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NOTE: This policy has been revised. The revised policy will be effective January 1, 2027.

Medical Policy Manual Surgery, Policy No. 215

Hypoglossal Nerve Stimulation

Effective: April 1, 2026

Next Review: June 2026
Last Review: March 2026

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

When patients with obstructive sleep apnea cannot tolerate positive airway pressure, or when continuous positive airway pressure (CPAP) treatment has failed, hypoglossal nerve stimulation may be considered.

MEDICAL POLICY CRITERIA

Note: Contract language takes precedent over medical policy. Some member contracts have specific benefit limitations for orthognathic surgery.

I. Hypoglossal nerve stimulation may be considered **medically necessary** in adults with obstructive sleep apnea when all of the criteria below (A.-E.) are met:

A. Has an AHI greater than or equal to 15 and less than or equal to 100 with less than 25% central apneas (see Policy Guidelines); and

B. Has PAP failure (residual AHI greater than or equal to 15 or failure to use CPAP greater than or equal to 4 hr per night for greater than or equal to 5 nights per week) or the patient is not an appropriate PAP candidate (see Policy Guidelines); and

C. Has a body mass index less than 40 kg/m^2; and

D. Has non-concentric retropalatal obstruction on drug-induced sleep endoscopy. Note: Concentric collapse decreases the success of hypoglossal nerve stimulation and is an exclusion criterion from the Food and Drug Administration; and

E. One of the following is met:

1. Patient is 22 years of age or older; or
2. Patient is between 18 and 22 years of age and one of the following is met:
   a. Patient has had an adenotonsillectomy; or
   b. Adenotonsillectomy is contraindicated for the patient.

II. Hypoglossal nerve stimulation may be considered **medically necessary** in adolescents or young adults with Down syndrome and obstructive sleep apnea when all of the criteria below (A.-E.) are met:

A. Patient is age 10 to 21 years; and

B. Has an AHI greater than 10 and less than 50 with less than 25% central apneas after prior adenotonsillectomy (see Policy Guidelines); and

C. Have either a tracheostomy or be ineffectively treated with PAP due to noncompliance, discomfort, un-desirable side effects, persistent symptoms despite compliance use, or refusal to use the device; and

D. Has a body mass index less than or equal to 95th percentile for age (see Policy Guidelines); and

E. Has non-concentric retropalatal obstruction on drug-induced sleep endoscopy. Note: Concentric collapse decreases the success of hypoglossal nerve stimulation and is an exclusion criterion from the Food and Drug Administration.

III. Revisions to an existing hypoglossal nerve stimulator may be considered **medically necessary** after the device has been placed.

IV. The replacement of all or part of an existing hypoglossal nerve stimulator and/or generator is considered **medically necessary** when the existing hypoglossal nerve stimulator and/or generator is malfunctioning, cannot be repaired, or is no longer under warranty.

V. Hypoglossal nerve stimulation is considered **not medically necessary** in individuals with obstructive sleep apnea when Criterion I.B. or Criterion II.C. is not met, including PAP refusal.

VI. The replacement of all or part of an existing hypoglossal nerve stimulator and/or generator is considered **not medically necessary** when Criterion IV. is not met.

VII. Hypoglossal nerve stimulation is considered investigational when Criteria I. or II. are not met due to factors other than PAP failure or intolerance (excluding Criteria I.B. and II.C.).

VIII. Hypoglossal nerve stimulation is considered investigational for all other indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

There is divergence on scoring rules for hypopneas between the recommendations of the American Academy of Sleep Medicine (AASM) and the Center for Medicare Services (CMS), the latter being more restrictive.[1] Policy Criteria are based on apnea-hypopnea index (AHI) scored with either the AASM or the CMS scoring rules,[2, 3] either of which are acceptable in this medical policy.

The most recent (2012) AASM rules define apnea in adults as a drop in the peak signal excursion by ≥ 90% of pre-event baseline using an oronasal thermal sensor (diagnostic study), positive airway pressure (PAP) device flow (titration study), or an alternative apnea sensor, for ≥ 10 seconds. Hypopnea in adults is scored when the peak signal excursions drop by ≥ 30% of pre-event baseline using nasal pressure (diagnostic study), PAP device flow (titration study), or an alternative sensor, for ≥ 10 seconds in association with either ≥ 3% arterial oxygen desaturation or an arousal.

