining upper airway patency (18). Kato et al (19) showed that the contractions of jaw and leg muscles are nonspecific motor phenomena in response to arousals rather than respiratory events. They concluded that jaw muscle contractions can remain to occur in OSAS patients using an oral appliance. Nonspecific motor events can be a confounding factor for assessing motor events and associated clinical symptoms in patients with frequent arousals such as OSAS. With that in mind, it can be reasoned that If jaw muscle activity reduces with an MAD in situ, the reinforcing effect of the upper airway reduces as well. Hence the observed worsening of OSA with the 0%-MAD in situ.

Also, stabilization splints resulted in a worsening of OSA. The same mechanisms may apply as elaborated above. It should be noted that in everyday dental practice, increases in vertical dimension without mandibular protrusion are commonly applied, not only by means of stabilization splints but also in, e.g., restorative dentistry and prosthetic dentistry. Therefore, dentists should be attentive while taking their patients' oral history, with focus on the possibility of an OSA being induced or an existing OSA deteriorating with a bite rise. Taken in account that there are many undiagnosed sleep apnea patients (20), this becomes even more important (21).

Future research

The studies in this thesis have contributed to increasing our insight into the effects and side effects of MADs as well as those of nCPAP and occlusal stabilization splints in OSA patients.

To further unravel the complex comorbidity network of OSA, more research is needed, amongst which treatment efficacy studies. To that end, RCTs still represent the study design of first choice. As can be gathered from the RCTs included in this thesis, the quality of RCTs focusing on the treatment of OSA will benefit from the following design issues:

1. Including multiple nights for polysomnographic recordings. While polysomnogra-

phy remains the current gold standard in sleep investigations, guidelines for single night recordings versus multiple consecutive recordings in a sleep laboratory have amongst others been disputed because of the so-called first-night effect, meaning a poor sleep quality due to the novelty of sleeping with equipment mounted for polysomnography (22). The probability of missing moderate OSA in a single night has been measured to occur in up to 60% of the cases (23). This could be attributed to the first-night effect. In addition, single-night diagnostic sleep studies are more prone to wrongly categorize OSA in mild, moderate, and severe than multiple-night recordings. Hence, repeated measurements will help to improve patient categorization and thus clinical decision making. Moreover, because of the fact that PSG recordings have a high cost, there is a need for a lower cost, but still safe, reliable and valid method.

2. Including a placebo condition. Comparing results from the placebo and the no-placebo (i.e., active treatment) groups suggests whether changes in the test group result from the treatment or by effects not related to the treatment. Test and placebo groups are equally important, as shown by the results of numerous clinical trials. It should be noted that the response to a placebo group is not necessarily just a psychosocial response to the simulation of treatment. In fact, the observed response to placebo in studies may also reflect the natural course of the disease, fluctuations in symptoms, regression to the mean, response bias with respect to the patient's reporting of subjective symptoms, and the effects of other concurrent treatments. To prove a new treatment effective above and beyond the psychological results of a simple belief in the ability of the drug/appliance to be effective, researchers need to compare the results of the experimental treatment for an illness with those obtained from the placebo (24). Therefore, placebo groups should be included in the study design of future studies.
3. Using long-term follow-ups. It is very important to follow up participants, to investigate long-term outcomes, for a number of reasons. In particular, long-term effects may be different from short-term effects. Initial effects may wear off or may become greater over time, or there may be "sleeper" effects that only appear several years after the intervention. For example, MAD therapy sometimes produces time-related dental and skeletal side effects. After a long period of treatment, the dental

side effects can become clinically relevant and therefore the clinician should inform the patients about the possible changes prior to starting the treatment. Since these side effects are progressive, patients need to be continuously monitored over time. Also, there can be differences in the outcome measures when the follow-up period is extended and the participants become older or, for example, gain weight. For those reasons, long-term follow-ups are of great value.

Besides the need for well-designed RCT's, multiple studies are needed in order to test the same hypothesis, using comparable methodology. Only then, systematic reviews and meta- analyses are possible. Systematic reviews and meta-analyses are increasingly important sources of information for clinical practice. If well conducted, they synthesize large amounts of information and provide estimated effect sizes that have greater precision and generalizability than individual studies (25).

