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Improvements in current treatments and emerging therapies for adult obstructive sleep apnea

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Abstract

Obstructive sleep apnea (OSA) is common and is associated with a number of adverse outcomes, including an increased risk for cardiovascular disease. Typical treatment approaches, including positive airway pressure, oral appliances, various upper airway surgeries, and/or weight loss, can improve symptoms and reduce the severity of disease in select patient groups. However, these approaches have several potential limitations, including suboptimal adherence, lack of suitability for all patient groups, and/or absence of adequate outcomes data. Emerging potential therapeutic options, including nasal expiratory positive airway pressure (PAP), oral negative pressure, upper airway muscle stimulation, and bariatric surgery, as well as improvements in existing treatments and the utilization of improving technologies are moving the field forward and should offer effective therapies to a wider group of patients with OSA.

Introduction

OSA is characterized by intermittent partial or complete occlusions of the upper airway (termed hypopneas and apneas, respectively) due to a combination of excess tissue and inappropriate upper airway muscle relaxation. OSA is a common disorder, affecting 5% to 10% of middle-aged adults and up to 20% of adults over 65 years of age [1]. Untreated OSA may cause, or has been associated with, several adverse outcomes, including daytime sleepiness, increased risk for motor vehicle accidents, increased risk for cardiovascular disease, depression, and poorer quality of life [2-5]. The prevalence of adverse outcomes is typically dose-dependent in the context of an increased number of apneas and hypopneas per hour of sleep, as reflected in the apnea/hypopnea index (AHI), and the severity of oxygen desaturation.

Typical treatments for patients with OSA include PAP therapy, oral appliances (those that advance the mandible and those that prevent relapse of the tongue), various surgeries that modify the upper airway, and/or weight loss (dietary, pharmacologically, and surgically induced). This article will initially review PAP therapy, its limitations in clinical practice, and the potential use of improved technology and telemedicine to improve PAP adherence. The discussion will also cover several emerging technologies and improvements in existing therapies that may enhance and improve treatment for patients with OSA in the near future.

Positive airway pressure therapy

Continuous positive airway pressure (CPAP) therapy is the most common treatment used across the spectrum of OSA severity and is the recommended initial treatment for most patients with moderate to severe OSA [6]. With adequate patient adherence, CPAP consistently improves symptoms of daytime sleepiness attributable to OSA in those with moderate to severe disease and may improve blood pressure and other cardiovascular outcomes [2,4,5,7].

Although many individuals have excellent adherence to CPAP therapy across all patients for whom it is prescribed, adherence is suboptimal, and overall adherence with CPAP therapy averages approximately 50% (range of 30% to 70%) [1]. Interventions demonstrated to improve

initial CPAP adherence include education (increased office visits, pamphlets, group meetings, and phone calls), heated humidification, and cognitive behavioral therapy added to education [6,8]. These interventions have been demonstrated to improve adherence to one degree or another in many, but not all, patients in several short-term studies. Advanced technology PAP devices, such as autoPAP (APAP), bilevel therapies, and expiratory relief devices, have not been shown to consistently improve adherence in patients who are CPAP-naïve or in patients who have been intolerant to standard CPAP therapy [9-12]. Although various approaches to treatment and advancements in technology have evolved to improve adherence, compliance with CPAP therapy has remained relatively unchanged over time [13].

One area of expanding technology related to PAP therapy that has received little research attention involves the use of PAP device-generated adherence data to improve patient outcomes. Most current PAP devices measure the adequacy of control of OSA by using manufacturer-specific propriety algorithms to define OSA events and in some cases to respond and resolve abnormal breathing events. This information is available from multiple sources and can be accessed from the PAP device, in-office software extracted from a data card, and/or cloud-based data sources.

