New and Unconventional Treatments for Obstructive Sleep Apnea

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Summary Although continuous positive airway pressure, oral appliances and surgical modifications of the airway are considered as part of the routine management of patients with obstructive sleep apnea, many new and unconventional therapies exist. Many of the trials using these new alternatives have been limited by insufficient data, poor trial design, small sample size, unclear inclusion criteria, lack of randomization, and lack of blinding, and on occasion are biased by retrospective design. Bariatric surgery, positional therapy, auto-titrating positive airway pressure, serotonin agents, wake promoting agents, genioglossus stimulation surgery, supplemental oxygen, nasal dilators, nasal expiratory resistor devices and oropharyngeal exercises will be reviewed. As obstructive sleep apnea impacts the individual and society at large, further research is needed to explore new therapeutic treatment options for obstructive sleep apnea. Therapeutic trials for obstructive sleep apnea must be of

rigorous design to prove clinical effectiveness while taking into account both patient satisfaction and cost effectiveness.

Keywords obstructive sleep apnea · snoring · positional therapy · bariatric surgery · nasal valves · neuromuscular stimulation · positional therapy · weight reduction · electrical stimulation · nasal dilators · continuous positive airway pressure · CPAP · APAP

Abbreviations

CPAP Continuous Positive Airway Pressure
OSA Obstructive Sleep Apnea
AHI Apnea Hypopnea Index
APAP Auto-titrating Positive Airway Pressure

Introduction

Obstructive sleep apnea (OSA) is highly prevalent and is estimated to affect 20 % of US adults [1]. In view of the increasing obesity epidemic in this country, there is an increasing prevalence of OSA. The night-time symptoms of apneas, snoring and fragmented sleep with excessive daytime sleepiness accompanied by cognitive and attention deficits affects the individual's quality of life. In addition, OSA is an independent risk factor for hypertension, diabetes, stroke and cardiac rhythm disturbances. The effects on the bed partner from marital discord related to lost sleep from snoring in the OSA patient, along with the higher risk of occupational injury and lost work productivity, is often under-appreciated. OSA impacts both the individual and society and should be classified as a modern public health issue, thus making therapeutic treatment options for OSA patients of high importance.

Nasal continuous positive airway pressure is considered the gold standard of therapy for OSA [2]. The literature suggests that not only does CPAP improve daytime

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sleepiness [3], and snoring, but a reduction in hypertension [4], car accidents [5, 6] and mortality [7] is also seen in patients compliant with therapy. In addition, CPAP has shown itself to be a cost effective treatment option compared to lifestyle measures [8]

There is a wide range of CPAP compliance rates reported in the literature, varying by study design and definitions of compliance, with values ranging from 46 % to 85 % [9, 10]. Patients report various reasons for non compliance: psychological causes such as claustrophobia, discomfort from mask or skin irritation, or just inconvenience, especially in occupations where travel and time on the road are considerable and transporting CPAP would be cumbersome. CPAP is not a cure, and requires daily use and in some patients, even when compliant residual symptoms of daytime sleepiness may continue. These reasons have motivated both patients and researchers to explore alternative therapies to CPAP. The object of this review is to explore the scientific evidence behind some of the newer and unconventional alternatives to CPAP as treatments options for OSA.

Auto-titrating Continuous Positive Airway Pressure

Conventional CPAP may be prescribed for patients at a fixed pressure, usually from 5 cm to 20 cm based on the results from the in-laboratory CPAP titration study. The pressure may need to be adjusted over time due to weight changes, newer medications that relax the soft tissues, and age. Some patients with predominant REM related OSA or positional OSA require higher CPAP pressures during certain parts of the night but the pressure requirement may not need to be kept as high in NREM sleep and in non-supine sleep. The auto-titrating positive airway pressure device (APAP) has the advantage of auto adjusting the pressure from 5 cm to 20 cm while the patient sleeps, thus increasing if needed should the patient enter REM sleep or supine sleep. This may allow a lower pressure to be maintained during other parts of the night potentially providing more comfort and improved compliance compared to conventional fixed pressure CPAP.

Drummond et al. used APAP in a cohort of patients at high risk for OSA who were waiting to have a diagnostic baseline polysomnogram. The 109 subjects were randomized to either usual care or a trial of APAP for one month. In the APAP group, there was a significant reduction in daytime sleepiness and sleep related quality of life, where as there was no difference in sleepiness nor sleep related quality of life in the usual care group. The authors suggested that empiric treatment of suspected patients at high risk for OSA based on the Berlin questionnaire with auto-titrating CPAP is safe and effective [11].