The pathophysiology of OSA varies between individuals and is composed of different underlying mechanisms. Several components, including the upper airway anatomy, effectiveness of the upper airway dilator muscles arousal threshold of the individual, and inherent stability of the respiratory control system determine the pathogenesis of OSA (26). Their recognition may have implications for the health care team. For example, supplemental oxygen therapy can help to stabilize breathing in OSA patients with inherent respiratory instability, and avoidance of supine position can minimize airway obstruction in patients with a predisposition to upper airway collapse in this posture. MAD treatment is maybe more effective in patients with anatomical problems and not in patients with respiratory instability. So far, however, evidence is limited and more research is needed to further unravel this issue. Finally, it is of importance to focus future research projects on a clinically relevant issue like non-response. Despite increasing knowledge, there are always individual cases that do not respond to a certain treatment. Better understanding why one individual does have a favorable treatment outcome while another one does not, is of the utmost importance for a cost-effective healthcare. To that end, more research should be performed that focusses on phenotyping, so that treatments can be developed that will have less non-responders than we currently see in clinical practice that is based on research outcomes at the group level (27). Personalized dentistry is the key!

References

1. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial. Respiration. 2011;81:411-419.
2. Aarab G, Lobbezoo F, Heymans MW, Hamburger HL, Naeije M. Long-term follow-up of a randomized controlled trial of oral appliance therapy in obstructive sleep apnea. Respiration. 2011;82:162-168.
3. Nikolopoulou, M., Naeije, M. , Aarab, G. , Hamburger, H. L., Visscher, C. M. and Lobbezoo, F. The effect of raising the bite without mandibular protrusion on obstructive sleep apnoea. Journal of Oral Rehabilitation. 2011;38:643-647.
4. Levin, KA. Study design VII. Randomised controlled trials. Evidence-based dentistry 2007;8:22-23.
5. Silverman, SL. From Randomized Controlled Trials to Observational Studies. The American Journal of Medicine. 2009;122:114 – 120.
6. Sørensen, H. T., Lash, T. L. and Rothman, K. J. Beyond randomized controlled trials: A critical comparison of trials with nonrandomized studies. Hepatology. 2006;44:1075-1082.
7. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar 23;340:c332.
8. Edwards C, Mukherjee S, Simpson L, Palmer LJ, Almeida OP, Hillman DR. Depressive Symptoms before and after Treatment of Obstructive Sleep Apnea in Men and Women. J Clin Sleep Med. 2015;11:1029–1038.
9. Lee SA, Han SH, Ryu HU. Anxiety and its relationship to quality of life independent of depression in patients with obstructive sleep apnea. Journal of Psychosomatic Research. 2015; 79:32-36.
10. Cameron, C. Patient compliance: recognition of factors involved and suggestions for promoting compliance with therapeutic regimens. Journal of Advanced Nursing. 1996;24: 244-250.
11. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag. 2008;4:269–286.

