New Frontiers in the Treatment of Sleep Apnea: Unilateral Hypoglossal Nerve Stimulation

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What is It?

Unilateral stimulation of the hypoglossal nerve (the nerve that controls the movement of the tongue) is a new treatment for people with moderate to severe obstructive sleep apnea (OSA) who are unable to use CPAP. CPAP, oral appliances, and some surgeries work "from the outside in" to prevent the tissues from relaxing and blocking the upper airway (nasal and oral passages) [1]. This nerve stimulation therapy works "from the inside out" to move the muscles and keep the airway open. The device includes a nerve stimulator that activates the tongue muscle, causing it to open the upper airway. The device is implanted under local anesthesia after which it is turned on and tuned to adjust its settings to most effectively eliminate apneas (Figure 1). Patients then turn it on before going to sleep and turn it off when getting up. The device only treats apnea when it is turned on.

This therapy can prevent the collapse of the upper airway which occurs in obstructive sleep apnea patients. However, it cannot restore breathing which occurs as result of central sleep apnea.

Development

Unilateral hypoglossal nerve stimulation therapy was approved by the FDA in April 2014 as an implanted system that works with the structure of the patient's mouth, throat, and tongue. The approval was the result of more than 20 years of research done with animals and humans on the role of muscle contraction in obstructive sleep apnea. About 10 years ago, Inspire Medical Systems and others formed and began sponsorship of clinical trials to first examine such factors as: what is the harm, and does it work? This investigation continued to smaller and then larger clinical trials [2]. The early trials helped to identify patient characteristics that best predicted a positive treatment response for the stimulator, known as Inspire. A larger study, consisting of 126 patients, was designed and conducted in collaboration with the FDA and published in the *New England Journal of Medicine* in 2014 [3]. Follow-up on this study group was conducted at regular intervals for five years after the original implant.

Does it Work?

There are three aspects of therapy to consider: the patient, the placement of the device, and the performance of the device.

This therapy is only recommended for certain patients. The FDA trial included patients who were unable to tolerate or use PAP therapy, had an apnea hypopnea index (AHI) greater than 20 and less than 60, had a body mass index of less than 32 kg/m2, and had no obvious anatomic blockages during wakefulness; in a separate study, patients did not have a concentric camera shutter-like closure of the back of the throat. Patients had to have good heart and lung health, less than 25 percent of apneas as central, and no chronic conditions of the nerves or muscles.

Implantation, or the placement of the device, was generally uneventful with post-operative soreness, swelling, and skin infection cited as the majority of the side effects. Less than two percent of the cases that were performed yielded serious results and there were no deaths related to the use of the device.

When evaluated after one year, it was found that significant improvements were made in many aspects of sleep apnea—including the AHI level, measures of sleepiness, and quality of life. The FDA trial reported that the AHI was lowered by more than 50 percent, and 80 percent of patients reported that sleepiness and quality of life also improved. Immediately after the 12 month visit, there was a group of 46 patients who responded well to the Inspire therapy and half of that group had their device turned off for a week. Those that had the device turned off, saw their sleep apnea return to a similar degree and all asked for their device to be turned on again. Both groups had identical positive responses 18 months after implantation. Treatment for patients within the Stimulation Therapy for Apnea Reduction (STAR) trial population continued three years post implantation.

Who Benefits from Stimulation Therapy?

Stimulation therapy is considered to be a "rescue therapy" because it is invasive and a permanent implant (like a hip replacement). Before patients consider stimulation therapy, they need to try alternative treatments, such as PAP or an oral appliance.

Since the device works by stimulating the tongue to move, the device may not work as well in patients who are obese since obesity may make the airway stiffer and smaller. The original trial used a BMI of less than 32, but the FDA permits consideration of patients with a BMI up to 35 (the level used in Europe).

Before stimulation therapy can be recommended for a patient, they must receive an ENT examination and undergo a drug-induced sedation endoscopy. This procedure will help determine how and where the upper airway might close during sleep. Specifically, the physician might look for a concentric collapse at the back of throat. If present, the chance for success appears to be lower.

Assessment for this Therapy

To determine candidacy for this study, a sleep study conducted within six to 12 months and an unsuccessful attempt at other sleep apnea treatments is required. It is important to remember that PAP therapy and oral therapy have made great advancements. Also note that the implantable system requires anesthesia and the potential for a lifetime with a device inside the patient's body.

The Costs

Costs for this new therapy varies depending on the hospital. Insurance companies determine the implantation on an individual basis. Medicare regulates coverage at a regional level. Each hospital determines its pathways and this may vary across centers.

The assessments, the office airway examination, and the endoscopy are procedures that are generally covered by insurance; however, plans vary by co-pay, deductible, and health benefit accounts.

