New Therapies for Obstructive Sleep Apnea
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Abstract and Introduction

Abstract

A strong demand for new obstructive sleep apnea (OSA) therapies exists and several are emerging. Hypoglossal nerve stimulation is designed to activate upper airway muscles. The initial study from Inspire (Maple Grove, MN) suggests that the device will work well in a very selective group of OSA patients. However, it is likely to be quite expensive. The Winx device (ApniCure, Redwood City, CA) works by establishing a vacuum in the oral cavity, which pulls the uvula and soft palate forward and stabilizes the tongue position. The current device works in approximately 40% of patients and the early data suggest adherence may be quite good. The Provent device (Theravent, San Jose, CA) has been available for several years and is disposable. It is to be attached to the nares nightly and establishes substantial expiratory resistance. Multiple studies suggest that Provent can successfully treat OSA in about 35 to 50% of the patients. However, acceptance and adherence may be a problem. OSA phenotyping is not a therapy, but a way to determine exactly what causes airway collapse in each patient, which can vary substantially. This may allow for individualization of apnea therapy. New methods to prevent supine sleep and surgically implantable devices to treat OSA are also evolving.

Introduction

Nasal continuous positive airway pressure (CPAP) remains the standard of care for patients with obstructive sleep apnea (OSA). However, poor adherence to CPAP limits its clinical effectiveness leading to a need for additional therapeutic options. Such options have historically included mandibular advancing devices, a variety of surgical procedures designed to enlarge the pharyngeal airway, and several behavioral approaches (weight loss, avoiding alcohol and sedatives near bedtime, maximizing nasal patency, and avoiding sleep in the supine position). Despite there being several treatments for OSA, in many cases, none of these options ultimately lead to successful elimination of the disordered breathing due to either inadequate efficacy or poor patient tolerance. Thus, considerable effort continues to find new OSA therapies that are both effective and acceptable.

In this article, new therapies for OSA will be discussed. This will include treatments that are currently on the market and available to patients and several which are near entry into the market. In all cases the method of treatment will be described, as well as its effectiveness, side effects, adherence (if data are available), and estimated cost. The order of presentation in no way reflects any of these outcomes.
Genioglossal Stimulation

All evidence suggests that decrements in the activity of pharyngeal dilator muscles during sleep contribute to pharyngeal collapse in patients with OSA. In addition, the genioglossus has been well established as an important muscle in the maintenance of pharyngeal patency. Thus, stimulation of this muscle (or the hypoglossal nerve that innervates it) is a logical approach to apnea therapy. Early studies in both animals and humans, using techniques that generally allowed for relatively short periods of stimulation, suggest that this methodology may effectively reduce or eliminate disordered breathing in some patients. Thus, the world awaited a clinically available method to accomplish such stimulation chronically.

Apnex

Two credible companies have begun serious efforts to develop such a technology. Apnex (Roseville, MN) had the first publication reporting on a feasibility study using such a device. Their stimulator was planted subcutaneously and attached to one hypoglossal nerve (unilateral stimulation). The firing of the device was synchronized to inspiration using a thoracic bioimpedance signal from two subcutaneous wires. The first study by Eastwood et al reported on data from 19 patients followed for 6 months postimplant. Important inclusion criteria included a body mass index (BMI) < 40 kg/m² and an AHI between 20 and 100 events per hour with > 80% of events being hypopneas. These patients at baseline had a mean BMI of 32.7 kg/m² (range, 26.7–38.7) and an AHI of 43.1 ± 17.5 events per hour. At 6 months, the mean AHI had fallen to 19.5 ± 16.7 events per hour, a 55% reduction with a much larger effect being observed in patients with a BMI < 35 kg/m² than in those with a BMI > 35 kg/m² (AHI of 14.0 ± 7.7 vs. 31.5 ± 24.6 events per hour at 6 months, respectively). Overall, 67% of the patients met the combined success criteria of a 50% or greater decrement in AHI and a 6-month AHI of < 20 events per hour. The patients used the device on 89 ± 15% of the nights for 5.8 ± 1.6 hours per night. There were also statistically significant improvements in subjective measures of sleepiness (Epworth sleepiness scale [ESS]), quality of life (sleep apnea quality of life index and functional outcomes of sleep questionnaire [FOSQ]), sleep quality (Pittsburgh Sleep Quality Index), and depression (Beck Depression Index). Somewhat surprisingly, the larger (n = 31) and longer (12 month) trial, a continuation of the above study, using the same technology yielded less impressive results. The AHI only fell from 45.4 ± 17.5 to 25.3 ± 20.6 events per hour. In addition, there were three serious device-related adverse events (an infection requiring removal of the device and two lead dislodgements requiring replacement).