12. Meurice JC, Marc I, Carrier G, Series F. Effects of mouth opening on upper airway collapsibility in normal sleeping subjects. Am J Respir Crit Care Med 1996;153:255–259.
13. Keisuke M, Özbek M.M, Lowe A.A, Sjöholm T.T, Love L, Fleetham JA, Ryan C.F. Mandibular posture during sleep in patients with obstructive sleep apnoea. Archives of Oral Biology.1999;44:657-664.
14. Lowe AA. Oral appliances for sleep breathing disorders. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine, 3rd ed. Philadelphia: Saunders; 2000. p. 929–939.
15. Landry-Schonbeck A, de Grandmont P, Rompr € e PH, Lavigne GJ. Effect of an adjustable mandibular advancement appliance on sleep bruxism: a crossover sleep laboratory study. Int J Prosthodont. 2009;22:251–259.
16. Carra MC, Huynh NT, El-Khatib H, Remise C, Lavigne GJ. Sleep bruxism, snoring, and headaches in adolescents: short-term effects of a mandibular advancement appliance. Sleep Med. 2013;14:656-661.
17. Mainieri VC, Saueressig AC, Fagondes SC, Teixeira ER, Rehm DD, Grossi ML. Analysis of the effects of a mandibular advancement device on sleep bruxism using polysomnography, the BiteStrip, the sleep assessment questionnaire, and occlusal force. Int J Prosthodont. 2014;27:119–126.
18. Manfredini, D., Guarda-Nardini, L., Marchese-Ragona, R. et al. Sleep Breath. 2015;19: 1459.
19. Kato T, Katase T, Yamashita S, Sugita H, Muraki H, Mikami A,Okura M, Ohi M, Masuda Y, Taniguchi M. Responsiveness of jaw motor activation to arousals during sleep in patients with obstructive sleep apnea syndrome. J Clin Sleep Med. 2013;9:759-765.
20. Simpson L, Hillman DR, Cooper MN, Ward KL, Hunter M, Cullen S, James A, Palmer LJ, Mukherjee S, Eastwood P. High prevalence of undiagnosed obstructive sleep apnoea in the general population and methods for screening for representative controls. Sleep Breath. 2013; 17:967-973.
21. Motamedi KK, McClary AC, Amedee RG. Obstructive sleep apnea: a growing problem. Ochsner J. 2009;9:149–153.
22. Newell J, Mairesse O, Verbanck P, Neu N. Is a one-night stay in the lab really enough to conclude? First-night effect and night-to-night variability in polysomnographic

recordings among different clinical population samples. Psychiatry Research. 2012;100:2-3:795-801.

23. Stöberl, A. S., Schwarz, E. I., Haile, S. R., Turnbull, C. D., Rossi, V. A., Stradling, J. R. and Kohler, M. Night-to-night variability of obstructive sleep apnea. J Sleep Res. 2017;26:782-788.
24. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: Recent advances and current thought. Annu Rev Psychol. 2008;59:565–590.
25. Mulrow CD. Rationale for systematic reviews. BMJ. 1994;309:597–599.
26. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am J Respir Crit Care Med. 2013;188:996–1004.
27. Gagnadoux F, Le Vaillant M, Paris A, et al. Institut de Recherche en Santé Respiratoire des Pays de la Loire Sleep Cohort Group. Relationship between OSA clinical phenotypes and CPAP treatment outcomes. Chest. 2016;149:288–290.

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Summary

Obstructive sleep apnea (OSA) has an estimated prevalence in male and female adults of 14% and 5%, respectively, with prevalence rates increasing over the past decades due to increasing rates of obesity and ageing of the population. OSA has several complications, including daytime fatigue and sleepiness, cardiovascular problems (e.g., hypertension, a greater risk for coronary artery disease, heart attack, stroke), memory problems, morning headaches, mood swings or feelings of depression, and nocturia.

Continuous positive airway pressure (CPAP) has been proposed as the most effective treatment for severe OSA patients. Mandibular advancement devices (MADs) are considered as a primary treatment option in mild and moderate OSA patients and in patients who do not tolerate CPAP. The rationale behind the efficacy of MADs is that advancement of the mandible and tongue improves upper airway patency during sleep by enlarging the upper airway and by decreasing upper airway collapsibility. During MAD treatment, the mandibular protrusion position of the MAD is often titrated by the dentist or patient to improve its efficacy. However, MADs are associated with several potential side effects. Amongst others, MAD therapy may result in excessive salivation, mouth dryness, tooth pain, gum irritation, headaches, temporomandibular joint discomfort, and morning-after occlusal changes. MAD therapy may also produce long-term dental and skeletal side effects. Despite these possible short-term and long-term side effects, compliance by OSA patients to MAD treatment is found to be higher as compared to CPAP.

The studies included in this thesis all aim at further clarifying the therapeutic effects and side effects of MADs in the management of OSA. Four out of the five studies are part of a large placebo-controlled randomized clinical trial (RCT) in which the effects of an MAD were compared to those of nasal CPAP (nCPAP) and an intraoral placebo appliance. The fifth study aims to examine the effects of an occlusal stabilization splint in OSA patients.

