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Review Article

**OBSTRUCTIVE SLEEP APNEA (OSA) MANAGEMENT:
SYSTEMATIC REVIEW IN LITERATURE****Alaa Alanazi^{1*}, Salem Alsohaimi², Fayez Alruwaili³, Abdulaziz AlSudairi⁴, Mohammed Algarni⁵, Tamam Alshammari⁶, Abdullah Alhomaiddhi⁴, Khulud Alqahtani¹, Hager Alqahtani⁷, Raed Hashem⁴**¹Almaarefa University, Riyadh, Saudi Arabia.²Jazan University, Jazan, Saudi Arabia.³Arabian gulf University, Manama, Bahrain.⁴King Saud University, Riyadh, Saudi Arabia⁵Taif university, Taif, Saudi Arabia.⁶University of Hail, Hail, Saudi Arabia.⁷ Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia.**Abstract:**

This review is aiming to systematically summarize and compare the literature on Obstructive sleep apnea. The present review was conducted by searching in Medline, Embase, Web of Science, Science Direct, BMJ journal and Google Scholar for, researches, review articles and reports, published over the past years. Books published on management Obstructive sleep apnea. If several studies had similar findings, we randomly selected one or two to avoid repetitive. Based on findings and results this review found that there is Different management options are now available for an effective management of this disease. Based on multidisciplinary approach and combination of treatments like and the basic one is the continuous positive airway pressure (CPAP) is still recognized as the gold standard treatment. Nasal CPAP (nCPAP) is highly effective in controlling symptoms, improving quality of life and reducing the clinical sequelae of sleep apnea. Mandibular advancement devices, particularly if custom made, are effective in mild to moderate OSA and provide a viable alternative for patients intolerant to CPAP therapy. In addition to the Alternative options include weight control, mandibular advancement devices and a number of upper airway surgical approaches.

Keywords: Obstructive sleep apnea (OSA), managements, Continuous positive airway pressure, weight loss**Abbreviations used in this paper:** OSA: Obstructive sleep apnea CPAP: continuous positive airway pressure, nCPAP: Nasal continuous positive airway pressure CPAP, AHI: apnoea-hypopnoea index.**Corresponding author:****Alaa Alanazi,**

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INTRODUCTION:

This disorder is characterized by intermittent closure/collapse of the pharyngeal airway causing apnoeic episodes during sleep [1]. It's a common chronic disorder affecting about 2–4% of the adult population, with the highest prevalence reported among middle-aged men [2]. The condition is characterized by repetitive episodes of complete or partial collapse of the upper airway (mainly the oropharyngeal tract) during sleep, with a consequent cessation/reduction of the airflow [3].

Many studies have demonstrated that OSA is a highly prevalent disorder, both in the general population and in specific disease-related and population sub-groups [4-6]. The reported prevalence of OSA has increased over time, in part due to increasing rates of obesity. Obesity is recognized as a major risk factor for OSA [7,8] and there has been an enormous increase in rates of obesity throughout the world over the past 25 years [9-13].

The diagnosis of OSA is made through different levels of nocturnal monitoring of respiratory, sleep and cardiac parameters (polysomnography or nocturnal cardio-respiratory polygraphy), aimed to detect the obstructive events and the following changes in blood oxygen saturation (SaO₂) [14,3]. The most commonly used index to define the severity of OSA is the apnoea/hypopnoea index (AHI), calculated as the number of obstructive events per hour of sleep and obtained by nocturnal cardiorespiratory monitoring [14]. The etiology of OSA is multifactorial, consisting of a complex interplay between anatomic, neuromuscular factors and an underlying genetic predisposition toward the disease [15-16]. Risk factors include snoring, male gender, middle age, menopause in women, obesity and a variety of craniofacial and oropharyngeal features such as a large neck circumference, retro- or micrognathia, nasal obstruction, enlarged tonsils/adenoids, macroglossia and low-lying soft palate [15, 16]. Over the years, recurrent episodes of apnoeas, intermittent hypoxia and sleep fragmentation affect the function of different organs and systems, mainly the brain and the cardiovascular system, and alter the body metabolic balance [15,17]. This leads to a variety of clinical sequelae accepted as the OSA syndrome. Daytime sleepiness, due to nocturnal sleep fragmentation, is a key symptom of OSA, being present in more than 80% of the patients. As the disorder progresses, the sleepiness becomes increasingly dangerous, causing impaired performance at work and major work-related and road accidents [15,18].