Apnex subsequently conducted a pivotal trial with their hypoglossal nerve stimulator for Food and Drug Administration (FDA) approval the results of which will never be published. This trial apparently failed to demonstrate a between group (treated vs. control) difference in AHI reduction (ClinicalTrials.gov number NCT01446601) due to, in part, a substantial improvement in sleep-disordered breathing in the control
group. Thus, the company Apnex is no longer in business and this particular technology will never reach the public.

Inspire

The second company reporting development efforts in this area is Inspire (Maple Grove, MN). They have evolved a similar device producing unilateral hypoglossal nerve stimulation from an implanted subcutaneous pulse generator. However, the Inspire device is synchronized with inspiration using a pressure sensor placed between the two intercostal muscles in the fourth intercostal space (Fig. 1). The first article addressing this technology by Van de Heyning et al\textsuperscript{[5]} was a feasibility study used primarily to determine patient characteristic that would predict the success of this approach. In an initial study of 20 patients they identified three predictors of response to genioglossal stimulation: a BMI < 32 kg/m\textsuperscript{2}, an AHI < 50 events per hour, and the absence of complete, concentric palatal collapse on drug-induced sleep endoscopy. Using these inclusion/exclusion criteria, these investigators subsequently identified eight new OSA patients and implanted the Inspire device in these patients. The mean AHI fell from 38.9 ± 9.8 to 10.0 ± 11.0 events per hour at 6 months postimplant in these eight patients.
Neurostimulation was accomplished with a stimulator placed in the right infraclavicular area. This stimulator was connected unilaterally to the right hypoglossal nerve to activate the genioglossus muscle. To phase this stimulation to respiration (inspiration), a sensor was placed in the fourth intercostal space between the internal and external intercostal muscles. (Reprinted with permission from Van de Heyning PH, Badr MS, Baskin JZ, et al. Implanted upper airway stimulation device for obstructive sleep apnea. Laryngoscope 2012;122:1626–1633).

The pivotal trial was conducted in 126 participants with the characteristics described above (AHI of 20–50 events per hour, BMI < 32 kg/m², and no complete concentric collapse). These patients (mean BMI of 28.4 kg/m² and median AHI of 29.3 events per hour) were implanted with the pulse generator with the primary outcome being the AHI at 12 months postimplant. Of note, polysomnography (PSG)
was also conducted at 1, 2, and 6 months postimplantation with stimulation parameters adjusted as needed. The median AHI at 12 months was 9.0 events per hour with 66% of the patients achieving a 50% reduction in AHI plus a final AHI < 20 events per hour. The median ESS fell from 11.0 to 6.0 and the FOSQ rose from 14.6 to 18.2. Finally, in 23 successfully treated patients, the stimulator was turned off at 12 months for 7 days and a PSG repeated. In this group, the AHI rose from 8.0 to 23.0. Two patients over the course of the study had to have the stimulator repositioned due to discomfort for a serious adverse event rate of < 2%.

Conclusion

Genioglossal stimulation using the Inspire device is a potentially exciting new way to treat OSA. Although not FDA approved at this writing, such approval seems likely. These data suggest that this device will effectively treat approximately two out of the three carefully selected patients based on BMI, AHI, and drug-induced sleep endoscopy. Although effective in these selected patients, the cost of this therapeutic approach is likely to be substantial. No cost figures have been provided, but one would estimate that the combined cost of the pulse generator, the sleep endoscopy, the surgical implantation, and the multiple PSGs to titrate the stimulator would have to approach $30,000 to 35,000 per patient. Whether this will turn out to be an acceptable figure to payers and patients is unclear at this time.