In **Chapter 2**, we compared the effects of an objectively titrated MAD with those of nCPAP and placebo on symptoms of psychological distress. The hypothesis was that there is no significant difference between objectively titrated MAD and nCPAP therapies in improving psychological distress symptoms in mild/ moderate OSA patients. Both MAD and nCPAP showed significant improvements of symptoms of psychological distress after 6 months of treatment. However, these significant improvements were not different from those observed in the placebo group. Interestingly, the participants with higher values of psychological distress at baseline showed less reduction in the apnea-hypopnea index (AHI) than participants with lower values at baseline. This suggests that a patient's psychological distress level at the start of a treatment may play a role in the treatment outcome.

In **Chapter 3**, we compared the effects of MAD with those of nCPAP and placebo on self-reported symptoms of common sleep disorders and sleep-related problems in mild and

moderate OSA patients. All participants were randomly assigned in the three groups and filled out the validated Dutch Sleep Disorders Questionnaire (SDQ) twice: one before treatment and one after six months of treatment. All groups showed significant improvements over time in symptoms corresponding with insomnia, excessive daytime sleepiness, psychiatric sleep disorder, periodic limb movements, sleep apnea, sleep paralysis, daytime dysfunction, hypnagogic hallucinations/dreaming, restless sleep, negative conditioning, and automatic behaviour. Taking into account that the placebo group also showed significant improvements in these symptoms, we concluded that the positive effects on these symptoms may not be explained by real improvement in sleep quality. Rather, they are most likely to be caused by sleep hygiene advises and general information about their condition given at baseline, as well as the attention given to the patients by the researcher.

In **Chapter 4**, we aimed to investigate the possible association of MAD treatment and nCPAP treatment with increased pain in the temporomandibular complex in a placebo-controlled trial. We compared the temporomandibular side effects of an MAD with those of nCPAP in mild to moderate OSA patients. All participants underwent a shortened functional examination of their masticatory system at baseline and after 6 months to establish the presence of clinical signs of temporomandibular disorder (TMD) pain. Mandibular function impairment (MFI) was assessed using the MFI questionnaire (MFIQ), which is a validated questionnaire that can be used to assess the impact of TMDs on mandibular function in daily life. We found no significant differences between the three treatment groups in the frequency of clinical signs of TMD pain at baseline and at therapy evaluation after 6 months. Further, there was no significant difference between the three different treatment groups in their level of MFI in daily life either. We hypothesize, based on the transient nature of the TMD side effect in MAD treatment, that the TMD pain in our MAD group had already disappeared in the first few months. Therefore, no difference in clinical signs of TMD pain between the MAD, nCPAP, and placebo groups was found in our study, as we re-assessed them only after 6 months. In line with previous studies, we conclude that because of the transient nature of TMD pain, this pain is not a reason to contra-indicate an MAD treatment.

In **Chapter 5**, we wanted to assess the influence of raising the bite without mandibular protrusion on respiratory variables in OSA patients. This study tested the hypothesis that raising the bite without mandibular protrusion in OSA patients is associated with an increase in AHI. We concluded that an increased jaw gape without mandibular protrusion might be associated with a risk of aggravation of OSA for some, but not for all OSA patients. This is a very important finding for dental practitioners, especially considering that there are many undiagnosed OSA patients.

In **Chapter 6**, we wanted to determine the influence of occlusal stabilization splints on sleep-related respiratory variables in OSA patients. Occlusal stabilization splints are commonly used to protect the teeth against the possible detrimental effects of sleep bruxism and to manage TMD. The use of stabilization splint yielded an increase of the AHI in all 10 participants. The raise was very small though, and we cannot assume that it is clinically relevant, but it is nevertheless an important outcome that stabilization splints may be associated with an aggravation of OSA.

The studies in this thesis have contributed to increasing our insight into the effects and side effects of MADs as well as those of nCPAP and occlusal stabilization splints in OSA patients. To further unravel the complex pathophysiology of OSA, more research is needed, amongst which treatment efficacy studies. To that end, RCTs still represent the study design of first choice. As can be gathered from the RCTs included in this thesis, the quality of RCTs focusing on the treatment of OSA will benefit from including multiple nights for polysomnographic recordings, including a placebo condition, and using long-term follow-ups.

