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Continuous positive airway pressure therapy in obstructive sleep apnea: benefits and alternatives

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA) is a highly prevalent condition affecting persons of all age with an increasing public health burden. It is implicated in cardiovascular disease, metabolic syndrome, neurocognitive impairment, reductions in quality of life, and increased motor vehicle accidents. The goals of OSA treatment are to improve sleep and daytime symptoms, and minimize cardiovascular risks. Areas covered: Continuous positive airway pressure (CPAP) is considered the gold standard therapy that delivers pressurized air into the upper airway to relieve obstruction during sleep. Although CPAP is an effective modality of treatment for OSA, adherence to therapy is highly variable. This article highlights the benefits of CPAP therapy, along with alternative treatment options including oral appliance, implantable and wearable devices, and surgery. Expert commentary: CPAP therapy is the gold standard treatment option and should continue to be offered to those who suffer from OSA. Alternative options are available for those who are unable to adhere to CPAP or choose an alternative treatment modality. The most interesting advances have been incorporating orthodontic procedures in conjunction with myofunctional therapy in prepubertal children, raising the possibility of OSA prevention by initiating treatment early in life.

1. Introduction

Treatment options for OSA include positive airway pressure (PAP) therapies, sleep apnea surgery, implantable and wearable devices. This is an up-to-date comprehensive review that discusses CPAP therapy and alternatives for the treatment of OSA.

Favorable effects of CPAP therapy in OSA continue to be realized. Since the initial introduction of CPAP by Sullivan in 1981, its application to expanding patient populations has produced new opportunities for clinical investigation [1]. The previous 5 years have also seen growth in alternative treatments, providing an ever-evolving basis for therapeutic comparison. This review’s aim is to summarize the recent strides made with respect to clinical success while highlighting those studies with comparative and placebo-controlled strategies when possible. With regard to CPAP treatment and cardiovascular outcomes, it is important to mention the frequent intersection between OSA and obesity in study participants. For our purposes, we will direct focus toward the use of CPAP in nonobese patients in order to underscore the ramifications of treating OSA as a disease in isolation.

2. Benefits of CPAP

2.1. Background

The association of sleep-disordered breathing and symptoms of sleepiness and poor quality of life derives from large population-based inquiries including the Sleep Heart Health [2] and Wisconsin Sleep Cohort studies [3]. Data from these investigations established firm relationships between respiratory disturbance during sleep and daytime sleepiness, even in those with milder forms of sleep-disordered breathing [4]. In addition, these data highlighted the development of depression as well as cardiovascular morbidity and mortality as a result of sleep disruption [5]. When considering an overview of clinical benefits related to CPAP, we will focus on recent investigations of quality of life (including sleepiness), neurocognition, cardiovascular health and metabolism.

2.2. Quality of life

The improvements in daytime function and sleepiness attributable to PAP have long been understood. Early randomized, placebo-controlled studies and subsequent systematic reviews formed the basis for CPAP prescription with the intent of targeting daytime sleepiness and mood symptoms [6,7]. A dose–response effect has also been found with respect to CPAP treatment and improvement in Epworth Sleepiness Scale scores [8], and these findings have had important public health implications, with meta-analyses showing a reduction in reported road traffic accidents with CPAP treatment. Antonopoulos and colleagues calculated a number needed to treat (NNT) of five – indicating the number of patients that would have to receive CPAP treatment to prevent the report of at least one road accident. The NNT for near miss
accidents was only two, and a significant reduction in accident-related events was also seen in tests performed on driving simulators [9]. However, it is important to note that neurocognitive impairment and daytime sleepiness do not normalize in a proportion of OSA patients despite adequate CPAP use [8].

Recently, studies assessing quality of life have considered expanded treatment courses and new patient populations. A Brazilian study found that after 1 year of CPAP use, patients with moderate severity OSA (apnea hypopnea index [AHI] >20 events per hour) and a body mass index (BMI) less than 40 kg/m² demonstrated a gain in terms of quality adjusted life years (QALY) [10]. Given that the majority of scientific study has focused on middle-aged adults, Martinez-Garcia and colleagues undertook to examine the elderly population. In patients over 70 years old with severe OSA (AHI >30 events per hour), 3 months of CPAP use (versus no treatment) improved quality of life measures, sleep-related symptoms, anxiety and depression as well as blood pressure and neurocognitive testing [11].

### 2.3. Neurocognition

With regard to neurocognitive symptoms, OSA has been known to inflict detrimental effects as judged by tests of sustained attention, visuospatial learning, executive function, motor performance, and constructional abilities [12], and this has been confirmed by a recent meta-analysis [13]. Studies examining the degree of reversibility of these deficits have encountered measured success. The APPLES study, a 6-month randomized, double blind, sham-controlled trial evaluated attention and psychomotor function (A/P), learning and memory (L/M) and executive and frontal lobe function (E/F). This demonstrated only an improvement in E/F at 2-month follow-up, particularly in those with more severe OSA [14]. In a meta-analysis of five studies examining the impact of OSA on executive functioning before and after treatment, all five domains of executive functioning demonstrated impairments, independent of age and disease severity. All domains were noted to have mild to moderate improvements with CPAP treatment [15].

In addition to neuropsychological testing, there has been recent interest in neuroimaging as a modality for assessing the neurologic detriment of OSA as well as the potential benefit of CPAP. The notion of evaluating structural changes in the brain associated with sleep apnea began in the late 1990s with use of magnetic resonance spectroscopy (MRS) [16]. Magnetic resonance imaging (MRI) has demonstrated structural changes in brain regions of OSA patients, including areas that regulate memory and executive function [17,18]. Functional MRI (fMRI) has also been explored. Prilipko and colleagues, noting that previous studies using transcranial Doppler have shown impaired cerebrovascular reactivity in OSA patients [19], utilized fMRI to examine the anatomical distribution of reactivity changes. Flow-sensitive alternating inversion recovery (FAIR) imaging before and after 2 months of therapeutic (active) or sub-therapeutic (sham) CPAP treatment demonstrated increased reactivity in the thalamus of CPAP patients. By contrast, those using sham CPAP had decreased reactivity [20]. In another study of elderly patients (>65 years old) randomized to 3 months of CPAP (versus conservative care), those in the CPAP group showed increased connectivity in the frontal gyrus while the control group had a higher percentage of cortical thinning [21].