Ip et al. has conducted the most extensive meta-analysis on the use of APAP compared to conventional fixed pressure CPAP, based on 24 randomized clinical trials. This analysis was complicated by the differences in study design, bias, machine algorithms and follow up time. Patients with comorbidities were excluded. The results demonstrated that APAP compared to fixed pressure CPAP demonstrated a mean reduction in Epworth Sleepiness Scale score by 0.5 points (95 % CI, 0.8 to 0.2 point reduction) and improved compliance by 11 minutes (95 % CI, 3 to 19 minutes). Although with APAP the meta-analysis did show the statistically significant reductions in the sleepiness and improved compliance, the clinical significance of this difference was questioned, and the recommendation was that the choice of therapy between APAP and CPAP should depend on patient preference and cost in view of these findings [12].

Due to rising health care costs and the desire to improve access to sleep care by avoiding in-lab testing, alternative diagnostic algorithms are being proposed. A large Veterans Health Administration trial “GoToSleep” is studying the feasibility of using the portable home sleep test for diagnostic confirmation of OSA followed by an APAP trial in patients with cerebrovascular disease and hypertension [13]. The trial is ongoing and has at its ultimate goal to reduce the requirement for in-laboratory sleep studies with the goal of improving access to care.

The American Academy of Sleep Medicine has developed a practice parameter on APAP devices and noted the following precautions: “A diagnosis of OSA must be established by an acceptable method. APAP titration and APAP treatment are not currently recommended for patients with congestive heart failure, significant lung disease (e.g., chronic obstructive pulmonary disease), daytime hypoxemia and respiratory failure from any cause, or prominent nocturnal desaturation other than from OSA (e.g., obesity hypoventilation syndrome). In addition, patients who do not snore (either due to palate surgery or naturally) should not be titrated with an APAP device that relies on vibration or sound in the device's algorithm.” The parameter has also emphasized the need for close follow up of patients being treated with APAP especially if there is poor resolution of symptoms [14, 15].

Pharmacotherapies

Several different pharmacotherapies have been tried to treat OSA; however, most have not been shown to be effective for OSA. Many of the trials have been limited by small sample size, unclear inclusion criteria, lack of randomization and lack of blinding [2].

Serotonin receptors are found in the central nervous system (brainstem) and in the peripheral nervous system

(nodose ganglion) and mediate different effects. While awake, central postsynaptic 5-HT₂ receptors mediate dilation of the upper airway and withdrawal leads to increase likelihood of collapse in NREM sleep. In the peripheral nervous system, serotonin release at 5-HT₃ receptors has been associated with REM related obstructive sleep apnea [16, 17].

Fluoxetine and paroxetine selective serotonin reuptake inhibitors have been showed in very small studies to reduce AHI in NREM sleep in some patients, whereas in others these medications had no effect [2].

Protriptyline has been used in smaller trials as well to treat OSA [2]. It is a tricyclic antidepressant that increases the upper airway tone via an effect on central norepinephrine transmission. Protriptyline and fluoxetine were compared in a head to head trial: the percent of REM time was reduced overall, but the REM AHI was not reduced overall but there was a greatest reduction in AHI in NREM sleep. This combination is not recommended to be used as part of therapy especially in view of the cholinergic side effects of protriptyline [2, 18].

Mirtazapine is an antidepressant that has mixed profile serotonin agonist/antagonist [19]. Carely et al. reported on two trials with mirtazapine to treat OSA. This medication is a mixed 5-HT₂/5-HT₃ antagonist that promotes serotonin release in the brain and was theorized due to its multiple receptors to effectively reduce AHI during both NREM and REM sleep in patients with OSA. Mirtazapine did not improve the AHI in either trial. Mirtazapine caused weight gain and lethargy in their trials. Therefore, mirtazapine is not recommended for the treatment of OSA [19, 20].

Evidence is lacking that oxygen therapy alone can be used to treat obstructive sleep apnea unless the patient has both OSA and sleep related hypoventilation [21]. The use of oxygen as the main therapy for OSA can often lead to a blunting of the hypoxic drive and thus causing a worsening of sleep related hypercapnia and prolongation of apneas, and thus oxygen is not recommended. A small trial in 8 OSA patients treated with oxygen 4 L/minute for 1 month, air at 4 L/minute for 1 month and CPAP for 1 month demonstrated that although oxygen alone improved oxygenation and hypopneas there was no effect on apneas or hypersomnolence [21–23].