Samenvatting

Obstructief slaapapneu (OSA) heeft een geschatte prevalentie van 14% en 5% bij mannelijke respectievelijk vrouwelijke volwassenen. De prevalentiecijfers stijgen in de afgelopen decennia als gevolg van toenemende obesitas en veroudering van de bevolking. OSA kent diverse complicaties, waaronder vermoeidheid en slaperigheid overdag, cardiovasculaire problemen (bijv. hypertensie, een groter risico op kransslagaderaandoeningen, hartaanval of beroerte), geheugenproblemen, ochtendhoofdpijn, stemmingswisselingen of gevoelens van depressie, en nocturia.

Continue positieve luchtwegdruk (Continuous Positive Airway Pressure; CPAP) wordt algemeen beschouwd als de meest effectieve behandeling voor ernstige OSA-patiënten. Bij lichte en matige OSA-patiënten en bij patiënten die geen CPAP verdragen worden mandibulaire repositieapparaten (MRA's) ingezet als primaire behandelingsoptie. Een MRA fixeert de onderkaak – en daarmee de tong – in een voorwaartse positie. Het doel van het MRA is het vergroten van de luchtweg en/of het reduceren van de neiging tot dichtvallen. Tijdens MRA-behandeling wordt de voorwaartse mandibulaire positie van MRA's vaak getitreerd door de tandarts of patiënt om de werkzaamheid ervan te verbeteren. MRA's worden echter ook geassocieerd met verschillende mogelijke bijwerkingen. MRA-therapie kan onder andere leiden tot overmatige speekselvloed, droge mond, tandpijn, tandvleesirritatie, hoofdpijn, kaakgewrichtsproblemen en occlusale beetveranderingen bij het ontwaken. MRA-therapie kan ook langdurige tand- en kaakstandveranderingen veroorzaken. Ondanks deze potentiële korte en lange termijn bijwerkingen blijkt de medewerking aan een MRA-behandeling onder OSA-patiënten groter te zijn in vergelijking met die aan een CPAP-behandeling.

De studies die deel uitmaken van dit proefschrift zijn allemaal gericht op meer inzicht in de therapeutische effecten en bijwerkingen van MRA's bij de behandeling van OSA. Vier van de vijf studies maken deel uit van een groot placebogecontroleerd gerandomiseerd klinisch onderzoek (Randomized Controlled Trial; RCT), waarin de effecten van een MRA werden vergeleken met die van nasale CPAP (nCPAP) en een intraoraal placebo-apparaat. Het vijfde onderzoek heeft als doel de effecten van een occlusale stabilisatiespalk bij OSA-patiënten te onderzoeken.

In **hoofdstuk 2** hebben we de effecten van een objectief getitreerd MRA vergeleken met die van nCPAP en placebo op symptomen van psychologische belasting. De hypothese was dat er geen significant verschil bestaat tussen objectief getitreerde MRA- en nCPAP-therapieën in het verbeteren van symptomen van psychologische belasting bij lichte en matige OSA-patiënten. Na zes maanden behandeling vertoonden zowel MRA als nCPAP significante verbeteringen in symptomen van psychologische belasting. Deze significante verbeteringen waren echter niet anders dan de verbeteringen die werden

waargenomen in de placebogroep. Interessant is dat de deelnemers met hogere waarden voor psychologische belasting bij aanvang minder reductie van de apneu-hypopneu-index (AHI) vertoonden dan deelnemers met lagere aanvangswaarden. Dit suggereert dat het niveau van psychologische belasting van een patiënt aan het begin van een behandeling een rol kan spelen in de uitkomst van die behandeling.