Investigation into the combined use of neuropsychometric testing and imaging has also been performed. Castronovo and colleagues performed the first study using fMRI to compare brain activation in OSA versus healthy controls during a cognitive test of working memory (the n-back task). Following 3 months of CPAP treatment in both groups, no difference was seen in n-back task. However, additional cognitive testing showed improvement in the OSA group where greater activation was seen in the left frontal cortex, medial precuneus, hippocampus, and decreased activation in the caudal pons. This was interpreted as a compensatory over-recruitment, as decreases of activation in prefrontal and hippocampal structures were observed after treatment [22] (i.e. due to OSA there was higher neuronal network activity and metabolism compared in controls).

Most studies testing the effect of CPAP on cognition have focused on brain regions that consistently exhibited increased activation with tasks requiring attention or executive control [23–25]. The network of those regions has been previously described as the Task Positive Network (TPN) as it exhibits an increase in activation when subjects engage in cognitive tasks. TPN comprises several functional networks reported in the cognitive literature such as the frontoparietal attention network, executive network, and right hemisphere-lateralized ventral frontal networks [26,27]. In recent years, however, it has become clear that a set of brain regions operates antagonistically to the TPN and that optimal coupling between this set and the TPN is mandatory for successful behavioral performance [28,29]. This network of TPN anti-correlated brain regions is more active during rest and responds with progressive deactivation to external goal-oriented task. It has been described and is commonly referred to as the Default Mode Network (DMN) in studies of functional connectivity or Task Negative Network/Task Deactivation Network (TNN/TDN) in studies of cognitive task performance [29–31].

Using fMRI and working-memory task, Prilipko and colleagues [32] performed an investigation examining the effects of CPAP on TPN and DMN networks of OSAS patients and compared results to those observed in healthy controls and in patients with sham CPAP. The main finding of the study was that active and sham CPAP had opposite effects on behavioral performance and cerebral activation. The findings of opposite response in deactivation of the temporal brain regions after 2 months of active and sham-CPAP treatment supported the hypothesis that OSA has a negative impact on the temporal lobe part of the DMN, possibly via the effects of nocturnal hypoxemia.

In parallel to the Prilipko et al. study, O'Donghue et al. [33] found metabolic abnormalities in the hippocampus of OSA patients comparable in magnitude to changes found in Alzheimer's disease. Those changes were no longer detectable after 6 months of CPAP treatment. Overall, the most consistent findings in structural neuroimaging studies of OSA patients are signs of hippocampal injury [17,34–36]. The study by
O’Donghue and colleagues suggests that the hippocampus, even if sensitive to OSA-related injury, has the potential for recovery with CPAP treatment. Prilipko and colleagues indicated that their study involving CPAP, sham CPAP and healthy controls showed two different aspects of CPAP treatment when considering cerebral task-related activation and deactivation and behavior parameters: elimination of episodes of nocturnal hypoxemia and decrease in sleep fragmentation with subsequent improvement of vigilance levels. For the authors, the ‘improvement of alertness’ effect is supported by the higher activation shown by healthy controls initially compared to OSA patients in the bilateral anterior insular/ inferior frontal regions (which constitute the ‘alerting’ node of the TPN) [37,38], as well as in the right ventral frontal cortex [27] and by the accentuation of these differences after sham CPAP treatment. However, one must not ignore the impairment of the DMN as mentioned above, particularly the temporal part of the system hypothesized to be related to hypoxemia. This would mean that depending on the importance of sleep fragmentation versus hypoxemia, there would be differences in the impact of OSA and response to CPAP treatment. Many of the symptoms brought up by OSA patients can be related to the findings outlined in these studies, and their results are important as they indicate that neurocognitive changes may be reversible with long and regular usage of CPAP.

2.4. Cardiovascular and metabolic effects

Both fatal and nonfatal cardiovascular events have been noted to occur with greater frequency in untreated middle-aged male populations with severe [39] as well as mild-to-moderate sleep apnea [40]. A dose–response association has been demonstrated between OSA severity (measured by AHI) and the presence of hypertension after controlling for BMI, neck and waist circumference, age, gender, and use of alcohol and nicotine [41]. In terms of treatment, CPAP’s effect on hypertension has been variable. A multicenter, randomized trial of 12 weeks of CPAP versus no therapy in patients with resistant hypertension and moderate-to-severe OSA showed a greater decrease in 24-hour mean and diastolic, but not systolic blood pressure [42]. Nocturnal blood pressure patterns (nocturnal dipping) were improved in those who used CPAP therapy [42]. Similarly, a more recent study addressed the utility of the antihypertensive effect of CPAP as an add-on therapy to angiotensin II receptor blockade treatment in patients with new-onset hypertension. CPAP add-on in those with OSA provided no additional benefit in terms of 24-hour blood pressure measurements, but did reduce nighttime systolic blood pressure [43].

Non-dipping of nocturnal blood pressure is associated with cardiovascular disease. Mokhlesi and colleagues reported an independent association between rapid eye movement (REM) OSA and incident non-dipping of blood pressure in a cohort of 269 adult patients (Wisconsin Sleep Cohort) [44]. When evaluating CPAP’s role with regard to cardiovascular endpoints, the criterion used as a measure of CPAP adherence should be taken into consideration. The Centers for Medicare and Medicaid Services CPAP adherence definition of at least 4 h of use per night may not be the ideal benchmark, as REM sleep is more prevalent in the second half of the night. Treatment of OSA with CPAP is often limited to the first half of the sleep period, as patients tend to pull their masks off after 4 h of sleep, leaving most of REM sleep untreated. Blood pressure’s response to CPAP may not be adequately tested when usage is limited to the first half of the night.

CPAP has been shown to be more effective in improving 24-hour mean blood pressure when compared to supplemental oxygen in those with either established cardiovascular disease or multiple cardiovascular risk factors [45]. In those with moderate OSA but without sleepiness, a Spanish study did not show a significant difference in the incidence of hypertension or cardiovascular events after 4 years of either CPAP therapy or no active intervention [46]. A subsequent meta-analysis likewise determined that CPAP did not have a consistent beneficial effect on blood pressure in patients with minimally symptomatic OSA [47]. However, it must be emphasized that many of these studies may have been underpowered and may not be adequately controlled for obesity. The use of micro-ribonucleic acid (miRNA) profiles for identifying patients with resistant hypertension who are responsive to CPAP treatment has shown promising results. Advanced clinical phenotyping provides an exciting prospect for future treatment strategies [48].