Armodafinil is a longer acting R-enantiomer of modafinil, both Federal Drug Administration approved wakefulness promoting drugs to treat OSA patients who are compliant on CPAP therapy but continue to have excessive daytime sleepiness [24]. The mechanism of action remains unknown to date, but is felt to be related to the orexin wake-promoting neurotransmitter system. On objective testing of OSA subjects on armodafinil compared to placebo, armodafinil showed on the multiple sleep latency test an increased sleep latency and an improvement in secondary

episodic memory. Some of the known side effects include rash, hypertension, headache, nausea, and psychiatric symptoms such as anxiety, depression, mania and psychosis. Compliance on CPAP does become an issue as well, as patients started on wake promoting medications are also noted to become less compliant on CPAP therapy [2, 24–26].

Given the role of obesity and the influence on OSA, the phase 2 study of Qsymia®, a centrally acting anti-obesity drug which includes a combination of low dose phentermine and topiramate is of interest. Both drugs have been used separately for several years in the obese population. In the combination trial using both phentermine and topiramate, the medications have been studied in a small number of OSA patients. The company reports the combination of medications work at reducing weight by altering the appetite and satiety center in the hypothalamus. The trial included a single-center randomized double-blind placebo-controlled trial of 45 obese OSA patients who had on diagnostic testing an AHI greater than or equal to 15 events and were non-compliant or were CPAP naïve. The primary end point of the trial was met, as there was a reduction in AHI over 28 weeks in the treated (AHI 46 per hour to 14 per hour) versus placebo group (44 events per hour to 27 events per hour) with a p value of 0.001 for treated versus placebo group. This was postulated to be related to the 10.2 % loss in body weight in the treated group compared to the 4.3 % loss of body weight in the placebo group (p <0.001 treated versus placebo). Further data is needed to look at the efficacy and safety of this drug in the OSA population at large and how this drug in the long run will allow weight loss to be maintained over time [27–29].

Positional Therapy

Positional OSA occurs when the AHI in non supine sleep is decreased by 50 % compared to supine sleep [30]. This may be due to the effects of gravity pulling both on the mass of tissue in the anterior cervical area and the tongue, leading to occlusion of the airway. The upright posture with the head of the bed at 60 degrees has a similar impact as noted in a small trial [31]. McEvoy et al. reported on 13 male patients with OSA who spent the first part of the night supine and the second part sitting at 60 degrees. Despite no change in sleep efficiency between the 2 postures, the mean supine AHI decreased from 48.9 ± 5.4 events per hour to a mean sitting AHI of 19.6 ± 6.9 events per hour, with a p value less than 0.0005 representing a statistically significant difference.

Permut et al. looked the use of a commercially available positional sleeper (Zzoma Positional Sleeper®) and compared it to CPAP in a group of patients with positional

OSA [32]. The positional sleeper is essentially a wedge of synthetic foam worn on the back with front tying belts to be placed on the waist, preventing patients from turning supine. There was no statistically significant difference in the positional device group versus the CPAP group in terms of normalizing the AHI to less than 5 events per hour (92 % versus 97 %, $P=0.16$). Sleep efficiency, arousals and architecture remained similar between groups.

Although effective at treating positional therapy, the long term compliance with this technique is problematic, as was demonstrated in the a large Australian study looking at the Tennis Ball Technique where patients with positional therapy had demonstrated relief with a tennis ball sewn into a shirt. It appears at follow up at 30 months only 10 % of patients continued to show long term compliance due to discomfort [33].

Bariatric Surgery

Obesity is an important risk factor for OSA, although a wide spectrum of individuals receives this diagnosis, including those with normal BMIs. The prevalence of OSA among obese individuals is high and directly correlates with increasing BMI [34]. Pharyngeal fat deposits lead to a decrease in pharyngeal patency, and this is the postulated mechanism causing OSA in obese patients. Weight reduction leads to a decrease in the pharyngeal critical pressure or P_{crit} [35] but may not be sufficient alone to eliminate obstructive sleep apnea in the majority of patients [34]. Current evidence suggests that patients with OSA may have greater P_{crit} reflecting an increase in upper airway collapsibility.