In **hoofdstuk 3** hebben we de effecten van MRA vergeleken met die van nCPAP en placebo op zelfgerapporteerde symptomen van veel voorkomende slaapstoornissen en slaapgerelateerde problemen bij lichte en matige OSA-patiënten. Alle deelnemers werden willekeurig ingedeeld in drie groepen en vulden de gevalideerde Dutch Sleep Disorders Questionnaire (SDQ) twee keer in: één keer voorafgaand aan de behandeling en één keer na zes maanden behandeling. Alle groepen vertoonden na verloop van tijd significante verbeteringen in symptomen van slapeloosheid, overmatige slaperigheid overdag, psychiatrische slaapstoornis, periodieke bewegingsstoornis van de benen en armen, slaapapneu, slaapverlamming, niet goed functioneren overdag, hypnagoge hallucinaties/droombeelden, rusteloze slaap, negatieve conditionering en concentratie/geheugen. Rekening houdend met het feit dat ook de placebogroep significante verbeteringen vertoonde in deze symptomen, concludeerden we dat de positieve effecten op deze symptomen mogelijk niet worden verklaard door een daadwerkelijke verbetering van de slaapkwaliteit. Ze lijken eerder te worden veroorzaakt door de slaaphygiëne-adviezen en algemene informatie over hun toestand, gegeven bij aanvang van de studie, evenals door de aandacht die de onderzoeker aan de patiënten schenkt.

In **hoofdstuk 4** wilden we de mogelijke associatie van MRA-behandeling en nCPAP-behandeling met verhoogde pijn in het temporomandibulaire complex onderzoeken in een placebo-gecontroleerde studie. We vergeleken de temporomandibulaire bijwerkingen van een MRA met die van nCPAP bij lichte en matige OSA-patiënten. Alle deelnemers ondergingen een verkort functieonderzoek van hun kauwstelsel bij aanvang en na 6 maanden. Dit gebeurde om de aanwezigheid van klinische symptomen van temporomandibulaire disfunctie (TMD-) pijn vast te stellen. Mandibulaire functiebeperking (Mandibular Function Impairment; MFI) werd beoordeeld met behulp van de MFI-vragenlijst (MFIQ), een gevalideerde vragenlijst die kan worden gebruikt om de impact van TMD op de mandibulaire functie in het dagelijks leven te beoordelen. We vonden geen significante verschillen tussen de drie behandelingsgroepen in de frequentie van klinische symptomen van TMD-pijn bij aanvang en bij evaluatie van de therapie na 6 maanden. Daarnaast was er ook geen significant verschil tussen de drie verschillende behandelingsgroepen in hun MFI-niveau in het dagelijks leven. We veronderstellen dat, op basis van de voorbijgaande aard van TMD-klachten bij MRA-behandeling, de TMD-pijn in onze MRA-groep al in de eerste paar maanden was verdwenen. In onze studie werd daarom geen verschil gevonden in klinische symptomen van TMD-pijn tussen de MRA-, nCPAP- en placebogroep, aangezien we deze

pas na 6 maanden opnieuw beoordeelden. In overeenstemming met eerdere studies concluderen we dat, ook vanwege de voorbijgaande aard van TMD-pijn, deze pijn geen contra-indicatie is voor een MRA-behandeling.

In **hoofdstuk 5** wilden we de invloed bepalen van het verhogen van de beet, zonder dat er sprake is van mandibulaire protrusie, op ademhalingsvariabelen bij OSA-patiënten. Deze studie testte de hypothese dat het verhogen van de beet zonder mandibulaire protrusie bij OSA-patiënten geassocieerd is met een toename van de AHI. We concludeerden dat een toegenomen mondopening, zonder dat er sprake is van mandibulaire protrusie, voor sommige, maar niet voor alle OSA-patiënten, geassocieerd kan zijn met een risico op verergering van OSA. Dit is een zeer belangrijke bevinding voor tandartsen, vooral gezien het feit dat er veel niet-gediagnosticeerde OSA-patiënten zijn.

In **hoofdstuk 6** wilden we de invloed bepalen van occlusale stabilisatiespalken op slaapgerelateerde ademhalingsvariabelen bij OSA-patiënten. Occlusale stabilisatiespalken worden vaak gebruikt om de tanden te beschermen tegen de mogelijke schadelijke effecten van slaapbruxisme en om TMD te behandelen. Het gebruik van de stabilisatiespalk leverde een toename op van de AHI bij alle tien deelnemers. De toename was echter erg klein, waardoor we niet kunnen aannemen dat het klinisch relevant is. Het is desalniettemin een belangrijke uitkomst dat het gebruik van stabilisatiespalken geassocieerd kan zijn met een verergering van OSA.