Although the data generated by these devices can reliably track PAP nightly usage, these propriety algorithms have several potential limitations, including the absence of standard definitions for respiratory events and leak tracking, which make it difficult to interpret and compare information between manufacturers and standardize approaches to therapy [14]. There are currently only a few studies validating the various PAP data outputs compared with the standard in-lab polysomnography definitions of respiratory events and these results are exclusive to the specific devices and software studied in those trials [15-17]. Despite these potential limitations, several randomized controlled studies have used the PAP-generated adherence data from several devices and manufacturers to track adherence and the efficacy of therapy in unattended settings, and the majority of these studies demonstrated outcomes similar to those of CPAP therapy determined by a formal in-lab titration study [12,18-20].

Given the expanding role of telehealth and shifts toward shared risk- and population-based models of health care, research should focus on the use of PAP-generated adherence data to improve PAP compliance and other OSA-related outcomes. Currently, the role of online PAP adherence monitoring and other telemedicine technologies to improve outcomes remains unclear [21]. A study by Fox and colleagues [22] did demonstrate a trend toward improved adherence in a group of patients monitored via online compliance tracking compared with usual care, but the outcomes in both the intervention and control groups demonstrated suboptimal compliance compared with historic controls. More research will be required to make this approach to therapy a reality. In addition to research, interventions that will be required to enhance PAP treatment using PAP output technology should include the following:

a) Standardization of respiratory event definitions between manufacturers as well as validation of the device outputs compared with the gold standard, polysomnography.

b) Improved access to PAP adherence data for front-line providers, including determining ways to more easily integrate PAP adherence data into the various electronic medical record software programs.

c) Education of non-sleep specialists on interpretation of the available adherence information. Given the limited time that most primary care providers have to spend with patients, thought from a manufacturer's standpoint should be focused on developing easy-to-interpret reports that use algorithms incorporating nightly adherence data, AHI, and leak data into an output that would indicate adequate or inadequate therapy and potential interventions to improve problems. These data would need to be easily accessible to the providers and patients and could potentially be accessed at the point of care via a smart phone-based application or web-based data warehouse.

d) Expansion of telehealth utilization by health-care systems and payers to monitor compliance on-line and develop chronic disease management programs for early intervention of patients with OSA, similar to current programs for asthma and diabetes mellitus management [23].

Improvements in non-continuous positive airway pressure therapies and emerging treatments for obstructive sleep apnea

As reviewed previously, despite advancements in PAP technology, many patients with OSA are unable or unwilling to tolerate this therapy; thus, alternative therapies may need to be considered. Typical alternative treatments include oral appliances, weight loss, and/or upper airway surgeries. Emerging therapies that may offer novel treatment approaches include nasal expiratory positive airway pressure (nEPAP), oral negative pressure devices, bariatric surgery, and upper airway muscle stimulation.

Oral appliances

Oral appliances are dental devices that improve OSA by maintaining the patency of the posterior pharynx. These devices are typically fit by a qualified dentist and maintain pharyngeal patency by advancing the mandible forward (mandibular repositioning appliances) or maintaining the tongue in an anterior position (tongue-retaining devices) or both. Oral appliances are typically indicated for patients with mild to moderate OSA and for patients with severe OSA who are intolerant or choose not to use CPAP therapy [24]. More recent data demonstrate that a trial of this approach to therapy may also be reasonable for patients with more severe disease (AHI >30 events per hour) [25]. In general, CPAP is more effective at resolving OSA events and improving oxygen saturations, although oral appliances tend to improve symptoms of daytime sleepiness to a similar degree as CPAP [26]. The impact of oral appliance therapy on hypertension, other cardiovascular outcomes, and mortality is not clear [27].

Despite the effectiveness of oral appliance therapy in mitigating OSA in certain patient groups, this approach to therapy has been limited by several factors, including cost, difficulty in predicting success or tolerability prior to initiating therapy, and the inability to monitor compliance with treatment. Recent advances in technology may improve some of these limitations, specifically the ability to predict therapeutic success prior to initiating treatment and compliance monitoring.