Winx

The Winx device (ApniCure, Redwood City, CA), introduced into a somewhat limited United States market in early 2013, has a unique way of treating OSA. The device consists of a console that generates negative pressure (−50 cm H₂O), tubing that connects the console to a mouthpiece, and a mouthpiece that is placed inside the oral cavity (Fig. 2). When negative pressure is applied in the mouth, the uvula and soft palate are pulled forward against the base of the tongue yielding a sealed space in the oral cavity (Fig. 2). If additional space is available, the tongue may move forward as well, although this has not been consistently observed. By pulling the uvula and soft palate out of the pharyngeal airway, patency is improved or restored during sleep in many patients.
Oral pressure therapy (Winx, ApniCure, Redwood City, CA). The left panel shows the nightstand console unit containing the vacuum pump and the saliva reservoir. The right panel shows the mouthpiece. "A" indicated the vacuum pressure and sensor tubing, "B" shows the lip seal, and "C" shows the vacuum aspiration port. (Reprinted with permission from Colrain IM, Black J, Siegel LC, et al. A multicenter evaluation of oral pressure therapy for the treatment of obstructive sleep apnea. Sleep Med 2013;14:830–837).

The primary study addressing the efficacy of this device\(^7\) included 63 patients (BMI of 32.3 ± 4.5 kg/m\(^2\)) with all severities of OSA. This group included untreated patients, patients on CPAP, and patients who had stopped using CPAP. To be included in this study, patients must have had a BMI < 40 kg/m\(^2\), at least one molar present in each oral quadrant, the ability to breathe easily through the nose, proper mouthpiece fit (maintenance of vacuum during a nocturnal study), a total sleep time of at least 4 hours, and self-reported tolerance of the device during the sleep study. The participants were studied (full night PSG) at baseline off therapy, on night 1 with the Winx device in place, and after 28 days of using the Winx device in the home. The median AHIs at baseline, night 1, and night 28 were 27.5, 13.4, and 14.8 events per hour, respectively. Adherence over the 28 days at home was 6.0 ± 1.4 hours for the entire group. Of note, using a therapeutic success definition of at least a 50% decrement in AHI and a treated AHI of < 10 events per hour, 20 of the 63 patients
(31.7%) were successfully treated. If a final AHI of < 20 events per hour was used, 26 of the 63 patients (41.3%) were treated successfully. Successful results with this device were not related to initial AHI or BMI. For the group not treated with CPAP at the beginning of the trial, the ESS fell from 12.1 to 8.6. Finally, there were no device-related serious adverse events in this study. However, oral discomfort, dental discomfort, and dry mouth were common events which resolved quickly in some patients and persisted for longer periods in others.

Conclusion

Based on the limited data outlined above, one would have to conclude that the Winx device can provide successful therapy for approximately 30 to 40% of OSA patients depending on one’s definition of success. All the exclusions used in this study need to be kept in mind as well, particularly the BMI < 40 kg/m$^2$. The data above would suggest that there is some oral discomfort on initiation of this device that generally clears over the first few days. Adherence with Winx was quite good in this study despite the discomfort, although this was only assessed after 28 days of use. Finally, based on communication with Apnicure, the maker of the Winx device, the price of the console is $600 to 1,000 depending on the payer and the mouthpiece (which needs to be replaced every 3–6 months) costs about $100 to 120.

Provent

Provent, which has been available clinically for approximately 4 to 5 years, is a unique method for treating OSA that is disposable after a single use (Fig. 3). A device is placed over each nostril on a nightly basis with each device having a fixed expiratory resistance (50 cm H$_2$O/L/s). The inspiratory resistance of the device is quite low. Thus, it is quite easy to breathe in nasally through the devices and quite hard to breathe out. Although, several mechanisms have been proposed, but how Provents prevents upper airway obstruction during sleep in patients with OSA is not completely clear.\textsuperscript{[8]}
Nasal expiratory positive airway pressure device (Provent, Theravent, San Jose, CA). Single-use valves are inserted over each nostril and sealed with an adhesive. The valves have low resistance on inspiration and high resistance on expiration. (Reprinted with permission from Berry RB, Kryger MH, Massie CA. A novel nasal expiratory positive airway pressure (EPAP) device for the treatment of obstructive sleep apnea: a randomized controlled trial. Sleep 2011;34:479–485).