De studies die deel uitmaken van dit proefschrift hebben bijgedragen aan het vergroten van ons inzicht in de effecten en bijwerkingen van MRA's, evenals die van nCPAP en occlusale stabilisatiespalken, bij OSA-patiënten. Om de complexe pathofysiologie van OSA verder te ontrafelen is meer onderzoek nodig, waaronder studies naar de effectiviteit van behandelingen. Daarbij vormen RCT's nog steeds de onderzoeksopzet van eerste keuze. Zoals kan worden afgeleid uit de RCT's in dit proefschrift, zal de kwaliteit van RCT's gericht op de behandeling van OSA toenemen zodra polysomnografische registraties gedurende meerdere nachten worden vervaardigd, een placebo-behandeling wordt geïncludeerd, en langdurige follow-ups worden gehanteerd.

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List of publications

List of publications

Ghizlane Aarab, **Maria Nikolopoulou**, Jari Ahlberg, Martijn W. Heymans, Hans L. Hamburger, Jan de Lange, Frank Lobbezoo. Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial on psychological distress. Clin Oral Investig. 2017;21:2371-2378.

Maria Nikolopoulou, Anna Byraki, Jari Ahlberg, Martijn W. Heymans, H. L. Hamburger, Jan de Lange, Frank Lobbezoo, Ghizlane Aarab**.** Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial on self-reported symptoms of common sleep disorders and sleep-related problems**.** J Oral Rehabil. 2017;44:452-460**.**

Maria Nikolopoulou, Ghizlane Aarab, Jari Ahlberg, Hans L. Hamburger, Jan de Lange, Frank Lobbezoo. Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial on temporomandibular side effects. Clin Exp Dent Res. 2020 Apr 4. DOI: 10.1002/cre2.288.

Maria Nikolopoulou, Machiel Naeije, Ghizlane Aarab, Hans L. Hamburger, Corine M. Visscher, Frank Lobbezoo. The effect of raising the bite without mandibular protrusion on obstructive sleep apnoea. J Oral Rehabil. 2011;38:643-647.

Maria Nikolopoulou, Jari Ahlberg, Corine M. Visscher, Hans L. Hamburger, Machiel Naeije, Frank Lobbezoo. Effects of occlusal stabilization splints on obstructive sleep apnea: a randomized controlled trial. J Orofac Pain. 2013;27:199-205.

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Chapter 2| **Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial on psychological distress**

GA, HH, MN1, and FL conceived and designed the study. GA was involved in additional study planning and implementation. GA, MN2, MH, and FL were involved in the processing, analysis, and interpretation of data. GA and MN2 drafted the manuscript. All authors were involved in revising the manuscript critically and gave final approval of the manuscript.

Chapter 3| **Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial on self-reported symptoms of common sleep disorders and sleep-related problems**

GA, HH, MN1, and FL conceived and designed the study. GA was involved in additional study planning and implementation. MN2, AB, GA, MH, and FL were involved in the processing, analysis, and interpretation of data. MN2 and AB drafted the manuscript. All authors were involved in revising the manuscript critically and gave final approval of the manuscript.

Chapter 4| **Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial on temporomandibular side effects**

GA, HH, MN1, and FL conceived and designed the study. GA was involved in additional study planning and implementation. MN2, GA, and FL were involved in the processing,

analysis, and interpretation of data. MN2, GA, and FL drafted the manuscript. All authors were involved in revising the manuscript critically. All authors approved the final version of the article.

Chapter 5| **The effect of raising the bite without mandibular protrusion on obstructive sleep apnoea**

GA, HH, MN1, and FL conceived and designed the study. GA was involved in additional study planning and implementation. MN2, MN1, FL, and CV were involved in the processing, analysis, and interpretation of data. MN2 and FL drafted the manuscript. All authors were involved in revising the manuscript critically. All authors approved the final version of the article.