Obesity, however, is not necessarily important in the pathogenesis of OSA. Weight loss after bariatric surgery may not be sufficient to resolve OSA [34]. Several studies, mostly case series, have looked into the effects of bariatric surgery as a treatment modality for OSA, and these studies have shown that OSA may persist after weight loss. A cohort of 24 patients undergoing bariatric surgery looked into the occurrence of OSA a year after surgical intervention. Mean BMI prior to surgery was 51 ± 10 and the mean AHI was 48 ± 34 (range 5–135). Bariatric surgery lowered the AHI (mean AHI 25 ± 18) but only one patient had resolution of OSA and the majority still had moderate-severe disease. The majority of patients felt better with weight loss with notable resolution and chose not to continue CPAP therapy. The subjective resolution of snoring after bariatric surgery does not equate to resolution of OSA [34].

A systematic review and meta-analysis on the effects of bariatric surgery was published in 2004. Twenty percent of the patients (2399/12 266) had sleep disordered breathing and OSA resolved in 86 % and resolved or improved in

84 % of the patients after bariatric surgery. The paper did not expound on the definition of resolution or improvement of OSA, and it did not mention whether sleep studies were done post-operatively [36].

One of the more effective treatments for long-term reduction of body weight is bariatric surgery. Studies have shown that snoring symptoms may resolve but OSA will still be present in majority of patients after bariatric surgery [34]. The overall improvement in health risk, however, after bariatric surgery is unquestionable due to the reduction in cholesterol level, hypertension, diabetes control and cardiac disease [37].

Didgeridoo Playing and Oropharyngeal Exercises

Playing the didgeridoo, a wind instrument of the indigenous Australians, was associated with a reduction in sleep-disordered breathing events and daytime sleepiness as reported in a randomized controlled trial of 25 patients with OSA and AHI ranging from 15–30 events per hour [38]. Using the didgeridoo entails circular breathing technique accomplished by the use of cheeks as a reservoir of air while breathing through the nose. Playing this wind instrument will train airway muscles, causing less collapse of oropharyngeal muscles during sleep, and consequently providing beneficial effect on OSA [38]. The study found that four months of training of the upper airways by didgeridoo playing reduced daytime sleepiness in people with snoring and OSA. AHI reduced from a mean of 22 to 12 in the didgeridoo group ($n=14$), compared to a mean of 20 to 15 in the control group ($n=11$) ($p=0.05$). Reduction in AHI may indicate less collapsibility of the upper airways with muscle training. Limitations of the study include small sample size, $BMI < 30$, and the selection of the control group (comprised of subjects waiting to undergo didgeridoo lessons).

Similarly, a prospective study done in Brazil looked into whether doing oropharyngeal exercises can improve pharyngeal patency and treat OSA. Thirty-one middle-aged patients with moderate OSA (mean AHI 22 ± 5) were randomized to 3 months of daily sham therapy ($n=15$) or a set of oropharyngeal exercises ($n=16$) consisting of isometric and isotonic tongue, soft palate, and lateral pharyngeal wall exercises. The treatment group had a significant decrease in OSA severity from a baseline AHI of 22 ± 5 decreasing to 14 ± 9 ($p < 0.01$). Limitations of the study include small sample size, and the difficulty in reproducing the oropharyngeal exercises used in the study [39].

As an offshoot of the didgeridoo study, an anonymous internet-based cross-sectional survey of professional orchestra players was undertaken to determine whether playing a wind instrument was associated with a lower risk of OSA, using the Berlin questionnaire. A total of 1,111 orchestra

members responded, including 369 (33 %) wind instrument players. The survey found that there was a correlation between playing a wind instrument and having a high risk of OSA; however, this association was not seen after correcting for age, gender, and BMI. The risk of OSA did not decrease with playing a wind instrument after adjusted analysis [40].

The improvement of OSA severity in didgeridoo players and in the patients doing oropharyngeal exercises might be anecdotal given the negative findings in the cross-sectional survey of orchestra players. There is no strong physiologic evidence linking pharyngeal training with improvement of OSA [40]. More studies are needed to support this mode of treatment for OSA.

Nasal Dilators

Nasal valve dilators increase air flow by opening the nasal passages and reduce nasal resistance. Through this mechanism, it is postulated that nasal dilators prevent hypopharyngeal collapse and consequently snoring and OSA. There are two types of nasal dilators. An internal dilator (e.g. Nozovent®) is inserted into the nostrils, leading to dilatation of the nasal passages by means of its elasticity. An external dilator (e.g. Breathe Right® nasal strip) consists of a strip placed outside the nose, and works by pulling the nostrils open.