The Center for Medicare Services (CMS) scoring rules state that apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30% reduction in thorocoabdominal movement or airflow as compared to baseline, and with at least a 4% oxygen desaturation.

POSITIVE AIRWAY PRESSURE (PAP) – Continuous (CPAP), Bi-Level (BiPAP) or auto adjusting (APAP)

PAP failure: defined as AHI greater than 15 events per hour while using PAP.

Not an appropriate PAP candidate: defined as being unable to use PAP therapy for at least four hours per night for five nights or more per week, with reasonable attempts having been made to address any medical, mechanical, or psychological problems associated with PAP, e.g., adjustment of pressure settings, appropriate medication and humidification, refitting of the mask, trial of alternative pressure delivery systems such as auto-adjusting positive airway pressure or bi-level positive airway pressure.

BMI PERCENTILES FOR DOWN SYNDROME

The United States Centers for Disease Control and Prevention (CDC) recommends specific growth charts for individuals with Down Syndrome ages 2 to 20.[4] The 95th percentile BMIs for males and females aged 2 to 20 with Down Syndrome are included in Appendix A (females) and Appendix B (males).[5]

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Current symptomology
- Conservative medical therapies failed
- CPAP trial results

- Documentation that the patient is not an appropriate PAP candidate with clinical rationale, if applicable (See policy guidelines)
- Sleep Study results, including apnea-hypopnea index (AHI) scored either by the American Academy of Sleep Medicine (AASM) scoring rules or the Center for Medicare Services (CMS) scoring rules.
- Drug-induced sleep endoscopy (DISE) results
- If a replacement is being requested, documentation that the stimulator and/or generator is malfunctioning, cannot be repaired, or is no longer under warranty

CROSS REFERENCES

1. Prefabricated Oral Appliances for Obstructive Sleep Apnea, Allied Health, Policy No. 36
2. Orthognathic Surgery, Surgery, Policy No. 137
3. Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome, Surgery, Policy No. 166
4. Absorbable Nasal Implant for Treatment of Nasal Valve Collapse, Surgery, Policy No. 209
5. Phrenic Nerve Stimulation for Central Sleep Apnea, Surgery, Policy No. 212

BACKGROUND

OBSTRUCTIVE SLEEP APNEA (OSA)

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction due to the collapse and obstruction of the upper airway during sleep. The hallmark symptom of OSA is excessive daytime sleepiness, and the typical clinical sign of OSA is snoring, which can abruptly cease and be followed by gasping associated with a brief arousal from sleep. The snoring resumes when the patient falls back to sleep, and the cycle of snoring/apnea/arousal may be repeated as frequently as every minute throughout the night.

Sleep fragmentation associated with the repeated arousal during sleep can impair daytime activity. For example, adults with OSA-associated daytime somnolence are thought to be at higher risk for accidents involving motorized vehicles (i.e., cars, trucks, heavy equipment). OSA in children may result in neurocognitive impairment and behavioral problems. In addition, OSA affects the cardiovascular and pulmonary systems. For example, apnea leads to periods of hypoxia, alveolar hypoventilation, hypercapnia, and acidosis. This, in turn, can cause systemic hypertension, cardiac arrhythmias, and cor pulmonale. Systemic hypertension is common in patients with OSA. Severe OSA is associated with decreased survival, presumably related to severe hypoxemia, hypertension, or an increase in automobile accidents related to overwhelming sleepiness.

There are racial and ethnic health disparities seen for OSA impacting the prevalence of disease and accessibility of treatment options, particularly affecting children. Black children are four to six times more likely to have OSA than white children.[6] Among young adults younger than 26 years, African American individuals are 88% more likely to have OSA compared to white individuals. Another study found that African American individuals 65 years of age and older were 2.1 times more likely to have severe OSA than white individuals of the same age group. These health disparities may affect accessibility of treatment for OSA and impact health outcomes. One analysis of insurance claims data, including over 500,000 patients with a diagnosis of OSA, found that increased age above the 18- to 29-year range ($p<0.001$) and Black race ($p=0.020$) were independently associated with decreased likelihood for receiving surgery for sleep apnea.[7] Lee (2022) found that Black men had a continuous mortality

increase specifically related to OSA over the study period (1999 to 2019; annual percentage change 2.7%; 95% confidence interval, 1.2 to 4.2) compared to any other racial group.[8]