Treatment of OSA and subsequent prevention of cardiovascular outcomes, such as the incidence of coronary events, stroke, and heart failure has not been addressed with a randomized approach. Prospective, observational studies have shown that treatment of OSA appears to reduce nonfatal (myocardial infarction, stroke, and acute coronary syndrome requiring revascularization) and fatal (death from myocardial infarction or stroke) cardiovascular events [39,40]. Early introduction of CPAP following ischemic stroke has shown promise with regard to neurologic recovery. Patients randomized to CPAP within a week of a first-ever ischemic stroke demonstrated better neurologic recovery after 1 month as evaluated by Canadian and Rankin scales. Although this improvement was not sustained at 3 months, at 68 months of follow-up, patients treated with CPAP had higher rate of cardiovascular survival [49].

Given the relationship between OSA and established cardiovascular outcomes, much attention has been directed toward OSA and pre-morbid disease. This has included investigation of inflammatory markers such as C-reactive protein [50] and measures of insulin resistance [51]. Chirinos and colleagues assigned patients with obesity, moderate-to-severe sleep apnea and CRP levels greater than 1.0 to receive CPAP, a weight loss intervention, or CPAP plus a weight loss intervention for 24 weeks. Those assigned to weight loss alone and the combined group showed reductions in CRP, insulin resistance, and triglycerides. However, none of these outcomes were demonstrated in the CPAP-only group [52]. Glucose tolerance, conversely, has shown improvement in morbidly obese patients with severe OSA. After randomizing obese (mean BMI >45 kg/m²), non-diabetic patients to either 12 weeks of CPAP or conservative treatment, Salord and colleagues noted a decreased incidence of glucose intolerance in the CPAP group. These results occurred without differences in weight
loss or changes in the homeostasis model assessment of insulin resistance, suggesting an improvement in peripheral insulin resistance [53]. Patients with pre-diabetes (fasting plasma glucose of 100–125 mg/dl and/or impaired 2-h glucose tolerance) and obesity (BMI $\geq 25$ kg/m$^2$) also appear to benefit from consistent CPAP use. In total, 39 such participants randomized to 8 h of nightly CPAP (versus oral placebo) over 2 weeks demonstrated increased insulin sensitivity and a reduction in blood pressure as well as serum catecholamine levels [54].

### 2.5. Drawbacks to therapy

Any discussion of the benefits of CPAP mandates mention of possible hazards associated with the treatment. The most important of these has been related to the mask interface used to deliver positive air pressure. The prolonged application of force to the facial skeleton can alter the magnitude and direction of skeletal growth in children and may impair the anatomical facial presentation in adults [55,56]. There is a rapid growing body of literature in children and adults since the first report of secondary facial hypoplasia related to continuous usage of nasal CPAP mask. These changes have been documented by comparing cephalometrics obtained before and after a variable duration of CPAP treatment. In children, Fauroux et al. reported facial flattening in 68% and clear maxillary retrusion in 37% of children aged 0–18 years using nasal CPAP, with a stronger association linked to longer nighttime use [57]. Roberts et al. studied 50 patients who were adherent to nasal CPAP therapy (mean age 10 years) and 50 non-adherent patients (mean age 8.5 years) for an average of 2.6 years. Adherent patients experienced negative change (retrusion) of the midface compared to forward growth seen in non-adherent patients, counterclockwise rotation of palatal plane, and upper incisor flaring [58].

Tsuda and colleagues looked at cephalometric variables in adults with OSA using CPAP. The average duration of nasal CPAP use was 35.0 ± 6.7 months. Significant retrusion of the anterior maxilla, a decrease in maxillary-mandibular discrepancy, a setback of the supramental and chin positions, a retroclination of maxillary incisors, and a decrease of convexity were demonstrated [59]. All publications indicate the same negative impact on the maxilla in children and adults. This is an important problem even more so in children that have periods of rapid facial growth between birth and 6 years of age, and during pubertal years. Many patients already possess facial characteristics that increase the risk of collapsibility of the upper airway during sleep [60]. Such a risk has led to orthodontic treatment of children with OSA aiming at expansion of the maxilla in three directions. The nasal mask worn all night has a complete opposite effect and worsens the facial abnormalities, thus increasing the risks of upper airway collapsibility. Addition of a chinstrap, one usually placed on the tip of the chin, adds pressure in a posterior-superior direction acting on the cartilages of the mandibular condyles and displacing the mandible in a posterior direction – only adding to the problem. Most of the reported studies were performed using either full face or nasal mask varieties.

Efforts have been made to use much lighter interfaces with regular follow-up by orthodontists and including periodic measurements of cephalometrics. Preliminary results from our clinic indicate that, in children, at 6-month follow up after initiating CPAP with a nasal mask, facial changes were not as marked compared to the use of full face masks. The issue of this negative impact of the CPAP interface is, to date, unresolved. Usage of myofunctional therapy (MFT) as a counter-measure has shown promising results, but adherence with treatment recommendations poses a challenge.

Myofunctional therapy and proper tongue positioning in the oral cavity has been described since 1918s. The procedure is performed to improve mandibular growth, nasal breathing and facial appearance. It is comprised of isotonic and isometric exercises which target oral (i.e. lip, tongue) and oropharyngeal structures (i.e. soft palate, lateral pharyngeal wall) and its aims are to promote change in body and head posture, change in breathing with a switch to predominantly nasal breathing, and elimination of abnormal swallowing, mastication, and speech. The procedure is aimed to promote normal usage of all oral facial muscles and normal posture at rest (including tongue posture). The first publication on MFT on adult OSA patients was published in 2009 by Guimaraes and colleagues [61]. After 3 months of re-education therapy, there was improvement in the AHI. Several studies have investigated the role of MFT in children with OSA, showing that significant improvement could be demonstrated with addition of MFT in association with other treatment approaches. A meta-analysis has shown that in 9 adult studies (120 patients), the pre- and post-MFT apnea hypopnea indices decreased from a mean of 24.5 ± 14.3 to 12.3 ± 11.8 events per hour, and lowest oxygen saturation improved from 83.9 ± 6.0% to 86.6 ± 7.3% [62]. Guilleminault and colleagues evaluated children who had normal AHI after adeno-tonsillectomy and palatal expansion, and found that at 4-year follow-up, 11 patients who initially underwent MFT remained normal (AHI 0.5 ± 0.4 events per hour), whereas 13 patients not subjected to orofacial muscle reeducation had recurrent OSA (AHI 5.3 ± 1.5 events per hour) after 4 years [63]. MFT decreases the AHI by approximately 50% in adults and 62% in children. Minimum oxygen saturation, snoring, and sleepiness outcomes improved in adults. MFT may serve as an adjunct to other treatments for OSA.