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After the Implant

Following implantation, there will be a follow-up visit with the ENT and a one-month visit to the sleep medicine physician to activate the device. Reassessment of the device's settings may occur one to two times before a sleep study is performed to verify and/or adjusting the settings. It is estimated that 80 percent of patients will need only one study after the device is implanted. Patients have a routine follow-up every three to four months for a year and then every six to 12 months.

Other Stimulator Devices

In addition to Inspire, other companies are now going through the process of development and clinical trials toward an FDA application. There are likely to be more options in the future.

References:

1. Jordan, A.S., D.G. McSharry, and A. Malhotra, Adult obstructive sleep apnoea. Lancet, 2014. 383(9918): p. 736-47.
2. Kezirian, E.J., et al., Electrical stimulation of the hypoglossal nerve in the treatment of obstructive sleep apnea. Sleep Med Rev, 2010. 14(5): p. 299-305.

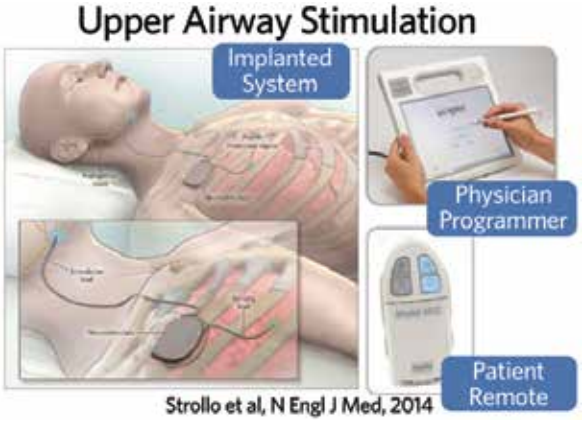

Figure 1

3. Strollo, P.J., Jr., et al., Upper-airway stimulation for obstructive sleep apnea. N Engl J Med, 2014. 370(2): p. 139-49.

Weight Loss in the Management of Sleep Apnea *(continued from page 5)*

In addition to diet, physical activity is a key component to an effective weight-loss plan. Although exercise is not as effective as diet in producing weight loss, regular aerobic exercise helps prevent weight regain. In addition, exercise has cardiovascular benefits the beyond effects on weight. Similarly, OSA severity improves with exercise independent of any weight loss effects. The most effective behavioral weight-loss programs combine diet and exercise with behavior change counseling. Randomized trials have demonstrated that the optimal plan should include in-person counseling sessions with a trained interventionalist meeting individually or as a group. The frequency of meetings should be weekly at first. Weight loss will be maximized if meetings continue (even though less frequently) beyond six months.

Pharmacologic Therapy

Medications are increasingly being utilized to facilitate weight loss and recent data suggest they may help with OSA as well. Randomized trials have found both phentermine-topiramate (Qsymia) and liraglutide (Saxenda) improve but do not cure OSA. Among moderate to severe OSA patients, phentermine-topiramate and liraglutide produced AHI reductions of 15 and six events/hr respectively beyond that obtained from diet and exercise alone. Clinicians can also facilitate weight loss by reviewing medications and replacing commonly used sleep medications such as quetiapine, doxepin, mirtazapine, and gabapentin which promote weight gain with alternatives such as topiramate, zolpidem, or pramipexole.

Surgical Therapy

Bariatric surgery is growing in popularity as procedural complication rates have diminished and it has become clear that long term weight loss outcomes are substantially larger than with behavioral or medical therapy. In addition, longitudinal studies demonstrate bariatric surgery reduces the incidence of diabetes, heart disease, cancer, and all-cause mortality. It is clear that obese OSA patients want to learn more about bariatric surgery. A recent study found that 35 percent of OSA patients presenting to sleep clinics would like to meet with a bariatric surgeon to learn more about surgical options. The most common bariatric operations currently are the gastric band, gastric sleeve, and gastric bypass procedures (see Figure). The gastric band is the least invasive and typically results in loss of 40 percent of excess weight at two years, while the gastric bypass is the most extensive procedure, typically resulting in loss of 60 to 70 percent of excess weight but also associated with more side effects. The gastric sleeve is the newest of the three procedures and provides an intermediate option with about 50 percent excess weight loss. Bariatric surgery can produce significant reductions in OSA severity, although some residual disease commonly persists. In one meta-analysis, the mean AHI fell from 55 to 16 events/hr with surgery. Two randomized trials have compared gastric banding to an aggressive dietary weight-loss program. Both studies found no statistically significant improvements; however, they were limited by small sample sizes. Further research is needed to better understand the potential role of the gastric sleeve and gastric bypass in OSA management.

Conclusions

Chronic disease management involves not just acute care but also treatment of underlying risk factors and prevention of common comorbidities. Just as we provide evidence-based treatments for smoking cessation to our patients with chronic obstructive pulmonary disease, we need to provide proven weight loss therapies as part of comprehensive sleep apnea care.