METHODS:

The present review was conducted Nonmember 2018 in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) declaration standards for systematic reviews. We reviewed all the topics on Obstructive sleep apnea (OSA) management, such as prevalence, risk factors or etiology, complication, and management. To achieve this goal, we searched Medline, Embase, Web of Science, Science Direct, and Google Scholar for, researches, review articles and reports, published over the past 15 years. Books published on Obstructive sleep apnea (OSA) management.

Our search was completed without language restrictions. Then we extracted data on study year, study design, and key outcome on Obstructive sleep apnea (OSA) management. The selected studies were summarized and unreproducible studies were excluded. Selected data is shown in the Table 1.

Studies has been rated as being high quality by an established evaluation process based on the DyunaMed criteria and it's based on the level of evidence as following:

Level 1 (likely reliable) evidence: representing research results addressing clinical outcomes and meeting an extensive set of quality criteria which minimize bias. example: Randomized controlled trial/meta-analysis.

Level 2 (mid-level) evidence: representing results addressing clinical outcomes, and using some methods of scientific investigation but not meeting the quality criteria to achieve level 1 evidence labeling. Example: well-designed non-randomized clinical trials.

Level 3 (lacking direct) evidence: representing reports that are not based on scientific analysis of clinical outcomes. Examples include case series, case reports, expert opinion and conclusions extrapolated indirectly from scientific studies.

Inclusion criteria

Inclusion criteria were:

Age: All ages' male or female patients diagnosed with OSA.

Race: All races.

Obstructive sleep apnea (OSA) management.

Exclusion criteria

Conditions other than Obstructive sleep apnea (OSA)

management. And Irrelevant articles [not related to the aim of this review and articles that did not meet the inclusion criteria in this review.

Data extraction and analysis

Information relating to each of the systematic review elements was extracted from the studies and collated in qualitative tables. Direct analysis of the studies of surgical treatments for hemorrhoids is made with extreme caution, as different sampling techniques can provide bias as overview of the assemblage.

RESULTS:

OSA should be approached as a chronic disease requiring long-term, multidisciplinary management. There are medical, behavioral, and surgical options for the treatment of OSA [22]. Adjunctive therapies are used as needed to supplement the primary treatment options. The patient should be an active participant in the decision on treatment type and taught to contribute to the management of his or her own disease [2]. Positive airway pressure (PAP) is the treatment of choice for mild, moderate, and severe OSA and should be offered as an option to all patients (Consensus). Alternative therapies may be offered depending on the severity of the OSA and the patient's anatomy, risk factors, and preferences and should be discussed in detail [22].

Positive Airway Pressure

First described by Sullivan in 1981 [19]. PAP provides pneumatic splinting of the upper airway and is effective in reducing the AHI [20]. PAP may be delivered in continuous (CPAP), bilevel (BPAP), or autotitrating (APAP) modes. Partial pressure reduction during expiration (pressure relief) can also be added to these modes. PAP applied through a nasal, oral, or oronasal interface during sleep is the preferred treatment for OSA.²⁰ CPAP is indicated for the treatment of moderate to severe OSA (Standard) and mild OSA (Option).¹⁸ CPAP is also indicated for improving self-reported sleepiness (Standard), improving quality of life (Option), and as an adjunctive therapy to lower blood pressure in hypertensive patients with OSA (Option) [21].