Adherence to treatment with CPAP can be considered a significant limitation when choosing amongst therapeutic options. Adherence to CPAP has been defined variably across studies, but generally ranges from an average percent time used per night of 3–5 h. When defined as greater than an average of 4 h of nightly use, 46–83% of patients have been reported to be non-adherent [64]. Previously identified factors that may contribute to lack of treatment adherence include disease and patient characteristics such as severity of sleep apnea and sleepiness, as well as CPAP titration procedures, technical aspects of the device (heated humidification, etc.) and psychological and social factors [65]. Even in those patients who have demonstrated adequate adherence to therapy, a discontinuation of as little as 2 weeks has been demonstrated to lead to rapid recurrence of OSA with worsening sleepiness, impaired endothelial function as well as increases in blood pressure and urinary catecholamine levels [66].
3. Alternative treatments

CPAP therapy is considered the gold standard for the treatment of OSA. While CPAP is highly efficacious, adherence to therapy remains a challenge, with adherence rates ranging from 29% to 81% [64]. Effectiveness of CPAP is intimately tied to adherence to therapy and treatment response. As a result, alternative treatment options are recommended for patients who are unable to adhere to CPAP therapy. Conventional alternative therapies include oral appliances and upper airway surgery. In addition to conventional treatment options, novel non-positive pressure therapies have emerged, albeit with variable success rates in regard to acceptance, adherence, and treatment efficacy. We will review conventional and non-positive pressure therapies, their mechanisms of action, efficacy, and evidence to support their use.

3.1. Oral appliance therapy

Oral appliances (i.e. mandibular advancement devices) are designed to improve upper airway caliber by holding the lower jaw in an anterior position during sleep, thereby preventing upper airway collapse. Studies utilizing imaging techniques suggest that the mechanism of action of the mandibular advancement device is to increase the volume of the upper airway, specifically the velopharynx region. Anterior tongue movement may also occur with anterior movement of the lower jaw [67, 68]. Randomized controlled studies comparing oral appliance therapy to placebo for the treatment of OSA reported statistically significant improvements in snoring, AHI, arousal index, oxygen saturation, and daytime sleepiness [69–72]. Variable outcomes were reported in regards to health related quality of life measurements, neurocognitive functioning, and cardiovascular benefits (blood pressure reductions) with use of oral appliance therapy [69–72]. Marklund and colleagues conducted a randomized study comparing oral appliance therapy to placebo for 4 months in patients with daytime sleepiness, snoring, or mild to moderate OSA. The authors concluded that oral appliance effectively reduced AHI and snoring, but had no significant effects on daytime sleepiness and quality of life [73].

3.1.1. Oral appliance versus CPAP

Randomized controlled trials evaluating effectiveness of oral appliance therapy versus CPAP with overnight in laboratory polysomnograms reported that both therapies improve OSA. However, CPAP does so to a greater extent and provides complete resolution of OSA. Hoekema and colleagues conducted a randomized controlled trial comparing oral appliance versus CPAP in 103 mild-to-severe OSA patients [74]. The authors showed that oral appliance therapy was at least effective in mild to moderate OSA (AHI <30 events per hour) compared to CPAP therapy [74]. The same authors conducted a 2 year follow up study on the same cohort and reported that both therapies showed significant improvements in polysomnographic and neurobehavioral outcomes in mild to moderate OSA, although CPAP was more effective in lowering the AHI, and resulted in higher oxyhemoglobin saturation levels compared to oral appliance therapy (p < 0.05) [75]. It is important to note that more patients dropped out with oral appliance therapy (47%) compared to CPAP therapy (33%). Phillips and colleagues conducted a randomized crossover design comparing CPAP versus mandibular advancement device on cardiovascular (24-hour blood pressure and arterial stiffness), neurobehavioral (subjective sleepiness, driving performance), and quality of life (functional outcomes of sleep questionnaire, Short Form-36) outcomes on 108 moderate to severe OSA patients (baseline AHI 25.6 ± 12.3 events per hour) after 1 month on therapy. Interestingly, the authors reported that CPAP was more effective than mandibular advancement device in reducing AHI (4.5 ± 6.6 versus 11.1 ± 12.1 events per hour, p < 0.01), but adherence (measured subjectively) to therapy was higher in mandibular advancement device (6.5 ± 1.3 versus 5.2 ± 2 h per night, p < 0.00001). Both therapies improved neurobehavioral domains and quality of life scores. Blood pressure was not significantly reduced with either therapy [76]. CPAP’s superior efficacy over mandibular advancement device in improving the AHI is likely offset by lower adherence to therapy, resulting in similar effectiveness for both treatments in other important domains.

The mean disease alleviation (MDA) concept is a measurement of overall clinical effectiveness for a particular treatment modality, and may be a useful measurement in the case of CPAP, where effectiveness is offset by lower adherence to therapy. In this aspect, combination therapy with CPAP and an adjunct therapy (e.g. mandibular advancement device, positional therapy, surgery, weight loss) would improve the MDA index of the primary treatment (i.e. CPAP), which as a single therapy would result in incomplete elimination of the disease [77–79].

Anadam and colleagues performed a large observational study evaluating cardiovascular mortality in CPAP versus oral appliance in severe OSA patients. Patients were followed for a median of 6.6 years [80]. The cardiovascular mortality was highest in the untreated OSA group, and significantly lower in both oral appliance and CPAP treated groups [80]. Bratton and colleagues performed a meta-analysis evaluating the impact of CPAP versus mandibular advancement device on blood pressure in patients with OSA. The reduction in diastolic and systolic blood pressure was significant, albeit modest in both groups [81]. The authors did not find a significant difference between blood pressure outcomes in CPAP versus mandibular advancement device. However, blood pressure improvements were greater in patients who used CPAP for longer periods during the night (1-h increments), and in those with higher blood pressure at baseline [81].

3.1.2. Long-term efficacy and adherence of oral appliance therapy

With success defined as a post treatment AHI of less than 10 events per hour, studies have reported higher success rates with CPAP compared to oral appliance therapy [82]. Regarding improvements in oxygen saturation indices, CPAP has clearly been shown to be superior compared to oral appliance therapy [76, 82, 83]. Aarab and colleagues conducted a randomized controlled trial evaluating long-term efficacy and adherence to
therapy in 43 mild-to-moderate OSA patients using oral appliance versus CPAP. They reported stability in the AHI, daytime sleepiness, and health-related quality-of-life improvements at 1-year follow up with oral appliance use [84]. Although oral appliance therapy is effective for the treatment of mild to moderate OSA, several studies reported a drop off of usage over time [75,85]. A recent study by Marklund reported that long-term treatment (median 16.5 years) with oral appliance resulted in significant deteriorations in disease severity and treatment efficacy, although 9 only patients participated in this study [86]. More recently, objective monitors of adherence to oral appliance therapy have been developed [77,87]. New adherence monitoring technology may improve clinical practice and serve as a valuable tool for researchers to clarify the role of oral appliance therapy in comparison to CPAP therapy for the treatment of OSA.