A polysomnogram performed in a sleep laboratory and, in adults, home sleep apnea testing with a technically adequate device, are considered the gold standard test used to diagnose OSA.[9] Objective measures of OSA are compiled using polysomnography monitors, which document the number of apneic (cessation or near cessation of airflow) and hypopneic (reductions in airflow associated with certain physiologica consequences) events per hour and combine them into the apnea-hypopnea index (AHI). AHI is a measure of severity of OSA. The American Academy of Sleep Medicine (AASM) provided an updated set of scoring rules in 2012.[2] Based on the 2012 AASM rules, apnea in adults is scored when there is a drop in the peak signal excursion by ≥90% of pre-event baseline using an oronasal thermal sensor (diagnostic study), positive airway pressure (PAP) device flow (titration study), or an alternative apnea sensor, for ≥10 seconds. Hypopnea in adults is scored when the peak signal excursions drop by ≥30% of pre-event baseline using nasal pressure (diagnostic study), PAP device flow (titration study), or an alternative sensor, for ≥10 seconds in association with either ≥3% arterial oxygen desaturation or an arousal. The Center for Medicare Services (CMS) also published a set of scoring rules.[3] The CMS scoring rules state that apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30% reduction in thoracoabdominal movement or airflow as compared to baseline, and with at least a 4% oxygen desaturation. The respiratory disturbance index (RDI) may be defined as the number of apneas, hypopneas and respiratory effort-related arousals (RERAs) per hour of sleep.

The final diagnosis of OSA rests on a combination of objective and subjective criteria (e.g. AHI or RDI and excessive daytime sleepiness) that seek to identify those levels of obstruction which are clinically significant. When sleep onset and offset are unknown (e.g., in home sleep studies) the AHI or RDI may be calculated based on the number of apneas, hypopneas, and/or RERAs per hour of recording time.

An increase in mortality is associated with an AHI greater than 15. More difficult to evaluate is the clinical significance of patients with mild sleep apnea. Mortality has not been shown to be increased in these patients, and frequently the most significant manifestations reported by the patient are snoring, excessive daytime sleepiness, witnessed breathing interruptions, awakenings due to gasping or choking, nocturia, morning headaches, memory loss, irritability, or hypertension.[10, 11] The hallmark clinical symptom of OSA is excessive snoring, although it is important to note that snoring can occur in the absence of OSA. Isolated snoring in the absence of medical complications, while troubling to the patient's bed partner, is not considered a medical problem requiring surgical intervention.

Table 1. Definitions of Terms for Obstructive Sleep Apnea

Terms	Definition
Apnea	The frequency of apneas and hypopneas is measured from channels assessing oxygen desaturation, respiratory airflow, and respiratory effort. In adults, apnea is defined as a drop in airflow by ≥90% of pre-event baseline for at least 10 seconds. Due to faster respiratory rates in children, pediatric scoring criteria define an apnea as ≥2 missed breaths, regardless of its duration in seconds.
Hypopnea	Hypopnea in adults is scored when the peak airflow drops by at least 30% of pre-event baseline for at least 10 seconds in association with either at least 3% oxygen desaturation or an arousal or at least 4% oxygen desaturation (depending on the scoring criteria). Hypopneas in children are scored by a

Terms	Definition
	≥50% drop in nasal pressure and either a ≥3% decrease in oxygen saturation or an associated arousal.
Apnea/Hypopnea Index (AHI)	The average number of apneas or hypopneas per hour of sleep
Obstructive sleep apnea (OSA)	Repetitive episodes of upper airway obstruction due to the collapse and obstruction of the upper airway during sleep
Mild OSA	In adults: AHI of 5 to <15 In children: AHI ≥1 to <5
Moderate OSA	In adults: AHI of 15 to <30 In children: AHI ≥5 to <10
Severe OSA	Adults: AHI ≥30 Children: AHI of ≥10
Continuous positive airway pressure (CPAP)	Positive airway pressure may be continuous (CPAP) or auto-adjusting (APAP) or Bi-level (Bi-PAP). CPAP is a more familiar abbreviation and will refer to all types of PAP devices.
CPAP Failure	Usually defined as an AHI greater than 20 events per hour while using CPAP.
CPAP Intolerance	CPAP use for less than 4 h per night for 5 nights or more per week, or refusal to use CPAP. CPAP intolerance may be observed in patients with mild, moderate, or severe OSA