Continuous positive airway pressure

Continuous PAP (CPAP), generally administered through the nose (nCPAP), is undoubtedly considered the gold standard treatment for OSA. Since its invention in 1983 by Dr Sullivan, the clinical application of this device has deeply modified the course of the disease over the last three decades, offering to thousands of patients the first noninvasive method to control their disorder [23]. Worldwide, nCPAP is constantly recommended as the first-choice

treatment for patients with moderate to severe OSA [24,25].

It has been consistently shown that, compared with placebo, CPAP reduces the number of nocturnal obstructive events (decrease in AHI to normal or nearly normal values) and the number of nocturnal arousals, improving sleep parameters and nocturnal SaO₂ from the first night of treatment. All daytime symptoms, particularly sleepiness, and nocturnal symptoms are, after a short period of constant use, reversed by CPAP [26,27].

Positional therapy:

The number and duration of respiratory disturbances in patients with OSA depend on body position and sleep stage [30]. The lateral position is believed to reduce the tendency for the tongue to fall backward, making the collapse of the pharynx less likely, as compared with the supine position. Cartwright suggested a categorization of the patients suffering from OSA into positional and non-positional [30]. The patients with positional OSA (POSA) were recognized as having twice as many apnoeas in the supine position compared with the lateral positions.³⁰ More than 50% of the patients with OSA have a reduction of at least 50% in the apnoea-hypopnoea index (AHI) when altering the sleep position from the supine to the non-supine positions [31-33]. An additional 30% of the patients with OSA have a lesser reduction in AHI from the supine position to other positions [31,34]. This position dependency of OSA has had limited clinical impact in the treatment of patients [35]. The change in the severity of disease due to the sleep position has been observed but the studies have mainly been performed on the supine and lateral positions [35].

Weight-Loss Interventions:

Three studies compared various weight loss interventions with control treatment for patients with mean baseline AHI scores between 9 and 37 events per hour. These studies generally apply to patients with BMIs greater than 30 kg/m². Follow-up ranged from 2.3 to 12 months. Patients in the weight-loss groups lost 10.7 to 18.7 kg compared with patients in the control groups, who lost 0.6 to 2.4 kg. One study randomly assigned patients with type 2 diabetes to a weight-loss program involving a portion-controlled diet and physical activity prescription or a diabetes support and education program that involved 3 educational sessions on diabetes management over 1 year involving diet, physical activity, and social support [36,37]. Another study compared patients on a 9-week low-energy diet with patients following their usual diets [38]. The third study randomly

assigned obese patients to a very low-calorie diet complemented with lifestyle changes or general counseling on diet and exercise only [37].

Oral appliances:

Over the last 10 years, oral appliances have gained increasing recognition as a useful alternative to CPAP for the treatment of patients with mild to moderate OSA and for those patients with severe disease intolerant to CPAP.⁴¹ The most commonly used oral appliances are mandibular advanced splints (MAS). These devices attach to both the upper and lower dental arches in order to advance and retain the mandible in a forward position. This will relocate

laterally the pharyngeal fat pads from the airway and the tongue base will move forward. Consequently, the upper airway will be widened, particularly in its lateral dimension, and the function of upper airway dilator muscles, particularly the genioglossus, will improve [42]. As the pharyngeal collapsibility is reduced, the risk of apnoeic events will be lowered. Treatment with MAS is safe, producing common, but transitory and very mild, side effects such as excessive salivation, dry mouth and gingivae irritation. Side effects that are more persistent include arthralgia, teeth pain and occlusal changes.^{43,44} Better outcomes and a better compliance have been obtained with custom-made devices [45].

Table 1: Randomized controlled studies (A) and major selected non-randomized studies (B) on the management of obstructive sleep apnea.