Oral appliance therapy works by advancing the lower mandible, tongue, and pharyngeal structures anteriorly. This advancement is balanced against potential side effects. During initial treatment adverse side effects are commonly reported, including temporomandibular joint pain, mouth dryness, tooth pain, gum irritation, sialorrhea, as well as headaches. These side effects are transient and generally resolve after about 2 months of treatment. In a long-term follow up (median 16.5 years) of oral appliance treatment, bite changes were reported including decreases in overjet and overbite, which may lead to reduction in mandibular advancement [86].

In patients with mild-to-moderate OSA, oral appliance may be considered as first line treatment. Objective testing may be considered when prescribing oral appliance in those with significant oxygen desaturation during sleep to ensure that hypoxemia is corrected [88]. Dental changes including occlusion, bite, and skeletal changes may occur after long-term treatment, and should be routinely monitored by a treating dentist who is familiar with oral appliance therapy.

### 3.2. Surgical therapies

Sleep apnea surgery aims to correct obstruction at the nasal, retropalatal, and retroglossal/hypopharyngeal regions. Identifying the appropriate candidate and choosing the appropriate surgical intervention are key factors toward surgical success. The decision on the type of surgical intervention is made with physical examination, imaging, and endoscopic procedures including nasopharyngoscopy and drug-induced sleep endoscopy (DISE).

#### 3.2.1. Nasal surgery

Chronic nasal congestion or obstruction may be due to structural abnormalities (deviated nasal septum, enlarged turbinates, nasal valve collapse) or inflammatory mucosal disease (allergic and nonallergic rhinitis, chronic rhinosinusitis, nasal polyps). Observational studies demonstrated that nasal congestion is associated with snoring and daytime sleepiness [89–91]. Randomized controlled studies have shown that in patients with allergic or nonallergic rhinitis and sleep disturbance, nasal steroids or anti-inflammatories could improve the quality of sleep and may be useful for patients with mild OSA; however, they are not by themselves an adequate treatment for the majority of OSA patients [92,93]. Similarly, nasal surgery may improve quality of life and snoring in a subgroup of patients with mild OSA and septal deviation, but it is not an effective treatment for OSA in itself [94–96]. On the other hand, in patients who do not tolerate CPAP therapy because of nasal obstruction, nasal surgery can improve CPAP adherence [97].

Nasal surgery alone has not been shown to cure or improve OSA; however, studies have reported improvements in daytime sleepiness and quality-of-life measures. Yalamanchi and colleagues conducted a retrospective review of combined nasal and sinus surgery on objective measurements of OSA by comparing polysomnographic data before and after surgery. Of the 56 patients, the majority had moderate to severe OSA (84%). The authors reported improvements in AHI from 22.3 ± 4.8 to 20.7 ± 8.2 events per hour in moderate OSA, and 52.3 ± 21.4 to 43.6 ± 23.9 events per hour in severe OSA; however, there was no significant change in mild OSA [98]. Although combined sinus and nasal surgery improved respiratory indices during sleep, it did not cure OSA or had a significant clinical impact.

#### 3.2.2. Tonsillectomy

Tonsillectomy as a stand-alone procedure has not been shown to cure OSA in adult patients. Retrospective studies have reported highly variable range of improvement (20–100%) in the apnea hypopnea index. Similar to the literature on nasal surgery, tonsillectomy has been offered to reduce CPAP pressure requirements, thereby improving CPAP adherence and comfort in adults with OSA and tonsillar hypertrophy. Two studies on tonsillectomy alone reported high surgical success rates (defined as AHI <20 events per hour and >50% reduction from baseline AHI). Senchak and colleagues conducted a prospective multicenter study evaluating effects of tonsillectomy alone in 19 adult OSA patients. The authors reported a success rate of 94.7%, along with significant improvements in median minimum oxygen saturation level and daytime sleepiness, particularly in young overweight men with moderate OSA, grade 3–4 tonsils, and low Friedman stage [99]. Tan and colleagues conducted a similar study on tonsillectomy alone in adults with OSA who had significant tonsillar hypertrophy (grade 3–4). The authors reported a surgical success rate of 74% (defined >50% reduction in AHI and a postoperative AHI <20) [100]. Tonsillectomy may be considered as a primary surgical treatment in carefully selected OSA patients with Friedman grade 3–4 tonsillar hypertrophy.

#### 3.2.3. Palatal surgery

Uvulopalatopharyngoplasty (UPPP) was introduced as a surgical option for the treatment of adult patients with OSA in 1981 [101]. UPPP has evolved over time into various approaches (e.g. lateral pharyngoplasty, relocation pharyngoplasty). The original procedure (UPPP) involves removal of the uvula, parts of the soft palate, tonsils, and closure of the tonsillar pillars. Despite the changes in technical approach, the common goal involves resection or repositioning of palatal tissues and pharyngeal wall in order to increase retropalatal space, thereby reducing upper airway obstruction. Success rates of palatal surgeries are highly variable,
ranging from 16% to 83%, depending on the definition of success, patient selection, and technique used [102]. Yousuf and colleagues conducted a prospective study to redefine ideal clinical parameters that could improve identification of patients who would likely benefit from UPPP. The authors identify Friedman stage 1 and 2, lower neck size, lower BMI, and obstruction predominantly at the retropalatal region by video endoscopy with Mueller’s maneuver, as significant factors for UPPP success. Using a questionable definition of ‘success’ as post-operative AHI <20 events per hour and 50% reduction from baseline AHI, the authors reported a success rate of 95% post-surgery and at 6 months [103]. The Sleep Apnoea Karolinska UPPP (SKUP3) trial evaluated UPPP in a carefully selected group of moderate to severe OSAS patients versus no surgery [104]. The investigators reported a significant reduction in the mean AHI with UPPP (60% versus 11%) at 6 months post-surgery. The Friedman stage I and II patients who entered into this study had large tonsils by definition or, when tonsils were small, the tongue was low, and consequently it was difficult to discern which operation (tonsillectomy versus palatal surgery) contributed most to the improvement in AHI.