IMPLANTABLE HYPOGLOSSAL NERVE STIMULATORS

Hypoglossal nerve stimulation involves the surgical implantation of a subcutaneous generator in the upper chest and an electrode tunneled from the generator to the hypoglossal nerve. The patient uses a hand-held remote to activate the device just prior to sleep and to turn it off upon waking. Some sensors detect inspiratory efforts, and the hypoglossal nerve is stimulated in a synchronized fashion. This stimulation is intended to maintain muscle tone of the tongue base to prevent airway occlusion.

Stimulation systems such as the Inspire II Upper Airway Stimulation System include respiratory sensing leads that permit intermittent stimulation during inspiration. Stimulation parameters are titrated during an in-laboratory polysomnography and can be adjusted by the patient during home use. The device is turned on only during sleep periods.

REGULATORY STATUS

The Inspire® II Upper Airway Stimulation System (Inspire Medical Systems) received FDA approval in 2014 (P130008) for a subset of patients aged 22 years and older with moderate to severe obstructive sleep apnea. Product code: MNQ. The original approval was for patients with an Apnea Hypopnea Index (AHI) of greater or equal to 20 and less than or equal to 65. In 2017, approval was granted to expand the AHI range to 15 to 65 events per hour (S021). In 2020, Inspire received approval to expand the indications to include adolescent patients age 18 to 21 with moderate to severe OSA (15≤ AHI ≤65) who:

- Do not have complete concentric collapse at the soft palate level
- Are contraindicated for, or not effectively treated by, adenotonsillectomy
- Have been confirmed to fail, or cannot tolerate, PAP therapy despite attempts to improve compliance
- Have followed standard of care in considering all other alternative/adjunct therapies

For this approval, existing adult clinical data and interim data from a pediatric feasibility study in patients with Down's syndrome were leveraged to support the reasonable assurance of safety and effectiveness of the proposed device in the pediatric sub-population of adolescents age 18 to 21.

In 2023 the FDA approved an expanded AHI for the Inspire Medical System for patients (18 and older) with an upper limit baseline AHI to 100 (increase from less than or equal to 65 to less than or equal to 100). Also, the FDA approved increasing the body mass index (BMI) warning to 40 kg/m^2 (increase from less than and equal to 32 to less than or equal to 40).[12]

There are hypoglossal nerve stimulation devices which have received an investigational device exemption (IDE) from the FDA. IDE allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data, however, the device is still in the developmental phase and not considered to be in commercial distribution.

- In 2014, ImThera™ Medical received FDA approval for an IDE trial with the aura6000® hypoglossal nerve stimulator system.
- In 2011, Apnex Medical received FDA approval to conduct a randomized investigational device exemption (IDE) trial for the Hypoglossal Nerve Stimulation (HGNS®) System. The trial was terminated and Apnex Medical has ceased operations.

In June 2020, the FDA approved an Investigational Device Exemption (IDE) trial for the Genio® system from Nyxoah. This is a battery-free, leadless and minimally invasive implanted hypoglossal nerve stimulator. The Genio System 2.1 received premarket approval from the FDA in 2025 (P240024) and is indicated for adult patients 22 years of age and older who have been confirmed to fail, cannot tolerate or are ineligible to be treated with current standard of care treatments including lifestyle modifications, PAP) treatments, oral appliances (such as mandibular advancement devices), and pharmacotherapy (such as tirzepatide).

EVIDENCE SUMMARY

Continuous positive airway pressure (CPAP) is the most widely accepted medical therapy for treatment of obstructive sleep apnea (OSA) and improvement of primary health outcomes such as cardiovascular disease, type 2 diabetes, and overall mortality associated with OSA. Hypoglossal nerve stimulation (HNS), sometimes referred to as upper airway stimulation, is proposed as a second line treatment for patients who have failed CPAP.

