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Review Article

# Hypoglossal nerve stimulation for obstructive sleep apnea: A review of the literature

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Christina M. Wray [a], Erica R. Thaler [b],*

[a] Perelman School of Medicine, The University of Pennsylvania, Philadelphia, USA
[b] Department of Otorhinolaryngology — Head and Neck Surgery, The Hospital of Pennsylvania, Philadelphia, USA

**Abstract** *Objective:* To review the indications and clinical evidence supporting hypoglossal nerve stimulation (HNS) therapy for the treatment of moderate-to-severe obstructive sleep apnea (OSA).

*Methods:* Peer reviewed literature on hypoglossal nerve stimulation therapy for obstructive sleep apnea from 2001 to 2016.

*Results:* The only currently FDA-approved HNS device for the treatment of moderate-to-severe OSA is produced by Inspire Medical Systems, which recently published its 36-month outcomes data from its Stimulation Therapy for Apnea Reduction (STAR) trial. HNS therapy is currently indicated for moderate-to-severe OSA patients who are CPAP-intolerant, have a body mass index $<32$, apnea-hypopnea index $<50$, and without a concentric pattern of upper airway collapse on sleep endoscopy.

*Conclusions:* Data from the STAR trial suggests that a subset of OSA patients can achieve a significant therapeutic response from hypoglossal nerve stimulation. However, these results may be limited in their generalizability to the broader OSA population.

* Corresponding author. 3400 Spruce Street, 5 Ravdin/Silverstein, Philadelphia, 19104, PA, USA.
  E-mail address: erica.thaler@uphs.upenn.edu (E.R. Thaler).

## Introduction

Obstructive sleep apnea (OSA) is a common chronic condition worldwide, characterized by upper airway collapse during sleep, resulting in obstructive apneas or hypopneas and causing frequent arousals. Moderate-to-severe OSA is estimated to affect approximately 15% of men and 5% of women in the United States, when defined as apnea hypopnea index (AHI) $\geq$ 15 events per hour, or AHI $\geq$ 5 events per hour plus at least one reported symptom of disturbed sleep.[1] Associated symptoms of disturbed sleep include snoring, daytime sleepiness, and neurocognitive impairment. Untreated OSA is associated with long-term negative health outcomes, including an increased risk of cardiovascular disease, all-cause mortality and reduced quality of life.[2,3]

Several therapeutic options are available for the treatment of moderate-to-severe OSA, including continuous positive airway pressure (CPAP), upper airway surgery, and upper airway stimulation. CPAP has been shown to reduce symptoms of disturbed sleep, improve quality of life and lower blood pressure among patients with moderate-to-severe OSA.[4] However, many patients are unable to tolerate CPAP therapy, and reported CPAP adherence rates range from 39% to 60%.[3] Surgical options for the treatment of OSA include tonsillectomy and adenoidectomy, uvulopalatopharyngoplasty (UPPP), transoral robotic surgery, radiofrequency ablation or coblation for resection of the tongue base, and maxillomandibular advancement, among others. UPPP, the most common surgical treatment for adult OSA, has been reported to reduce AHI by approximately 33%, with residual AHI averaging 29.8 at 12 months after surgery.[5] It is primarily indicated for patients with anatomic basis for obstruction.

In 2001, Schwartz et al[6] reported the first successful use of a hypoglossal nerve stimulation (HNS) to activate the genioglossus muscle and reduce OSA severity in a small cohort of patients. Subsequently, Apnex Medical developed the first commercially available implantable HNS device for OSA. Apnex published its first feasibility study in 2011, reporting a significant decrease in OSA symptoms following HNS implantation.[7] The company subsequently went out of business in 2013 following disappointing results from its pivotal randomized control trial.