Palatal surgery has not been recommended as an intervention to improve CPAP adherence or comfort. Rather, patients who underwent palatal surgery experience difficulties with CPAP adherence due to worsening of mouth leak, despite using lower pressure ranges compared to those who did not undergo palatal surgery [105]. Other side effects or complications of palatal surgery include velopharyngeal insufficiency, swallowing difficulties, taste changes, aerophagia, long-term CPAP intolerance, and decreased efficacy with time due to changes in flaccidity of soft palate.

3.2.4. Orthognathic surgery

Maxillomandibular advancement (MMA) surgery for OSA involves surgical intervention of the facial skeletal framework by osteotomies of the maxilla and mandible, thereby widening the posterior upper airway space. Previous short-term observational studies have shown significant improvements in AHI, daytime sleepiness, and health-related quality of life scores [106,107]. MMA has also been shown to be effective long term [108]. Boyd and colleagues conducted a prospective study evaluating long-term clinical effectiveness and safety of MMA surgery for the treatment of moderate to severe OSA [109]. In this study, 30 subjects (80% male, mean age 50.5 ± 9.6 years) who underwent MMA surgery were followed for a mean of 6.6 ± 2.8 years post-surgery. The AHI improved from a mean of 49.0 to 10.9 events per hour (p < 0.0001) at the time of long-term evaluation, with 46.7% of subjects maintaining an AHI <5 events per hour, and 83.4% of subjects maintaining an AHI <15 events per hour. The authors also reported significant improvements in diastolic blood pressure, daytime sleepiness, and health-related quality-of-life scores. Zaghi and colleagues performed a large meta-analysis evaluating MMA success in 518 OSA patients (73.5% had previously undergone other forms of sleep apnea surgery) [110]. The mean overall AHI improved from a preoperative value of 57.2 ± 25.4 to a post-operative value of 9.5 ± 10.4 events per hour. Using the same questionable definition mentioned above, the authors reported that 85.5% of patients met definition of ‘surgical success,’ while 38.5% met definition of ‘surgical cure’ (AHI <5 events per hour) after MMA surgery. Those with high residual AHI after failure of other surgical methods are most likely to benefit from MMA surgery. Oxygen indices and daytime sleepiness scores also showed significant improvements post MMA surgery [110].

Younger age, nonobese, and lack of comorbidities are factors that positively influence MMA success rate. Aging and weight gain are likely to significantly impair long-term success rate. MMA surgery should be considered as an alternative treatment option for a selected group of OSA patients who are unable to tolerate conventional therapies.

3.2.5. Multilevel surgery

Obstructive sleep apnea involves multilevels of obstruction of the upper airway. Multilevel surgery has become increasingly recognized as the salvage surgical approach in adult OSA patients who have failed conventional or alternative treatment options. Drug induced sleep endoscopy (DISE) is used as a method to identify sites of obstruction in order to guide best surgical approaches. Multilevel surgery studies are mostly observational or retrospective, with success rates highly variable and dependent on surgical approach(s) as well as expertise of the surgeon. One meta-analysis evaluating multilevel surgery reported again a ‘success rate’ of 66% without notion of ‘cure rate’ [111]. Younger age (<60 years old), lower BMI (<30 kg/m²), and lack of significant comorbidities are factors associated with higher multilevel surgical success rates.

3.2.6. Upper airway stimulation

The hypoglossal nerve stimulation (HNS) was approved by US FDA in 2014 as an alternative treatment option for OSA patients who could not adhere to PAP therapy. HNS is an implantable stimulator that unilaterally stimulates the hypoglossal nerve to recruit the genioglossus muscle to contract, thereby generating anterior displacement of the tongue, dilation of the pharynx, with the goal of relieving upper airway obstruction during sleep. See Figures 1(a,b).

The investigation by the STAR Trial Group was a multicenter prospective cohort study that evaluated effectiveness of surgical implantation of an upper airway stimulation device after 12 months of treatment in 126 patients with moderate to severe OSA (83% male) who had difficulty adhering to PAP therapy [112]. This carefully selected group of participants included those with an AHI greater 20 but less than 50 events per hour, BMI <32 kg/m², and screening DISE that identified upper airway collapse specifically at the retrolingual region. The investigators achieved primary outcomes with significant improvements in median AHI score (29.3 to 9.0 events per hour), oxygen desaturation index (ODI) score (25.4 to 7.4 events per hour) as well as secondary outcomes including improvements in daytime sleepiness and health related quality of life measures. In the therapy withdrawal group (23 patients), the AHI was significantly higher at 1-week assessment compared to the beginning of randomization (25.8 versus 7.6 events per hour). The overall rate of serious adverse events (requiring
surgical intervention) was less than 2% [112]. The study investigators performed an 18 month follow up on the durability of the hypoglossal nerve stimulation and reported a sustained effect on airway stability including sustained improvements in daytime sleepiness [113].

Hypoglossal nerve stimulation therapy may be an appropriate alternative option in moderate to severe OSA patients who are intolerant to PAP therapy. Because of limited data, no randomized studies, and no comparison studies to conventional therapies are available, this option may be considered in a carefully selected group of patients, who have otherwise tried and failed to adhere to conventional therapies.

4. Devices

4.1. Nasal expiratory PAP device (EPAP device)

With fiber-optic endoscopy, Morrell and colleagues reported that during sleep end expiratory cross-sectional area of the upper airway progressively decreased in breaths, leading up to an apnea [114]. This discovery led to further testing of a unidirectional flow-resistance device (EPAP device) that regulates flow through nostrils by creating an expiratory flow resistance without creating inspiratory resistance. See Figure 2. The expiratory flow resistance produces lung hyperinflation with subsequent tracheal traction, which is then transmitted to the upper airway to decrease collapsibility [115].

Rosenthal and colleagues conducted a three-way study in 34 OSA patients using three different expiratory resistant settings (50, 80, and 110 cm H2O/s) with follow-up overnight sleep studies at 30 days of treatment [116]. Although the authors did not report statistical differences in any of the three expiratory-resistant settings, they reported improvement in AHI on initial treatment night [24.5 ± 23.6 to 13.5 ± 18.7 events per hour, \( p < 0.001 \)], with continued improvement in AHI at 30 days from treatment (15.5 ± 18.9 events per hour \( p < 0.001 \)). Despite improved indices, when using a success criterion of AHI <10 events per hour, only 14 of 28 patients (50%) achieved this outcome at initial therapy, and 11 of 28 (39%) at 30 days following treatment. In total, 15% of patients withdrew from study due to ineffectiveness or did not like the treatment [116]. Following this study, a large multicenter randomized study involving 250 OSA patients using the EPAP device versus sham was conducted [117]. The EPAP device resulted in mean AHI reduction of 52.7% [mean baseline in EPAP device group 13.8 events per hour; sham group 11.1 events per hour]. It is worth noting that only 58% of patients completed a 3-month trial due inability to tolerate the device. Most of the patients also had mild OSA [117]. Objective assessment of adherence to therapy, as well as evaluation of important outcome measures including excessive daytime sleepiness and cardiovascular benefits have not been evaluated.