SYSTEMATIC REVIEWS

Alrubasy (2024) published a systematic review (SR) and meta-analysis of 30 studies (26 single-arm and 4 RCTs) that assessed the efficacy and safety of HNS devices—Inspire, Apnex, ImThera, and Genio—for treating OSA in adults intolerant to CPAP therapy.[13] Short-term results showed substantial reductions in AHI (mean difference: -20.11 events/hour), ODI (-13.05 events/hour), and ESS scores (-5.06 points), with corresponding improvements in FOSQ scores (+3.28 points). Long-term outcomes remained favorable, with sustained improvements in AHI (-15.60), ODI (-12.75), and ESS (-4.86). Most adverse events were minor and transient, including temporary stimulation discomfort (33% of cases) and tongue abrasions. Patient adherence was high, averaging 5.7 hours nightly use, with success rates (defined as ≥50% AHI reduction and AHI <20) ranging from 55-93% depending on device and follow-up duration.

Wollny (2024) published a SR and meta-analysis that focused on the safety of HNS in patients with OSA.[14] A total of 17 studies (n=1,962) were included. The analysis revealed a very low pooled mortality rate of 0.01% for HNS, with no therapy-related deaths reported. Over an average follow-up of 17.5 months, device survival at 60 months was high (98.34%). The most common adverse events occurred during implantation and the initial acclimatization period, with transient stimulation-related discomfort (0.08%) and tongue abrasions (0.07%) being the primary treatment-related side effects. The most common reasons for device removal were infections and patient requests. Surgical revision was rare (0.08%), and the most frequently reported treatment-related side effects were also rare, including transient stimulation discomfort (0.08%) and tongue abrasions (0.07%). The authors noted significant heterogeneity in adverse event reporting across studies and proposed a standardized framework for future HNS outcome reporting to improve data comparability.

Kim (2023) compared HNS to other OSA treatments in a systematic review (SR) and meta-analysis.[15] Studies were included if they measured polysomnography parameters and assessed sleep apnea-related quality of life (Epworth Sleepiness Scale [ESS]) both before and after HNS, and compared these outcomes with control, CPAP, or airway surgery (uvulopalatopharyngoplasty, expansion sphincter pharyngoplasty, or tongue base surgery) groups. A total of 10 studies with 2,209 patients who were treated with HNS or alternative interventions were included. HNS improved post-treatment AHI <10 and <15 events/hour compared with other surgical options including uvulopalatopharyngoplasty, expansion sphincterpharyngoplasty, or tongue-based surgery (odds ratio [OR]; 5.33; 95% CI, 1.21 to 23.42).

A SR with meta-analysis comparing outcomes of upper airway stimulation and other upper airway surgical procedures in the treatment of OSA was published by Neruntarat (2021).[16] Five articles (n=990) were included in the review and analysis. Patients in the “Stim” group underwent hypoglossal nerve stimulation (HNS, n=660) with the Inspire implant, and patients in the surgical intervention “Surg” group (n=330) underwent various surgical interventions including uvulopalatoplasty (UPPP), transoral robotic surgery, expansion sphincter pharyngoplasty, and palatal or tongue base surgery. Studies by Huntley,[17-19] Shah,[20] and Yu[21] were included in the analysis. The follow-up time ranged from 2 to 13 months. The mean cure rates in the Stim group and the Surg group were 63% and 22%, respectively, and the mean success rates were 86% and 51% (p<0.001). The apnea-hypopnea index (AHI) was significantly more reduced in the Stim group, -23.9 events/ hour (MD, 95% CI -25.53 to -22.29) compared with the Surg group, -15.5 events/hour (MD, 95% CI -17.50 to -13.45), p<0.001. Oxygen saturation nadir improvement was 8.5% (MD 95% CI 7.05% to 9.92%) in the Stim group and 2.2% (MD 95% CI-0.22% to 4.58%) in the Surg group, which is significantly higher in the Stim group (p<0.001). No significant difference in Epworth Sleepiness Scale (ESS) between groups was found. High risk of bias in multiple domains, including selective outcome reporting, incomplete outcome data, blinding, and participant selection was found for all included studies. Noted limitations in available data include retrospective study designs, limited follow-up times, and heterogeneity in patient characteristics.