- First, it is generally accepted that a substantial expiratory resistance to airflow will lead to an increase in baseline lung volume (increased functional residual capacity). Increased lung volume, primarily through longitudinal traction on
the trachea, stiffens the upper airway leading to a less collapsible pharynx.
[9] Thus, OSA patients breathing nasally through the Provent device have a higher lung volume at night and a more patent airway.

- Second, breathing nasally through an expiratory resistor will lead to substantial positive pressure in the upper airway during expiration. This positive pressure will undoubtedly dilate the pharynx during this phase of the respiratory cycle. However, negative pressure is still required during inspiration. It has been proposed that a more dilated airway on expiration will be less collapsible during inspiration when negative pressure develops.

- Finally, at least one study[8] suggests that the Provent device leads to substantial hypoventilation during both wakefulness and sleep with a marked increase in arterial Paco$_2$ (39.7 ± 5.3 to 47.1 ± 6.0 mm Hg). The elevated Paco$_2$ leads to increased respiratory drive to both pump and upper airway dilator muscles that could improve respiratory pattern and upper airway patency.

Whatever the mechanism, there is a substantial literature which suggests that Provent does work in some patients with OSA. The first study[10] by Rosenthal et al (50 OSA patients with an AHI > 5 events per hour with 28 completing the trial) involved a baseline PSG off therapy, three PSGs on different expiratory resistors (50, 80, 110 cm H$_2$O/L/s), and a final PSG on the optimal resistor (lowest AHI) following 30 days use of this device in the home. The mean BMI for the group was 30.1 ± 5.9 kg/m$^2$. The findings were multiple. First, all three resistors yielded a similar AHI response. Second, the AHI fell from 24.5 ± 23.6 (baseline) to 13.5 ± 18.7 (average result from three resistors) to 15.5 ± 18.9 (following 30 days use in the home). Third, the participants reported using the device on 94.4% of the nights in the home. Fourth, there were few, if any device-related adverse events. Finally, if success with this therapy is a 50% or greater decrement in AHI and a final AHI < 20 events per hour, then 35.3% of the patients were successfully treated. A similar larger ($n = 127$, AHI > 10) and longer (3 month) study of Provent using an 80 cm H$_2$O/L/s resistor by Berry et al[11] reported fairly similar results. For the intent to treat group ($n = 92$), the median AHI initially (week 1) fell from 16.7 to 7.1 and was 8.1 events per hour at 3 months. A second group of patients using a sham device had no improvement in sleep-disordered breathing at either time point. In the treatment group the ESS fell from 9.9 ± 4.7 to 7.2 ± 4.2 and the patients reported using the device on 88.2% of the nights over the 3-month study. In addition, the authors report that 51% of patients had either a 50% decrement in AHI or a final AHI < 10 events per hour. Finally, there were several comfort complaints while using the device including symptoms such as dry mouth, breathing discomfort, nasal congestion, nasal discomfort, insomnia, headache, and so on. This study was subsequently extended to 12 months of Provent use the results of which are a second publication by Kryger et al.[12] For the patients to be included in the 12 month study, they had to be successfully treated with the Provent device (50% or greater
reduction in AHI or AHI < 10 events per hour) and should be using it regularly during months 1 and 2 of the 3-month trial (> 4 hours per night on > 5 nights per week). Of the 51 eligible patients, 34 were still using the Provent device at 12 months. In this group, the median AHI at 12 months was 4.7 events per hour (15.7 at baseline off therapy) and the ESS fell from 11.1 ± 4.2 to 6.0 ± 3.2. Finally, the median percentage of nights the device was used all night was 89.3%.