The EPAP device may be a last resort treatment option for mild OSA. Success rate and adherence to therapy are modest at best. Contraindications include severe OSA, central sleep apnea, severe nocturnal oxygen desaturations, chronic nasal blockade, persistent nasal allergies or sinusitis, or use of sedating medications. We recommend testing with an overnight in laboratory polysomnogram to determine effectiveness and tolerance prior to prescribing.

4.2. Oral pressure therapy (OPT)

Unlike CPAP, which applies PAP to the upper airway, the oral pressure therapy (OPT) applies negative pressure therapy by
means of oral suction to the upper airway. See Figure 3. Utilizing MRI, Schwab and colleagues reported a 75% increase in average retropalatal airway in both lateral and anterior-posterior dimensions by moving the soft palate and tongue anteriorly and superiorly [118]. Colrain and colleagues performed the only multicenter prospective randomized 4-week treatment study on OPT in 63 patients (70% male) with mild-to-severe OSA [119]. The median AHI improved from 27.5 to 13.4 events per hour on the first treatment night, and remained at 14.7 events per hour at 28 days of treatment. The ‘responder’ group (20 patients), defined as AHI ≤10 events per hour and a reduction of AHI ≥50% from baseline, had a median AHI of 8.7 events per hour at 28 days on treatment. Adherence to OPT was 87.5% (usage >4 h). The authors also reported clinically significant improvements in sleep architecture (increase in REM sleep, reduction in arousals) and subjective sleepiness as measured by Epworth Sleepiness Scale. Unfortunately, the authors did not report patient characteristics that predicted OPT success [119].

Farid-Moayer and colleagues conducted a prospective study on 76 patients (74% male) using OPT in a single-night study evaluating effectiveness of the OPT in mild to severe OSA [120]. The average BMI ranged from 22.6 kg/m² to 57.9 kg/m², with some being classified as morbidly obese who may be at risk for severe nocturnal hypoventilation. Treatment AHI reduced to 24.6 ± 25.7 from a baseline of 38.7 ± 27.5 events per hour (p < 0.001). The oxygen desaturation index modestly improved from a baseline of 30.1 ± 23.7 to 15.8 ± 19.1 (p < 0.001). Although results reached statistical significance, it is important to note that only 38% of patients had an AHI less than 10 events per hour (normal being <5 events per hour). Oxygen desaturation events did not normalize, likely due to a high BMI with comorbid nocturnal hypoventilation. Nigam and colleagues performed a meta-analysis on OPT in OSA patients and reported an overall modest ‘success’ rate between 25% and 37% (based on at least 50% reduction in baseline AHI and a post treatment AHI <10 events per hour) [121].

Although results of these studies reached statistical significance with improvements in sleep apnea parameters, baseline AHI and oxygen desaturation index were not suppressed in the majority of patients to the extent that is considered to be optimal (<5 events per hour). The OPT may be considered in mild to moderate, nonobese patients with OSA, who have been tried or counseled on conventional therapies. The current OPT device offers usage but not efficacy monitoring. We recommend testing the OPT in an overnight in laboratory polysomnogram to determine effectiveness prior to prescribing.

Many of the presented studies are handicapped by using a definition of ‘variable success,’ and do not give enough attention to residual complaints or symptoms at long-term follow up. Condos et al. [122] used CPAP to evaluate ‘inspiratory flow limitation’ and validate the nasal cannula pressure transducer concept, and successfully demonstrated the concept of ‘incomplete opening of the upper airway’ resulting in ‘incomplete treatment.’ Guilleminault et al. [123] emphasized the negative impact of chronic ‘upper airway resistance’ and ‘inspiratory flow limitation,’ which was reaffirmed by Palombini and colleagues [124]. These investigations emphasized the impact of CPAP in which pressures may be adjusted noninvasively over time to treat disease progression.

5. Summary

CPAP therapy is the gold standard treatment option and should continue to be offered to those who suffer from OSA. The main drawback of CPAP is variable adherence to therapy due to multiple factors, and potential consequent orofacial changes from long-term use of mask interface. Alternative options are available for those who are unable to adhere to CPAP or choose an alternative treatment modality, but these options should be offered to a carefully selected group of patients, as treatment efficacy are variable and long term side effects are not well studied or available. The most interesting advances have been incorporating orthodontic procedures in conjunction with myofunctional therapy in prepubertal children, raising the possibility of OSA prevention by initiating treatment early in life, in those with risk factors that are known to lead to OSA.

6. Expert commentary

CPAP is widely used as the treatment of choice for OSA. However, in patients with comorbid OSA and obesity, CPAP may not be the ideal treatment. Weight loss has been the focus of attention. Studies have involved obese subjects with comorbid OSA, and in order to properly evaluate the impact of CPAP on OSA, obese patients should be excluded from subject selection.

When considering nonobese patients, different ‘phenotypes’ exist and therefore treatment responses may not be similar depending on gender, age of onset of OSA, and time of treatment initiation. These factors are not taken into consideration when evaluating patient’s response to treatment. Many studies on OSA did not institute placebo-controlled groups and often, outcomes studies have limited number of subjects enrolled. Despite these issues, CPAP has been shown to favorably impact neurocognitive impairment related to OSA in selected patient population.
CPAP has clearly been shown to improve sleep disruption and quality of life in OSA patients. The impact of OSA on cardiovascular system is more difficult to assess as many studies have involved overweight or obese subjects. However, despite the confounding obesity factor, there is suggestion that CPAP modestly improves high blood pressure and reduces sleep-related cardiac arrhythmias. The impact of OSA on systemic inflammation, oxidative stress, and autonomic nervous system changes during sleep has not been investigated in placebo-controlled studies. Non-adherence to treatment is an issue, and controlled studies evaluating the impact of treating nasal obstruction (e.g. surgery, allergy treatment) to improve CPAP adherence are lacking.

What is well demonstrated is the negative impact of CPAP mask interface on orofacial growth in children, and worsening of craniofacial abnormalities in adults. Myofunctional therapy has been used to modify the negative impact of CPAP mask interface on orofacial growth and improve gas exchange during sleep; however, long-term studies are lacking. Mandibular advancement devices can have a negative impact on the oral structure including change of bite to a variable degree and variable speed. Long-term comparison of different types of mandibular advancement devices and an evaluation of benefits versus detrimental effects are lacking.