Costantino (2020) published a SR with meta-analysis of studies evaluating the clinical outcomes of HNS in the treatment of moderate to severe OSA.[22] The SR included 12 prospective studies, excluding redundant cohorts of the same studies with varied follow-up lengths such as the STAR Trial[23-26] and the German Post-Market studies[27, 28] No randomized controlled trials comparing HNS to CPAP or other surgical interventions were identified. Of the 350 patients (median age 54.3 [IQR 53 to 56.25] years), 239 were implanted with the Inspire®

system, 59 were implanted with the ImThera™ system, and 52 were implanted with the Apnex system. All of the studies were considered to be of generally high quality, having satisfied at least six of the eight NICE quality assessment tool items. In all studies, the American Academy of Sleep Medicine (AASM) apnea and hypopnea definitions[2] were used, except that a 4% oxygen desaturation was required for a hypopnea to determine AHI. Analyses of long-term outcomes were conducted with data from the nine studies which had follow-up timepoints of six- and 12-months separately from the STAR trial data, which reported longer-term follow-up timepoints of 18-, 36-, and 60-months. At 12 months, the mean AHI difference was - 17.50 (Inspire; 95% CI: - 20.01 to - 14.98, p<0.001), - 24.20 (ImThera™; 95% CI: - 37.39 to 11.01, p<0.001), and - 20.10 (Apnex; 95% CI: - 29.62 to - 10.58, p<0.001). The mean AHI reduction after five years was - 18.00 (Inspire®, - 22.38 to - 13.62, p<0.001). The Epworth sleepiness scale (ESS) mean reduction was - 5.27 (Inspire®), - 2.90 (ImThera™), and - 4.20 (Apnex) at 12 months and - 4.40 (Inspire) at 60 months, respectively. Five-year serious device-related adverse events requiring surgical intervention in the STAR trial were 6% (8/126 patients), and the other studies included in the meta-analysis (n=195) reported a comparable complication rate at six and 12 months. Among the nine studies included in the meta-analysis, the overall success rate at 12 months (defined as a 50% reduction in AHI and overall AHI less than 20), was 72.4% (Inspire®, n=211), 76.9% (ImThera™, n=13), and 55% (Apnex, n=31).

A 2015 SR identified six case series with a total of 200 patients treated with HNS.[29] No controlled trials were identified. Two series were identified on the Inspire II System and included the STAR trial described below. Three series were identified with the HGNS system and included the study of 31 patients described above. One series of 13 patients was identified with the aura6000 System (ImThera Medical). When data were combined for meta-analysis, AHI and Oxygen Desaturation Index (ODI) improved by 50% (eg, AHI from 44 to 20, ODI from 21 to 10), and the ESS improved from 12 to 7. All of the included studies described minor complications such as tongue weakness, tongue soreness, pain/swelling at the neck incision, fever, and lack of tongue response to stimulation. Of the 200 patients, nine (4.5%) had serious device-related adverse events that led to removal of the stimulator.

RANDOMIZED CONTROLLED TRIALS

Schwartz (2023) published results from the ImThera Medical Targeted Hypoglossal Neurostimulation Study #3 (THN3), which investigated the efficacy and safety of targeted HNS of the proximal hypoglossal nerve in patients with moderate-to-severe OSA (AHI 20 to 60 events per hour).[30] This was a multicenter, randomized, open-label trial in which all patients (n=138) were implanted with the HNS system (aura6000; ImThera Medical), and randomly assigned 2:1 to HNS device activation at one or four months after implant for the treatment and control groups, respectively. Efficacy was measured at month four, as well as after 11 months of therapy (study months 12 and 15 for treatment and control groups, respectively). The study included mostly males (86.2%) and white individuals (91.3%). The results demonstrated that at month four, the treatment group had significantly better outcomes compared to the control group for AHI and ODI scores. However, after 11 months of active therapy, the difference between the treatment and control groups was not statistically significant for AHI (relative risk [RR], -7.5; 95% CI, -16.0 to 1.4) but remained significant for ODI (RR, 10.4; 95% CI, 1.6 to 18.8). Limitations include homogeneity of the study population and difference in starting points for treatment between groups.