Recently, an independent assessment of Provent was reported by Rossi et al. This group used a CPAP withdrawal methodology whereby CPAP therapy is stopped in a group of moderate-to-severe OSA patients for a 2-week period with various metrics including AHI, oxygen desaturation index (ODI), and ESS being assessed at the end of the 2 weeks. In this study 67 OSA patients were randomized to continued CPAP, or use Provent, or placebo Provent for the 2-week study. Following 14 days of therapy, there was no difference in AHI, ODI, or ESS between the Provent and the placebo arms with continued CPAP being superior to both for AHI and ODI. The authors concluded that “Provent cannot be recommended as an alternative short-term therapy for patients with moderate-to-severe OSA already on CPAP.”

Conclusion

Several conclusions can be reasonably drawn from the data above. First, the Provent device can successfully treat approximately 35 to 50% of the OSA patients with the vast majority of patients studied having mild-to-moderate OSA. Patient's response to this device can be determined by conducting a short sleep study with the device in place. However, more severe patients may respond less well, as suggested by Rossi et al. Second, adherence with the device is difficult to gauge as the only metric available is self-reported. That being said, of the 119 patients who were randomized to the treatment arm of the 3-month trial, only 34 were still using it successfully at the end of 1 year. Thus, a reasonable percentage of patients are unable to tolerate this device in a sustained fashion. Finally, the current cost of the Provent device, as per purchase online, is about $2 per night or $60 per month.

Physiological Phenotyping

Phenotyping is not a new therapy for OSA, but is a method to understand better why an individual patient has sleep apnea, such that future therapies could be individualized for each patient. As this approach may drive new therapies, it seemed appropriate to discuss this methodology in this review.

Phenotyping is based on the concept that there are four primary traits, which dictate whether a patient will develop OSA or not. These are as follows:

- **Upper Airway Anatomy/Collapsibility**: This is the most important trait as there must be at least some anatomic deficiency (small size) of the pharyngeal airway for a patient to develop OSA. If the upper airway is reasonably patent when the pharyngeal dilator muscles are passive (minimal activity), it is very unlikely that the individual will develop OSA. That being said, there is
substantial variability in upper airway anatomy in patients with OSA with considerable overlap with normal nonapneic subjects. Thus, other variables must be important in apnea pathogenesis.

- **The Upper Airway Response**: Pharyngeal patency is largely a balance between upper airway anatomy, as described above, and the activity of several pharyngeal dilator muscles. These muscles can obviously compensate for anatomic deficiencies during wakefulness and in many individuals they can do so during sleep as well. However, this is quite variable. In some individuals, these muscles are quite responsive to standard stimuli (airway negative pressure and rising \( \text{Paco}_2 \)) during sleep while in others, little response can be elicited. In addition, increasing muscle activity in some patients promptly opens the airway while in others the muscles lead to little or no airway dilatation. Thus to be effective, the muscles must, during sleep, both respond to increasing negative airway pressure and rising \( \text{Paco}_2 \) and mechanically function to restore or maintain airway patency. Again, this is quite variable between individuals.

- **Arousal Threshold to a Respiratory Stimulus**: When airway patency is reduced during sleep (apnea, hypopnea, or high resistance) respiratory drive increases and once a threshold level of drive is achieved, arousal from sleep will occur. This threshold is quite variable between individuals and is importantly based on the two traits described above. If an individual has a small pharyngeal airway, he/she needs pharyngeal muscle activation during sleep to open the airway. However, these muscles generally respond slowly during sleep as \( \text{Pco}_2 \) rises and airway pressure becomes progressively more negative in response to the obstruction. Thus, the individual must stay asleep long enough for these muscles to activate and restore airway patency thus establishing stable sleep. If arousal occurs too quickly, the individual will cycle between sleeping hypopnea and waking hyperpnea. As a result, a low arousal threshold to increasing respiratory drive predisposes an individual to sleep apnea.