Intervention	Author	Sample	Outcomes measurement	Finding	Level of evidence
positive airway pressure	Gupta A, et al. 2018. ²⁸	679	-apnea-hypopnea index (AHI). -Barthel Index and modified Rankin scale	These findings suggest significantly better stroke outcomes and statistically nonsignificant favorable outcomes in terms of recurrence of vascular events for patients with stroke and OSA who use CPAP treatment.	Level 2
Continuous positive airway pressure	Patel SR. 2003. ²³	706	- Epworth Sleepiness Scale score	Continuous positive airway pressure therapy significantly improves subjective and objective measures of sleepiness in patients with OSA across a diverse range of populations. Patients with more severe apnea and sleepiness seem to benefit the most.	Level 2
Positional therapy	Bidarian, et al. 2015. ²⁹	27	Resolution of sleepiness	Prone positioning reveals promising results in improving the apnoea-hypopnoea index (AHI) and oxygen desaturation index (ODI) in patients with obstructive sleep apnoea (OSA).	Level 3
Weight-Loss Interventions	Johansson K, et al. 2011. ³⁹	63	Apnoea-hypopnoea index, the main index for severity of obstructive sleep apnea.	Initial improvements in obstructive sleep apnoea after treatment with a very low energy diet can be maintained after one year in obese men with moderate to severe disease. Those who lose the most weight or have severe sleep apnoea at baseline benefit most.	Level 2
Oral appliances	Lettieri CJ, et al. 2011. ⁴⁰	-805. - 602 (74.8%) treated with an adjustable and 203 (25.2%) a fixed oral appliance.	apnea-hypopnea index (AHI) < 5 events/h or < 10 events/h with resolution of sleepiness (Epworth < 10).	Adjustable devices produced greater reductions in obstructive events and were more likely to provide successful therapy, especially in moderate-severe OSA. Fixed appliances were effective in mild disease, but were less successful in those with higher AHIs. Given these findings, the baseline AHI should be considered when selecting the type of oral appliance.	Level 2

DISCUSSION:

From the literature and the reviewed studies, we found that, in the last two decades, advances in sleep medicine and the availability of improved diagnostic tools have led to a better recognition and treatment of the disease [46]. The management of patients with OSA requires a multidisciplinary approach and many treatment options are currently available. Positive airway pressure (PAP), available since the beginning of the 1980s, provides the most effective and commonly used treatment. Alternative options include weight control, mandibular advancement devices and a number of upper airway surgical approaches [46].

Also studies found a dose-response association between weight loss and improvement in the apnoea-hypopnoea index, with patients who lost the most improving the most. At follow-up, 30 (48%) men no longer required continuous positive airway pressure, and six (10%) had total remission of obstructive sleep apnoea. There were also marked improvements in metabolic risk and the physical dimension of quality of life, which no longer differed from the level in the general population [39].

Oral appliances are an effective therapeutic option for the treatment of snoring and SDB across a broad range of disease severity. However, the response to therapy is non-uniform with some subjects having a very good response, and others having no response. Currently, there are no satisfactory clinical predictors of good and poor responders, and ideally patients should have objective assessment both before and after therapy has been established. There should be careful evaluation of patients' weight when reviewing therapy as weight gain will lead to recurrence of snoring and OSA despite the use of Oas [47].

CONCLUSIONS:

Finally, we can say that there is Different management options are now available for an effective management of this disease. Based on multidisciplinary approach and combination of treatments like and the basic one is the continuous positive airway pressure (CPAP) is still recognized as the gold standard treatment. Nasal CPAP (nCPAP) is highly effective in controlling symptoms, improving quality of life and reducing the clinical sequelae of sleep apnea. Mandibular advancement devices, particularly if custom made, are effective in mild to moderate OSA and provide a viable alternative for patients intolerant to CPAP therapy. In addition to the Alternative options include weight control, mandibular advancement devices and a number of upper airway surgical approaches.