Heiser (2021) published the results of a multicenter, double-blind, randomized, sham-controlled, crossover trial to examine the effect of implanted hypoglossal nerve stimulation

(Stim, n=45) or sham stimulation (Sham, n=44) using the Inspire HNS.[31] Inclusion criteria were moderate-to-severe OSA (AHI ≥15), CPAP intolerance, and the absence of complete concentric retropalatal collapse during drug-induced sleep endoscopy. The UAS devices implanted in the participants were programmed to the setting assigned to their respective groups, i.e., Stim (continued therapeutic stimulation, average amplitude 1.6 V ± 0.7) and Sham (stimulation voltage set at 0.1 V as a subtherapeutic stimulation level and a deception for the patient). All participants received therapeutic stimulation during the first visit (baseline visit), and once randomized, the Stim–Sham group received therapeutic stimulation while the Sham–Stim group received sham stimulation for one week. Crossover occurred during the second week, in which the Stim–Sham group received sham stimulation while the Sham–Stim group received therapeutic stimulation. Primary outcome measures were the proportion of AHI responders (defined as AHI ≤15/h) between parallel randomized groups and self-reported sleepiness measure using the ESS questionnaire at the one-week visit. At one week, the AHI response rate was 76.7% with Stim and 29.5% with Sham, a difference of 47.2% (95% CI: 24.4 to 64.9, p < 0.001). The average ESS change from the Stim–Sham group was 0.4 ± 2.3 and from the Sham–Stim group was 5.0 ± 4.6, with a significant difference of 4.6 (95% CI of 3.1 to 6.1, p = 0.001). The change of AHI and ESS from the baseline to the one-week and two-week visits between the Stim–Sham and Sham–Stim groups and found no statistical evidence of a carryover effect for AHI (p=0.55) or ESS (p=0.23). The homogenous study population (81% male, 100% Caucasian) limits the generalizability of the study findings. In addition, the authors note that most participants randomized to the sham arm became aware of the group allocation, which may impact study outcomes. Longer-term outcomes are not reported. This study was funded by the device manufacturer (Inspire Medical Systems, Inc) and study authors received fees and/or other funding from the device manufacture and no clear attempt to mitigate potential bias is provided.

NONRANDOMIZED STUDIES

Observational Comparative Studies

Heiser (2023) published a study comparing HNS with PAP treatment in 126 propensity matched patients in a real-world setting.[32] A clinically important symptom improvement was seen at 12 months in both cohorts, though there was a greater difference in the Epworth Sleepiness Scale (ESS) improvement in patients treated with HNS (8.0 ± 5.1 points vs. 3.9 ± 6.8 points; p=0.042). In both groups, mean post-treatment AHI was significantly reduced (HNS: 8.1 ± 6.3/hour [h]; PAP: 6.6 ± 8.0/h; p<0.001). Adherence after 12 months among patients treated with HNS was higher than in those receiving PAP therapy (5.0 ± 2.6 h/night; 4.0 ± 2.1 h/night) but not with statistical significance. Several of the study authors received fees and/or other funding from the device manufacture and no clear attempt to mitigate potential bias is provided.

Nonrandomized evidence consists of studies that compared HNS with historical controls treated with UPPP or a variant of UPPP (expansion sphincter pharyngoplasty, see Table 2) and a study that compared HNS with transoral robotic surgery. AHI success by the Sher criteria ranged from 87% to 100% in the HNS group compared with 40% to 64% in the UPPP group (see Table 3). Post-treatment ESS was below 10 in both groups. It is not clear from some studies whether the patients in the historical control group were similar to the subset of patients in the HNS group, particularly in regard to the pattern of palatal collapse and from patients who did not return for postoperative PSG (see Tables 4 and 5).

Several comparative studies have addressed these concerns by only including patients who meet the criteria for HNS in the control group. Yu (2019) compared outcomes for patients who met the criteria for both HNS (non-concentric collapse on drug-induced sleep endoscopy) and transoral robotic surgery (retroglossal obstruction).[21] When patients with similar anatomic criteria were compared, HNS led to significantly better improvements in AHI, cure rate (defined as AHI <5), and the percentage of time that oxygen saturation fell below 90%. Huntley (2021) selected patients in the control group who met criteria for HNS (non-concentric collapse on drug-induced sleep endoscopy and body mass index [BMI] criteria) but had been treated at their institutions by single or multi-level palatal and lingual surgery.[17] There was no explanation of why the different treatments were given during the overlap period of 2010 to 2019, but the HNS patients were older and heavier. HNS resulted in a modestly greater decrease in AHI (HNS: -21.4 vs -15.9. p<0.001), but not in ESS (HNS: -4.7 vs -5.8, p=0.06). More patients in the HNS group achieved success by the Sher criteria (70% vs 48 to 49%) suggesting that there might be a clinical benefit for some patients.