Inspire Medical Systems currently manufactures the only FDA-approved HNS device for OSA. The Inspire device is an implantable, pacemaker-like pulse-generator with a sensing lead, implanted between the external and internal intercostal muscles to detect ventilator effort, and a stimulation lead, which is implanted submentally and stimulates the branches of the hypoglossal nerve responsible for protrusion, predominantly those to the genioglossus muscle, the primary tongue protrusor muscle and dilator of the upper airway. In 2016, Inspire published the 36-month outcomes data for its pivotal study, the STAR trial, the most comprehensive study on HNS outcomes to date.[8]

## STAR trial

The STAR trial is the largest ongoing clinical trial to assess sleep apnea outcomes from hypoglossal nerve stimulation. The prospective cohort study enrolled 126 CPAP-intolerant OSA patients, and has reported OSA-related outcomes following implantation of the Inspire HNS device.[9] Exclusion criteria included body mass index (BMI) > 32; AHI <20 or >50, or central and/or mixed apnea index >25% of the AHI on polysomnogram (PSG); and complete concentric collapse at the level of the velopharynx observed with drug-induced sleep endoscopy (DISE). The mean age of study participants was 54.5, mean BMI was 28.4, and mean baseline AHI was 32. Eighty-three percent of study participants were male. The primary endpoints were AHI and oxygen-desaturation index (ODI) at 12 months, 18 months and 36 months. Sham treatment was considered to not be feasible because of the invasive nature of the operation so no control group was included in the study. HNS therapy compliance rates remained high, with daily use reported at 86% at 12 months and 81% at 36 months.[8]

Of 126 enrolled patients, 124 patients were included in the 12-month follow up. At 12 months, mean AHI decreased 52%, from 32.0 to 15.3, while the median AHI decreased 68%.[9] Mean ODI decreased 52% from 28.9 to 13.9, while median ODI decreased 70%. Data was reported in aggregate, and no information on individual improvements in primary endpoints, other than responder rate, was reported. STAR trial responders were defined by the Sher criteria as demonstrating a reduction of at least 50% in AHI from baseline, and an AHI <20 after treatment. By ODI criteria, responders demonstrated a decrease in ODI of >25% from baseline. At 12 months, 66% of participants were responders by AHI criteria, and 75% were responders by ODI criteria.

Ninety-eight patients completed 36-month follow up and agreed to a voluntary PSG.[8] The 36-month PSG group did not differ in baseline characteristics from the original cohort; however, this group included a smaller percentage of 12-month non-responders than the 12-month group in aggregate. Of this group, mean AHI decreased 62%, from 30.4 at baseline to 11.5 at 36 months. Seventy-four percent achieved response to treatment as defined by the AHI Sher criteria.

The STAR trial also reported on improvements in secondary quality-of-life endpoints, including the Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ) and snoring as reported by bed partner. At baseline, 33% of patients had an ESS <10, the threshold for normal subjective sleepiness. At 36 months, 77% had a normal ESS. Similarly, at baseline, 15% of patients had a normal FOSQ, while after 36 months, 63% had a normal FOSQ. Soft or no snoring, as reported by a bed partner, increased from 17% at baseline to 81% at 36 months.[8]

At 36-month follow up, reported adverse events were minimal and not life threatening. Two devices were explanted at the patient's request, one due to discomfort and the other due to septic arthritis.[8] The only complication specific to the mechanism of the device was temporary tongue weakness reported in 17% of participants, the majority of which resolved spontaneously.[10]

## Baseline predictors of response to HNS therapy

The pathophysiology of OSA is characterized by multiple patterns of collapse of the upper airway. Most OSA patients have multilevel airway collapse, with four-level collapse at the levels of the velum, oropharynx, tongue base, and

epiglottis being the most common, followed by three-level collapse. Complete or partial anterior—posterior (AP) collapse is the most common pattern of collapse at all levels.[11] In a small sample of 21 patients undergoing pre-implantation DISE, Vanderveken et al[12] reported that the most commonly observed upper airway collapse patterns were AP collapse at the level of the palate and the tongue base. Five out of 21 patients demonstrated a complete concentric collapse (CCC) pattern, all at the level of the palate.

Due to its mechanism of action, HNS was initially hypothesized to be of maximum efficacy in patients with predominantly AP collapse at the level of the tongue base. However, Safiruddin et al[13] reported that upper airway stimulation may also be efficacious in treating OSA patients with some component of retropalatal collapse, and that patients with OSA demonstrated a greater baseline collapse at the retropalatal level during DISE compared to the retrolingual level. Notably, responders to HNS therapy had a statistically significant increase in retropalatal area in response to stimulation during awake endoscopy, compared to non-responders who did not demonstrate a significant increase in retropalatal area in response to stimulation.