Sleep apnea surgery may produce similar results compared to CPAP on carefully selected patients with short-term efficacy. Systematic studies comparing long-term morbidity between CPAP and surgical treatments are also lacking. The most interesting advances have been incorporating orthodontic procedures in conjunction with myofunctional therapy in prepubertal children. Limited preliminary results raise the question if OSA can be prevented by initiating treatment early in life to those with risk factors that are known to lead to OSA. This is a promising field of sleep apnea research, but again with very limited data at this stage.

In summary, despite known negatives, CPAP continues to be the gold standard therapy as it significantly improves quality of life in adult patients. Too often, there is a lack of focus on yearly evaluation of the negative impact of the CPAP mask interface, and myofunctional reeducation is not offered. The long-term benefits versus cost of CPAP usage on appropriately selected patients are unknown.

7. Five-year view

The interrelationship between OSA and obesity will be elucidated. Further studies will focus on combined treatment approach (CPAP plus weight loss), with an emphasis on formal weight loss programs rather than diet/exercise alone. Research on effective interventions to improve CPAP adherence will be conducted, and should provide us with new therapeutic approaches for those who struggle with CPAP use.

As OSA is a heterogeneous condition, it is not difficult to understand why CPAP remains a one size fits all, as it effectively ‘splints’ the upper airway open, regardless of site or severity of obstruction. As CPAP adherence is a major barrier to effective therapy, we project there will be focus on a new generation of custom made mask interfaces that would make the CPAP experience more tolerable.

Prospective studies will be conducted on cohorts treated with combination therapy (medical management plus CPAP therapy) versus medical management alone or sham CPAP. These studies will involve diverse ethnic groups. Two groups will be particularly looked at in the USA: African-Americans and Caucasians (including the so called ‘Hispanics’ as a subgroup of Caucasian), while Asians will be studied in India and Far-East Asia.

Studies focusing on the negative impact of CPAP mask interface on facial growth will be a priority. This will lead to further research on improved mask interfaces for children and adults with minimal impact on craniofacial profile (maxilla and mandible). This will also lead to studies evaluating beneficial effects of active and passive myofunctional treatment when using CPAP therapy long term, especially in children.

The utility and benefits of CPAP therapy in subjects with mild OSA who suffer from significant daytime impairment (particularly in pre-menopausal women) will be addressed in appropriately controlled prospective studies. These studies will also involve women with OSA who are deemed to be at risk for preeclampsia.

Prospective studies comparing long-term outcomes of age-matched subjects submitted to either CPAP therapy versus surgical interventions (maxillary mandibular advancement or surgically assisted rapid maxillary expansion) will be performed with sufficient subgroups by gender and ethnicity (particularly Caucasians versus Far-East Asian versus African-American). These studies will also look at CPAP adherence and the development of co-morbid cardiovascular disease, including obesity.

Finally, ongoing research on sleep apnea phenotyping with a focus on genetic or biomarkers are promising approaches that will shape treatment for the future, but these approaches will take some time to materialize into the clinical arena. Larger-scale research across a wide range of ethnic groups is needed. As CPAP will remain the gold standard treatment for OSA for the near future, the quest for new treatment continues.

Key issues

- Overall impression from limited placebo-controlled clinical trials suggests that CPAP therapy improves neurocognitive impairment and quality of life in non-obese adult OSA patients at the cost of continuous nightly usage of equipment, and unspecified risk of progressive craniofacial impairment related to the CPAP mask interface.
- The role of CPAP on cardiovascular changes associated with OSA is difficult to fully assess, as obesity is a common variable in many studies.
- There are limited placebo-controlled (CPAP/sham CPAP) prospective studies available to determine effects of CPAP therapy on cardiovascular, metabolic, and neurocognitive impairments.
- There is an absence of prospective long-term clinical trials on effects of CPAP in appropriately selected male and female patients looking at effects of gender, ethnicity,
aging, as well as long-term outcomes including craniofacial changes, with and without myofunctional therapeutic interventions.

- There is an absence of prospective parallel cohorts comparing short and long-term outcome of specific surgical treatments (e.g. maxillomandibular advancement surgery, surgical assisted rapid maxillary expansion), and of mandibular advancement device compared to CPAP.
- There is an absence of studies on prospective treatment of polysomnographically ‘mild’ sleep disordered breathing (e.g. upper airway resistance syndrome, chronic airflow limitation syndrome) and efficacy of CPAP therapy.
- There is an absence of effort to appropriately recognize and treat early in life risk factors known to be associated with development of OSA in children, and long-term evaluation of these efforts.
- Oral appliance can be considered as initial therapy for mild to moderate OSA patients, however there is lack of robust randomized clinical trials comparing oral appliance to CPAP or alternatives, along with lack of solid data on long-term efficacy.

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### References

Papers of special note have been highlighted as either of interest (∗) or of considerable interest (∗∗) to readers.

- This meta-analysis attempted to ascertain OSA and cognitive impairments as measured by objective neuropsychological testing. The results highlight the detrimental effects of OSA on neurocognitive symptoms, including memory, psychomotor speed, executive functioning, attention, processing, reasoning, and psychomotor speed.
This study evaluated REM-related OSA and its relationship to obstructive sleep apnea: a randomized controlled trial. JAMA. 2012;307(20):2161–2168.


- The study attempted to identify plasma micro-ribonucleic acid RNA profiles that predict blood pressure responses to CPAP treatment in patients with OSA and resistant hypertension.


- This study evaluated combined treatment with CPAP and weight loss regimen versus CPAP or weight loss alone in patients with moderate to severe OSA and obesity for 24 weeks.


- This study evaluated long-term use of nasal CPAP therapy and side effects related to craniofacial growth abnormalities in children.


• This study evaluated the long-term use of oral appliance versus CPAP therapy.


• This meta-analysis compared the impact of CPAP and mandibular advancement device on blood pressure in patients with OSA.


91. McNicholas WT. The nose and OSA: variable nasal obstruction may be more important in pathophysiology than fixed obstruction. Eur Respir J. 2008;32(1):3–8.


- This meta-analysis summarizes the clinical efficacy and safety of MMA surgery in treating OSA based on the available literature.


- This study was a large meta-analysis evaluating MMA success in 518 obstructive sleep apnea patients.


- This study evaluated inspiratory flow limitation (IFL) as an important parameter for identifying sleep-related breathing disorders in the setting of normal AHI.