Typical predictors of success with oral appliances include less severe disease, younger age, lower body mass index, smaller neck circumference, and those with more positional (supine-dependent) OSA. Despite these predictors, the ability to accurately predict success with OA therapy prior to initiating treatment is approximately 50% of unselected patients in clinical practice [28]. Early studies have suggested that success with oral appliance therapy could be better predicted by using various technologies, although these interventions have yet to be widely adapted to clinical practice [29]. Recently, data have demonstrated that oral appliance therapy success can be accurately predicted in the majority of patients during a single night polysomnography by using a remotely controlled mandibular positioner (MATRx; Zephyr Sleep Technologies, Calgary, Canada) [30]. Remmers and colleagues [30] prospectively studied 67 predominantly obese, male patients with mild to severe OSA (mean AHI of 25.2 ± 14.8) and demonstrated that a successful oral appliance titration could be achieved in 87% of the patients. In this group of patients, the average effective target protrusion position was 68% of the maximum mandibular protrusion range. In general, the remotely controlled titration was well tolerated by patients with minimal sleep disruption related to appliance adjustments during the study. Although this approach may prove useful in determining an effective oral appliance prescription and avoid the current trial-and-error process to determine a therapeutic oral appliance prescription, further studies will be required to determine the effectiveness of this approach in clinical practice.

Another major limitation to expanding the use of oral appliance therapy has been the inability to objectively monitor compliance with treatment. Recent studies have demonstrated potential advancements in this area as well [31,32]. Dieltjens and colleagues [31] studied 51 men with mild to moderate OSA who were treated with oral appliance therapy over the course of 1 year. Compliance with therapy was objectively monitored by using a thermal sensing device embedded in the oral appliance. Regular use, defined as at least 4 hours per night on 70% of the nights, was observed in 83% of the patients over the course of the year. There was high agreement between subjective and objective compliance over the course of the study, and subjective compliance was typically overestimated by 30 minutes per night.

Although these results appear promising, larger studies will need to be performed to confirm these findings, and reimbursement strategies will need to be developed to cover the cost of these technologies in clinical practice [33]. Additional advancements that could help expand the use of oral appliance therapy may include the ability of oral appliances to autotitrate therapy on a night-to-night basis and the ability of these devices to transfer objectively monitored compliance data to cloud-based technologies so providers could monitor treatment efficacy in real time.

Nasal expiratory positive airway pressure

Nasal expiratory resistive devices are another potential treatment that has been introduced as an alternative to PAP therapy for OSA. These disposable adhesive devices are placed over the nostrils and increase resistance to flow during exhalation while not adversely affecting flow during inhalation, thus increasing upper airway patency by creating expiratory positive airway pressure (EPAP).

Initial small studies in patients with mild to moderate OSA demonstrated a significant reduction in the AHI and oxygen desaturation index, and the greatest benefit was observed in those with more mild disease [34,35]. Berry and colleagues [36] performed a larger randomized controlled trial (n = 250) in a group of treatment-naïve patients with predominantly mild OSA. Patients were randomly assigned to either treatment with nEPAP (Provent; Theravent Inc., San Jose, CA, USA) or sham

devices over a 3-month study period. At the conclusion of the study, there was a significant reduction in subjective daytime sleepiness and the AHI compared with the sham group, although the average reduction in the AHI in the treatment group was only 42.7% compared with baseline. Approximately 51% of the group treated with nEPAP were considered successfully treated (defined as at least 50% reduction in AHI or AHI of less than 10) as compared with 22.4% of the those patients treated with sham therapy (P = 0.001). A long-term (12-month) follow-up study was completed on those patients who had been treated successfully and had been compliant with therapy (subjective compliance of at least 4 hours per night, at least 5 nights per week) during the larger randomized controlled trial [37]. These data demonstrated persistent benefit with a reduction in AHI and daytime sleepiness in those who remained on therapy, although these outcomes were observed in a very select group of patients. This treatment is not applicable to patients with severe OSA, as a recent randomized study in patients with severe OSA demonstrated persistent severe disease with the Provent nEPAP devices compared with CPAP therapy [38].