- **Loop Gain (Ventilatory Control Instability)**: Loop gain is an engineering term used to describe the gain of any physiologic system controlled by feedback loops. Respiratory control is such a system primarily designed to control arterial \( \text{Pco}_2 \). Without going into detail, the main determinant of loop gain is the hypercapnic ventilatory response (HCVR) the slope of which is quite variable between individuals. A steep HCVR can lead to a high loop gain and subsequently unstable ventilatory control. In an individual with a high loop gain small disturbances in ventilation (like a hypopnea) yield a large response (hyperpnea) leading to a waxing and waning of ventilation. When this happens, upper airway obstruction can occur at the nadir of the respiratory cycle. Thus, a high loop gain can predispose to OSA in an individual with an anatomically predisposed upper airway.
Although still a research technique, the methods to quantify these traits have been described in several recent articles\textsuperscript{[15,16]} and will not be addressed here. However, suffice it to say, all four traits can be measured during sleep by intermittently dropping CPAP from the holding pressure (optimal CPAP) to lower pressure levels leading to partial or complete airway collapse. This challenges both the pharyngeal airway and the respiratory system with the responses to these pressure drops defining the four traits described above. There are also ongoing efforts to quantify these traits based on the normal metrics measured during standard polysomnography. Once the traits have been measured, they can be put into a graphic model\textsuperscript{[15,16]} demonstrating why the individual has OSA and how much the traits would need to be manipulated to reduce or eliminate disordered breathing. Therapeutic approaches to alter these traits include the following:

- **Upper Airway Anatomy/Collapsibility**: Dental appliances, upper airway surgery, and the Winx device.

- **The Upper Airway Response**: There are currently no methods available to influence pharyngeal dilator muscle activity either awake or asleep. However, efforts to develop drugs to accomplish this are underway\textsuperscript{[22]}

- **Arousal Threshold to a Respiratory Stimulus**: Hypnotics such as eszopiclone\textsuperscript{[23]} and trazodone\textsuperscript{[24]} have been studied.

- **Loop Gain (Ventilatory Control Instability)**: Both oxygen\textsuperscript{[25]} and acetazolamide\textsuperscript{[26]} can lower loop gain.

Thus, single agents or combinations of these approaches could theoretically be used to treat OSA based on physiologic phenotyping.

### Other

#### Sleeping Position Control (Avoiding Supine Sleep)

There is a substantial literature indicating that in many patients OSA is more severe while sleeping in the supine as opposed to the lateral posture. In such patients, avoiding supine sleep can markedly reduce if not eliminate sleep-disordered breathing. Previously the methods used to avoid supine sleep were relatively crude such as the placement of an uncomfortable object (like a tennis ball) into the back of a pajama shirt. This did not promote long-term compliance. Recently, new devices have evolved that can be placed on the chest and will both monitor body position and provide a vibratory stimulus when the patient assumes the supine position.\textsuperscript{[27,28]} Studies suggest that these devices can accurately measure body position and that the vibration stimulus can minimize sleep time in the supine posture.\textsuperscript{[27,28]} Thus, sleep-disordered breathing can be substantially reduced in appropriately selected patients.

#### Surgical Implants (The Advance System)
Although slings (Repose, Medtronic, Minneapolis, MN) to advance the tongue and implants (Pillar, Medtronic, Minneapolis, MN) to stiffen the palate have been around for some time, neither of them has achieved much traction in the treatment of OSA. Recently, an implant that consisted of a tissue anchor in the tongue, an adjustable spool attached to the mandible, and a tether between the two (The Advance System, Aspire) has been tested in OSA therapy. Early studies\(^{29,30}\) in patients with primarily tongue-based collapse suggested a reasonable efficacy of the device (AHI reduction from 22.8 to 11.8 events per hour in one study and 35.5 to 27.3 events per hour in another). However, technical problems such as barb fracture of the tissue anchor and disconnection of the tether line limited the success of the device. The manufacturer, in response, developed an Advance System II with stronger tissue anchor barbs and a subsequent study in 19 OSA patients\(^{31}\) showed a 38.9% success rate (> 50% reduction in AHI and final AHI at 6 months of < 20 events per hour). Again technical problems, this time slippage of the spool, prevented better outcomes. The company that developed this device (Aspire Medical Inc.) subsequently went out of business. The review of this product was included here because this therapeutic approach (an implantable, adjustable device to advance the tongue) is likely to be a successful therapy for OSA once the technical problems have been solved.

References