There are limited studies looking into the effects of nasal dilators as treatment of OSA. The majority of these studies demonstrate that nasal valve dilators do not effectively treat OSA. A prospective interventional study published in 2000 investigated the effects of Nozovent® on sleep disordered breathing in 26 patients with moderate to severe OSA. Objective measurements of snoring and apneas during sleep were almost unaffected by the use of Nozovent® nasal dilator for a month. The majority of bed partners reported only a mild reduction in snoring [41].

Based on limited studies, the use of nasal dilators is not recommended as a treatment option for OSA.

Nasal Expiratory Resistor Devices

A nasal expiratory resistor device (Provent® sleep apnea therapy) is a one-way valve which produces a high expiratory resistance during expiration, serving as a splint to keep the upper airways patent. Previous studies have shown that application of expiratory positive airway pressure (EPAP) through a valve reduced the frequency and duration of apneas in patients with OSA. The mechanisms of action for EPAP was elucidated by Patel et al. in their prospective study looking at the effects of Provent® sleep apnea therapy in 20 patients with moderate to severe OSA (mean AHI 34+/- 30). Postulated

mechanisms include: (1) upper airway dilatation from the pressure generated during expiration, (2) mild elevation of CO₂ from hypoventilation leading to greater respiratory drive, (3) lung hyperinflation from increased end-expiratory pressure increasing tracheal traction and decreasing upper airway collapsibility. In the study by Patel et al., RDI was significantly reduced with the nasal resistor device compared to the diagnostic sleep study (27 +/- 29 vs 49 +/- 28) [42].

The largest and most recent trial looking into nasal resistor therapy was a prospective multi-center, sham-controlled, parallel-group, randomized, double blind trial done on 250 patients in 19 sites. The nasal EPAP device significantly reduced the AHI and improved subjective daytime sleepiness compared to the sham treatment in patients with mild to severe OSA with excellent adherence over a 3 month period. At 3 month follow up, the median change in the AHI was 43 % for the nasal EPAP group compared to 12 % for the sham group. Drop-out rates were high for both groups (16 % nasal EPAP, 14 % sham) by the third month, but rates were not statistically different. Patients with severe arterial oxygen desaturation, upper airway surgery, and nasal occlusion were excluded [43].

Nasal expiratory resistor device is an alternative treatment option for patients with mild-severe OSA intolerant to CPAP. This device is relatively new in the market, so clinical experience is limited.

Electrical Stimulation of the Upper Airway

Upper airway occlusion observed in OSA results from a decrease in the neuromuscular pharyngeal tone occurring in an anatomically narrowed airway. Previous reports have discussed the role of upper airway dilator muscles controlling upper airway patency during sleep. The main pharyngeal dilator is the genioglossus, which is innervated by the hypoglossal nerve. Several trials have looked into hypoglossal nerve stimulation as therapy for OSA. A recently published multicenter trial of eight patients with moderate to severe OSA studied the effects of hypoglossal nerve stimulation by an implantable stimulating device (Inspire™ I system) over 6 months. These patients had a statistically significant decrease in AHI from a baseline range of 48–52 to 17–23 after one month of hypoglossal stimulation during sleep ($p < 0.001$). Sleep stage analysis demonstrated a trend towards a reduction in stage 1 sleep and an increase in slow wave sleep. There was a significant decrease in the pharyngeal critical pressure or Pcrit with the stimulation of the hypoglossal nerve [44]. Current evidence suggests that patients with OSA may have greater Pcrit, which reflects the increase in upper airway collapsibility.

Another prospective trial looked further into genioglossus stimulation, and compared the effects on the Pcrit of

stimulating the anterior versus the posterior areas of the genioglossus. Fourteen middle-aged obese males (mean BMI 32) with severe OSA (mean AHI 54) were studied. Stimulation of the posterior part of the genioglossus stabilized the pharynx more (i.e. had a significant reduction in the Pcrit) than the anterior part, and the best results were obtained in patients with large tongue and narrow pharynx [45].

More studies are needed to elucidate further the role of hypoglossal nerve stimulation in treating OSA. Optimization of the implantable stimulating device features and determination of patient selection criteria for hypoglossal nerve stimulation are necessary [44].

Conclusion

Although there are many reported alternatives to CPAP therapy, only few have strong scientific support in the form of well designed multi-center randomized controlled clinical trials. In view of the large prevalence of obstructive sleep apnea and the projection for the increasing number of cases projected over time, further research is warranted to explore additional unconventional alternatives to PAP therapy. Alternatives therapies need to target the patient's request for comfort, transportability, and ease of use while still providing proof of both clinical and cost effectiveness.

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