The proposed mechanisms of action for the nEPAP devices include (a) increased functional residual capacity (FRC), producing tracheal traction and reducing upper airway collapsibility, or (b) passive dilatation of the upper airway by the expiratory pressure, carrying over into inspiration, or (c) both. Braga and colleagues [39] performed a magnetic resonance imaging study on 10 individuals to assess the effect of nEPAP on lung volume and upper airway cross-sectional area. Their results demonstrate that, although there was a trend toward increased upper airway cross-sectional area, nEPAP impacts sleep-disordered breathing by significantly increasing FRC and lung hyperinflation, causing increased tracheal traction and decreased upper airway collapsibility. In addition, they observed a reduction in ventilation and increase in the arterial partial pressure of carbon dioxide ($PaCO_2$). Thus, there are several mechanisms by which nEPAP devices positively impact obstructive sleep apnea.

In summary, the nEPAP devices can improve OSA severity and daytime symptoms, although the best results are typically observed in patients with more mild disease. This form of treatment may be considered an alternative to CPAP or oral appliance therapy in patients with less severe disease and should not be used in patients with severe OSA, significant oxygen desaturation, nasal occlusion, comorbid obstructive lung disease, or underlying hypercapnea. Although in the larger trial by Berry and colleagues [36] compliance with therapy was 88.2%, these devices, in practice, have experienced limited use for several reasons. In my experience, proper nightly application of the device is difficult for many patients even with proper education, which in many cases may result in suboptimal adherence. Other potential barriers to use in clinical practice include limited insurance coverage, requirements for special nasal pressure cannulas in the sleep laboratory to objectively document efficacy, and the inability to objectively document efficacy on an ongoing basis. These potential technical limitations could be overcome for patients in whom nEPAP therapy was felt to be an appropriate treatment.

Oral negative pressure therapy

An oral negative pressure device has recently been introduced (Winx®, Apnicure Inc., Redwood City, CA, USA). As an alternative to applying positive pressure to maintain the patency of the upper airway, this device generates negative oral pressure by drawing the tongue and soft palate in more anterior positions via a mouthpiece connected to a suction mechanism. An initial single-center feasibility study evaluating 76 subjects with mild, moderate, or severe OSA treated with negative oral pressure therapy demonstrated improvements in OSA severity and oxygen desaturation, and 38% of the patients achieved an AHI of not more than 10 events per hour [40]. Based on these initial data, a recent short-term prospective multicenter randomized controlled trial evaluated 63 middle-aged, predominantly obese subjects across the spectrum of OSA severity [41]. The device was well tolerated, and an average nightly use over the 30-day study period was 6.0 ± 1.4 hours per night. After 30 days of treatment, those randomly assigned to oral negative pressure therapy demonstrated a significant reduction in their OSA severity (mean AHI of 27.5 events per hour on control night to 14.8 events per hour after treatment), although only 20 of the 63 subjects demonstrated a clinically significant response to therapy defined by an AHI of not more than 10 and not more than a 50% reduction in the AHI compared with control values. Those in the treatment group also demonstrated improved sleep quality, reduced sleep fragmentation, and improved subjective daytime sleepiness.

In summary, the role of this technology in the treatment of OSA is evolving. Oral pressure therapy may be a reasonable alternative treatment to PAP therapy for adults with mild to moderate disease. The treatment is contraindicated in patients with advanced periodontal disease or loose teeth, nasal obstruction, or asthma or other advanced lung diseases, patients with a history of pneumothorax, and those under the age of 18. Because successful treatment with oral pressure therapy is not predictable prior to treatment, objective testing on therapy is necessary to document efficacy. Additional research is necessary to better define the appropriate populations for treatment and to determine appropriate algorithms for adequate follow-up.