REFERENCES:

1. Longmore, J M. Oxford Handbook of Clinical Medicine. Oxford: Oxford University Press, 2010;194
2. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993 Apr 29; 328(17):1230-5.
3. Alcohol and NREM parasomnias: evidence versus opinions in the international classification of sleep disorders, 3rd edition. Cartwright RD *J Clin Sleep Med.* 2014 Sep 15; 10(9):1039-40.
4. Arnardottir ES, Bjornsdottir E, Olafsdottir KA, Benediktsdottir B, Gislason T. 467 Obstructive sleep apnoea in the general population: highly prevalent but minimal symptoms. *Eur Respir J.* 2016;47(1):194-202.
5. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: The HypnoLaus study. *Lancet Respir Med.* 2015;3(4):310-8.
6. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LRA. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. *Sleep Med.* 2010;11(5):441-6.
7. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. *J Appl Physiol* (1985). 2005;99(4):1592-9.
8. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA.* 2000;284(23):3015-21.
9. Twells LK, Gregory DM, Reddigan J, Midodzi WK. Current and predicted prevalence of obesity in Canada: a trend analysis. *CMAJ Open.* 2014;2(1):E18-26.
10. Drieskens S, Van der Heyden J, Demarest S, Tafforeau J. Is the different time trend (1997-2008) of the obesity prevalence among adults in the three Belgian regions associated with lifestyle changes? *Arch Public Health.* 2014;72(1):18.
11. World Health Organization. Obesity: preventing and managing the global epidemic. Geneva: World Health Organization; 2000.
12. Zaninotto P, Head J, Stamatakis E, Wardle H, Mindell J. Trends in obesity among adults in England from 1993 to 2004 by age and social class and projections of prevalence to 2012. *J Epidemiol Community Health.* 2009;63(2):140-6.
13. Camara AD, Spijker JJ. Super-size Spain? A cross-sectional and quasi-cohort trend analysis of adult overweight and obesity in an accelerated transition country. *J Biosoc Sci.* 2010;42(3):377-

- 93.
14. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *American Academy of Sleep Medicine. J Clin Sleep Med.* 2012 Oct 15; 8(5):597-619.
 15. Guilleminault C, Quo SD. Sleep-disordered breathing. A view at the beginning of the new Millennium. *Dent Clin North Am.* 2001 Oct; 45(4):643-56.
 16. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* 2010 Jan; 90(1):47-112.
 17. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet.* 2009 Jan 3; 373(9657):82-93.
 18. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet.* 2014 Feb 22; 383(9918):736-47.
 19. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* 1981; 1:862-5.
 20. Gay P, Weaver T, Loube D, Iber C. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. *Sleep* 2006; 29:381-401.
 21. Kushida CA, Littner MR, Hirshkowitz M, et al. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. *Sleep* 2006; 29:375-80.
 22. Lawrence J, David Kristo, Patrick J, Norman F, Atul M, Susheel P, Kannan R, et al. Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults: Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. *Journal of Clinical Sleep Medicine.* 2009; 5:3
 23. Sullivan CE, Berthon-Jones M, Issa FG. Nocturnal nasal-airway pressure for sleep apnea. *N Engl J Med.* 1983 Jul 14; 309(2):112.
 24. Stasche N. Selective indication for positive airway pressure (PAP) in sleep-related breathing disorders with obstruction. *GMS Curr Top Otorhinolaryngol Head Neck Surg.* 2006; 5(): Doc06.
 25. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults.
 26. Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, et al. Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med.* 2009 Jun 15; 5(3):263-76.
 27. Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: results of a meta-analysis. *Arch Intern Med.* 2003 Mar 10; 163(5):565-71.
 28. Gupta A, Shukla G, Afsar M, Poornima S, Pandey RM, Goyal V, Srivastava A, Vibha D, Behari M. Role of positive airway pressure therapy for obstructive sleep apnea in patients with stroke: a randomized controlled trial. *J Clin Sleep Med.* 2018;14(4):511-521.
 29. Bidarian-Moniri A, Nilsson M, Rasmusson L, Attia J, Ejnell H. the effect of the prone sleeping position on obstructive sleep apnoea. *Acta Otolaryngol.* 2015 Jan; 135(1):79-84.
 30. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep* 1984; 7:110-14.
 31. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N. The role of sleep position in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*2006; 263:946-50.
 32. Sunnergren O, Brostrom A, Svanborg E. Positional sensitivity as a confounder in diagnosis of severity of obstructive sleep apnea. *Sleep Breath* 2013; 17:173-9.
 33. Oksenberg A, Gadoth N. Are we missing a simple treatment for most adult sleep apnea patients? The avoidance of the supine sleep position. *J Sleep Res* 2014; 23:204-10.
 34. 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: 629-39.
 35. Ravesloot MJ, van Maanen JP, Dun L, de Vries N. The undervalued potential of positional therapy in positiondependent snoring and obstructive sleep apnea – a review of the literature. *Sleep Breath* 2013; 17:39-49.
 36. Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB, et al; Sleep AHEAD Research Group of Look AHEAD Research Group. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: The Sleep AHEAD study. *Arch Intern Med.* 2009; 169:1619-26. [PMID: 19786682]
 37. Tuomilehto HP, Seppa JM, Partinen MM, Peltonen M, Gylling H, Tuomilehto JO, et al; Kuopio Sleep Apnea Group. Lifestyle intervention with weight reduction: first-line