Chapter 6| **Effects of occlusal stabilization splints on obstructive sleep apnea: a randomized controlled trial**

MN2, MN1, and FL conceived and designed the study. MN2 was involved in additional study planning and implementation. MN2, JA, FL, and CV were involved in the processing, analysis, and the interpretation of data. MN2, JA, and FL drafted the manuscript. All authors were involved in revising the manuscript critically and gave final approval of the manuscript.

Curriculum Vitae

About the author

Maria Nikolopoulou was born on the 9th April 1980, in Heraklion, Greece. She obtained her Dental Studies degree with distinction, at the University of Athens in 2007. She followed the Oral Kinesiology Advanced Master programme in ACTA Amsterdam, from 2007 to 2010, and obtained the title of Gnathologist. Since then, she has followed many Orofacial Pain and Dental Sleep Medicine courses around the world. She works as a full-time dentist-gnathologist in Crete, Greece, with a strong interest in Dental Sleep Medicine.

Acknowledgements

Being a part of the ACTA team has been an experience by itself. I have learned a lot and there are many people that I would like to thank for teaching me, helping me and supporting me through my PhD. That includes teachers, co-workers, assistants, friends and family that dedicated me time, expertise and support.

Dear Professor Lobbezoo, dear Frank, thank you for giving me the opportunity to work and learn from you. I am grateful for the inspiration, the knowledge and your generosity. Many thanks for all our discussions, for always being positive and enthusiastic regarding my research and for all your critical revisions for my articles and this manuscript.

Dear dr. Aarab, dear Ghizlane, thank you for guiding me in the world of Dental Sleep Medicine. You were always there from the start, helping me with everything from teaching me how to place the electrodes monitoring the patients' sleep, to revising my manuscripts and this thesis manuscript. It has been a great journey. You have always been positive and supported the project, even at very difficult times.

Dear dr. Hamburger, dear Hans, thank you for including me in your team, for the hospitality in Slotervaart Medical Center, for teaching me, for the endless support and for all the discussions. I am grateful.

Dear "Waak-Slaap" center team, thank you for the hospitality, for always being there. Without you, this project would never have been completed.

Dear friends and colleagues from the Clinical Neurophysiology of the Slotervaart Medical Center, I am grateful for the hospitality, the team work and all the help and support with all the equipment (even at late hours). I have so much enjoyed our collaboration!

Dear patients, without you my thesis would never finish. Thank you for participating in my research, for trusting and supporting me.

Dear dr. Visscher, dear Corine, thank you for the nice collaboration and for offering your knowledge in statistics and your critical thinking. I always felt welcome in your office and I am grateful for that.

Dear dr. van Selms, dear Maurits, thank you for helping me with the statistics and all the graphs that we made again and again! But most of all, thank you for always keeping the door open for me, for the wonderful discussions and for sharing your ideas with me. You are an inspiration!

Dear dr. Koutris, dear Michalis, thank you for introducing me to the ACTA world, for helping me from my very first day in Amsterdam. Thanks for the inspiring moments, for the laughs, for the celebrations, for the good and the bad times.

Dear Alwine te Veldhuis, dear Emeline te Veldhuis, dear Carlijn van der Lugt, you are the best co-workers I could have wished for. I am grateful for everyday that we spent together and I am looking forward to all our future trips together! Thank you for the great collaboration, for sharing knowledge, dreams and expectations, for every moment that we spent together inside and outside ACTA.

Dear Lida Kalogeraki, dear Victoria Ntrouka, I am grateful for your friendship. Thank you for always having the time to listen, for all the moments and the emotions. You are family to me.

Special thanks to my parents, Simeon and Evangelia Nikolopoulou. Thank you for your endless love and support. For giving me "the wings to fly and the roots to come back"!

Dimitri, thank you for the love and support, for helping me find the time and the will to work, and for insisting on finishing this thesis when life was keeping me too busy! You are simply my better half. You, together with Filippos and Evangelia, are my inspiration, my family, my life.