Surgery

Various surgical approaches have been used as treatments for OSA. Aside from tracheostomy and maxillomandibular advancement for patients with severe OSA who have failed a trial of CPAP therapy, the application of other upper airway surgeries for the routine treatment of OSA is limited because of a paucity of rigorous data evaluating most of these procedures [42]. In general, any upper airway surgical procedure should be considered only after a trial of CPAP or oral appliance therapy (or both) has been unsuccessful. Despite the limitations regarding procedures that surgically modify the upper airway, recent data support two surgical approaches that may offer viable alternatives to CPAP and oral appliance therapy.

Upper airway muscle stimulation therapy

The physiology of OSA is characterized by recurrent collapse of the upper airway that is due, in part, to a reduction in pharyngeal dilator muscle tone. Early studies in animals and humans demonstrated that electrical stimulation of the hypoglossal nerve could result in improved upper airway patency via stimulation of the genioglossus muscle, resulting in protrusion of the tongue [43]. Since these early feasibility studies, several companies have developed hypoglossal nerve stimulation (HGNS) devices. The Inspire HGNS device (Inspire Medical Systems, Maple Grove, MN, USA) has the most supporting data and is currently undergoing review by the US Food and Drug Administration. This device has a neurostimulator that is implanted under the skin in the upper chest (similar to a cardiac pacemaker), a stimulation electrode placed on the hypoglossal nerve, and a sensing lead that is placed between the internal and external intercostal muscles to detect ventilatory effort. The device is activated prior to bedtime and deactivated in the morning after awakening.

A recently published randomized controlled trial followed by a prospective cohort study evaluated 126 overweight, middle-aged, predominantly male patients with moderate to severe OSA who were previously intolerant to CPAP therapy [44]. The data demonstrated that the Inspire HGNS device significantly reduced the AHI by 68% (AHI 29.3 to 9 events per hour) and improved daytime sleepiness and quality of life during the initial randomized phase, and significant improvements were maintained at the 12-month follow-up. The device was generally well tolerated, and serious adverse events (one cardiac death felt not to be related to the device and one device requiring removal) were observed in less than 2% of the participants. Less severe device-related events included temporary tongue weakness after surgery (18%), tongue soreness (21%), and surgical site pain (40%). Permanent tongue weakness was not observed in any of the participants during the study. Only two study participants required repositioning and fixation of the device.

Not all HGNS devices have proven to impart clinical benefits. The Apnex HGNS device (Apnex Medical, St. Paul, MN, USA) demonstrated improvements in OSA severity and daytime symptoms in an initial smaller group of patients with predominantly severe OSA [45], but the follow-up pivotal phase 3 clinical trial was terminated after the device failed to achieve its primary outcome (ClinicalTrials.gov number NCT01446601). Finally, another HGNS device (Aura6000 System; ImThera, San Diego, CA, USA) is currently approved for use in Europe and is being evaluated in clinical trials prior to approval in the US.

These data demonstrate that HGNS therapy may offer an effective therapy for carefully selected overweight patients with moderate to severe OSA who are intolerant to CPAP therapy [46]. Further study is required to identify the best device, better define suitable candidates, and determine the cost-effectiveness for this type of therapy.

Bariatric surgery

OSA is associated with obesity, and an elevated body mass index is an independent risk factor for OSA in patients under the age of 60. Several studies have demonstrated that dietary weight loss is associated with significant improvements in OSA as measured by reductions in the AHI [47-49]. Unfortunately, as would be expected, most studies show that patients typically achieve only modest reductions in weight with diet and behavioral counseling alone and that clinically significant residual OSA persists in most patients.