While HNS may be effective for OSA patients with multilevel collapse, several studies indicate HNS is relatively ineffective for patients with CCC. An early feasibility study funded by Inspire suggested that patients with CCC were less likely to respond to HNS therapy, informing the DISE exclusion criteria of the STAR trial.[14] Vanderveken et al[12] subsequently reported that HNS treatment was successful in 81% of patients with a non-CCC pattern of collapse on DISE, while treatment success was achieved in 0/5 patients with CCC. This study confirmed that HNS is predominantly effective for patients with patterns of collapse other than CCC.

Because CCC is a predictor of therapy non-response, the Inspire HNS device is the first OSA therapy to require DISE as a prerequisite to surgical implantation. DISE, however, is an invasive and expensive diagnostic procedure. Higher BMI and higher AHI have been identified as the only relevant parameters for predicting CCC on DISE.[15] However, more than half of patients with BMI >32 demonstrate a non-CCC pattern on DISE, indicating that BMI alone cannot be used in place of DISE to predict CCC.

In addition to CCC on DISE, baseline BMI and OSA severity represent alternative predictors of patient response to HNS. Multiple studies report that lower baseline BMI, lower AHI, and lower ODI predict response to HNS. Of all parameters, the combined criteria of AHI <50 and BMI <32 most accurately predicted success and were used as inclusion criteria for the STAR trial.[8,14—16] Of note, a retrospective analysis of STAR trial responders reported that non-responders were more often younger and were less likely to have had prior upper airway surgery for OSA.[8,11]

## After the STAR trial: subsequent HNS outcomes

As HNS therapy has become more widely adopted, additional outcomes data has become available. The first published series of Inspire HNS outcomes outside of a clinical trial setting reported equally significant results.[17] In this population of 20 OSA patients, mean AHI was reduced from 33.3 to 5.1, with 95% achieving an AHI <15. Unlike the STAR trial, this study reported individual results, and the improvement in mean AHI was due to decreases in AHI across the majority of the study cohort. Other isolated case reports suggests that HNS can be safe and effective in patients with a history of multiple upper airway surgical procedures and in patients with an implanted cardiac defibrillator.[18,19] A study of the surgical learning curve associated with HNS procedures suggests that the average HNS implant time is 2.52 h and decreases significantly with surgeon experience.[10]

Cost has become is a major factor limiting widespread adoption of HNS therapy given that reimbursement for the procedure is currently limited. Costs associated with HNS are primarily associated with the cost of the device itself and the cost of the procedure. Nevertheless, Inspire HNS therapy has been shown to be cost effective, with a lifetime incremental cost effectiveness ratio (ICER) of $39,471 per quality-adjusted life year (QALY) for patients meeting the STAR inclusion criteria, less than the currently accepted cost-effectiveness threshold of $40—50K/QALY. Although HNS would therefore be considered cost effective, it remains significantly less cost effective than CPAP, which has an ICER of $15,915/QALY.[3]

## Conclusion

The Inspire HNS device remains the only FDA-approved neurostimulation therapy for OSA. Although HNS therapy has been shown to significantly reduce AHI in moderate-to-severe OSA patients, the therapy has only been proven effective in a small subset of CPAP-nonresponders with a BMI <32, an AHI <50 and a favorable pattern of upper airway collapse on DISE. Despite strict inclusion criteria, one-third of patients do not respond to Inspire HNS therapy by AHI criteria. ImThera Medical has developed an alternative HNS device, the aura6000, to target a broader patient population. Unlike the Inspire device, the ImThera device stimulates the hypoglossal nerve at a more proximal location, co-activating the tongue protrusors and retractors to stiffen the posterior aspect of the tongue and pharyngeal walls to open the airway.[20] The device does not use a sensing lead, and does not require a DISE prior to implantation. ImThera's phase II study was designed with broader inclusion criteria than the STAR trial, enrolling patients with BMI up to 37, with no upper limit on AHI and no restrictions on upper airway pattern of collapse. However, only 34.9% of patients qualified as responders by AHI criteria.[21] The ImThera pivotal study is currently underway.

Limitations to widespread adoption of HNS therapy include the invasiveness of the procedure, the cost of the device, and the requirement for pre-implantation DISE. Moreover, CPAP, the current gold standard for OSA management, is relatively cost-effective and non-invasive. For these reasons, HNS is not currently considered a first-line treatment option. HNS therapy, however, should be considered as a therapeutic option for patients meeting the inclusion criteria when more traditional therapeutic options have been exhausted.

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