- treatment in mild obstructive sleep apnea. *Am J Respir Crit Care Med.* 2009; 179:320-7. [PMID: 19011153]
38. Johansson K, Neovius M, Lagerros YT, Harlid R, Rössner S, Granath F, et al. Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial. *BMJ.* 2009;339: b4609. [PMID: 19959590].
 39. Johansson K, Hemmingsson E, Harlid R, Trolle Lagerros Y, Granath F, Rössner S, et al. Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study. *BMJ* 2011 Jun 1;342: d3017.
 40. Lettieri CJ, Paolino N, Eliasson AH, Shah AA, Holley AB. Comparison of adjustable and fixed oral appliances for the treatment of obstructive sleep apnea. *J Clin Sleep Med* 2011; 7:439–445.
 41. Ngiam J, Balasubramaniam R, Darendeliler MA, Cheng AT, Waters K, Sullivan CE. Clinical guidelines for oral appliance therapy in the treatment of snoring and obstructive sleep apnoea. *Aust Dent J.* 2013 Dec; 58(4):408-19.
 42. Chan AS, Sutherland K, Schwab RJ, Zeng B, Petocz P, Lee RW, Darendeliler MA, Cistulli PA. The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. *Thorax.* 2010 Aug; 65(8):726-32.
 43. Marklund M, Sahlin C, Stenlund H, Persson M, Franklin KA. Mandibular advancement device in patients with obstructive sleep apnea: long-term effects on apnea and sleep. *Chest.* 2001 Jul; 120(1):162-9.
 44. Cistulli PA, Gotsopoulos H, Marklund M, Lowe AA. Treatment of snoring and obstructive sleep apnea with mandibular repositioning appliances. *Sleep Med Rev.* 2004 Dec; 8(6):443-57
 45. Vanderveken OM, Devolder A, Marklund M, Boudewyns AN, Braem MJ, Okkerse W, et al. Comparison of a custom-made and a thermoplastic oral appliance for the treatment of mild sleep apnea. *Am J Respir Crit Care Med.* 2008 Jul 15; 178(2):197-202.
 46. Spicuzza L, Caruso D, Di Maria G. Obstructive sleep apnoea syndrome and its management. *Ther Adv Chronic Dis.* 2015;6(5):273-85.
 47. Marklund M, Stenlund H, Franklin KA. Mandibular advancement devices in 630 men and women with obstructive sleep apnea and snoring: tolerability and predictors of treatment success. *Chest* 2004; 125:1270–1278.