Surgical weight loss via various bariatric procedures has been associated with even greater reductions in weight as well as improvements in OSA. In general, there are dose-dependent improvements in OSA for a given amount of weight loss, although most patients, regardless of the method of surgical weight loss, have residual OSA despite significant reductions in weight [50-53]. Thus, based on the current data, bariatric surgery may lead to long-term improvements in OSA severity, although many patients may be left with significant residual OSA requiring other treatments.

In summary, although significant weight loss can lead to improvements in OSA, the data demonstrate that the majority of patients do not achieve or maintain enough weight loss to resolve their OSA and thus will require ongoing treatment. Given this information, weight loss

via diet or bariatric procedures should not be considered a primary therapy for OSA across the spectrum of disease severity and should be recommended as a secondary therapy or intervention that supplements a primary treatment such as CPAP or oral appliances. Finally, even for those patients who are able to lose a significant amount of weight and maintain that weight loss over time, objective sleep study testing should be performed to assess for residual disease prior to discontinuing CPAP therapy.

Summary

OSA is common and untreated disease is associated with several adverse consequences. Unfortunately, although currently available treatments can improve these outcomes, compliance with CPAP therapy is suboptimal for many patients and other currently available standard therapies have several limitations. Emerging therapies, improvements in existing treatments, and the utilization of improving technologies are moving the field forward and should offer effective interventions to a wider group of patients with OSA. The current data support the following:

a) PAP therapy is currently the mainstay of treatment across the spectrum of disease and should be considered the first-line therapy for most patients with OSA. Since adherence with PAP therapy remains suboptimal for many patients, future research needs to focus on processes that increase adherence through improved patient and provider education as well as the development and better utilization of advancing technologies.

b) Oral appliance therapy is indicated primarily for patients with mild to moderate OSA, and recent data demonstrate efficacy in some patients with more severe disease. The role of oral appliance therapy will expand as newer technologies improve the ability to predict success with treatment prior to initiating therapy as well as monitor compliance with ongoing treatment.

c) Weight loss, through either diet or bariatric procedures, should be recommended for all OSA patients who are overweight or obese. Most patients will have clinically significant residual OSA despite substantial weight loss. Thus, follow-up testing is recommended after significant weight loss has been achieved to objectively determine the need for ongoing OSA therapy.

d) Various upper airway surgeries can be considered for patients who cannot tolerate CPAP or oral appliance therapy, although the current data supporting various procedures are limited and more information is required to determine which procedures may benefit certain patient groups.

e) Hypoglossal nerve stimulation therapy may offer an alternative treatment for overweight patients with moderate to severe OSA. It currently remains investigational in the US, and further research is required to better identify appropriate patient groups, the best device, potential long-term side effects, and cost-effectiveness compared with standard treatments.

f) nEPAP devices can improve OSA severity and daytime symptoms, although the best results are typically observed in patients with more mild disease. This form of treatment may be considered an alternative to CPAP or oral appliance therapy in patients with less severe uncomplicated disease and should not be used in patients with severe OSA, significant oxygen desaturation, nasal occlusion, or comorbid lung disease or in patients with baseline hypercapnea.

g) Oral negative pressure therapy is a reasonable alternative treatment to PAP therapy for those with uncomplicated mild to moderate disease. Objective testing on therapy is necessary to document efficacy, as successful treatment with this therapy is difficult to predict prior to initiating treatment. Additional research is required to better define the appropriate populations for treatment and to determine appropriate algorithms for adequate follow-up.

h) Finally, future research should also expand the use of genomics, various biomarkers, and bioinformatics to better identify patient groups who may be at lower risk for adverse outcomes or will not benefit from specific OSA therapies (or both).

Abbreviations

AHI, apnea/hypopnea index; CPAP, continuous positive airway pressure; FRC, functional residual capacity; HGNS, hypoglossal nerve stimulation; nEPAP, nasal expiratory positive airway pressure; OSA, obstructive sleep apnea; PAP, positive airway pressure.

Disclosures

The author declares that he has no disclosures.

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