Another report from the ADHERE registry investigators (Mehra 2020) compared outcomes from HNS patients with patients who met criteria but had been denied insurance coverage.[33] In a post-hoc multivariate analysis, previous use of PAP and prior surgical procedures were predictors of insurance approval. In the group of patients who received HNS, the average use downloaded from the device was 5.6 h/night and 92% of patients had usage greater than 20 h/week. Most of the comparator group (86%) were not using any therapy at follow-up. The remaining 14% were using PAP, an oral appliance, or underwent OSA surgery. The AHI decreased to 15 events/h (moderate OSA) on the night of the sleep test in patients with HNS, with only modest improvement in patients who did not receive HNS. The hours of use on the night of the post-operative sleep study was not reported, and the HNS patients may have been more likely to use their device on the test night. In addition, the use of a home sleep test for follow-up may underestimate the AHI. The ESS improved in the HNS group but worsened in the controls. This suggests the possibility of bias in this subjective measure in patients who were denied coverage.

Table 2. Summary of Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	HNS	Traditional Surgery	Follow-Up
Mehra (2020)[33]	ADHERE registry	US, EU	2017-2019	OSA patients who were intolerant to CPAP and met HNS criteria of AHI 15 to 65, BMI < 35, and favorable pattern of palatal collapse[a]	250 registry patients treated with HNS	100 patients who qualified for HNS but were denied insurance coverage	6 to 24 months
Huntley (2021)[17]	ADHERE registry compared to retrospective controls	US, EU	• HNS 2010-2019 • Modified UPPP 2003-2019	OSA patients who were intolerant to CPAP and met HNS criteria of AHI 15 to 65, BMI < 35, and favorable pattern of palatal collapse[a]	465 registry patients treated with HNS who had 12 mo follow-up	233 patients who would have qualified for HNS and were treated by single level (68%) or multilevel (31%) surgery	173 days after surgery 383 days after HNS
Yu (2019)[21]	Retrospective series with historical controls	US	• HNS 2014-2016 • TORS 2011-NR	OSA patients with AHI >20 and <65, BMI ≤32, failed CPAP, favorable pattern of palatal collapse[a]	27 patients age 62 with retroglossal collapse amenable to TORS	20 patients age 53 y who would have qualified for HNS and were treated by TORS	NR
Shah (2018)[20]	Retrospective series with historical controls	US	HNS 2015-2016 UPPP 2003-2012	40 OSA patients with AHI >20 and <65, BMI ≤32, failed CPAP, favorable pattern of palatal collapse[a]	35% had previously had surgery for OSA	UPPP 50% of patients had additional surgical procedures	2-13 mo
Huntley (2018)[19]	Retrospective series with historical controls	US	HNS2014-2016 Modified UPPP 2011-2016	Retrospective review included treated patients who had a postoperative PSG	75 patients age 61.67 y with a favorable pattern of palatal collapse	33 patients age 43.48 y treated by ESP	To post-operative PSG

BMI: body mass index; CPAP: continuous positive airway pressure; ESP: expansion sphincter pharyngoplasty; HNS: hypoglossal nerve stimulation; OSA: obstructive sleep apnea; PSG: polysomnography; UPPP: uvulopalatopharyngoplasty.

[a] A favorable pattern of palatal collapse is not concentric retropalatal obstruction on drug-induced sleep endoscopy.

Table 3. Summary of Key Observational Comparative Study Results

Header Row	Baseline AHI (SD)	Posttreatment AHI (SD)	AHI Success (%) Sher Criteria	Baseline ESS (SD)	Posttreatment ESS (SD)
Huntley (2021)[17]					
HNS	35.5 (15.0)	14.1 (14.4)	70	11.9 (5.5)	7.3 (4.7)
Single or multi-level UPPP	35.0 (13.1)	19.3 (16.3)	48 to 49	11.3 (5.1)	5.9 (4.0)
p-Value	0.88	<0.001	<0.001	0.22	0.06
Mehra (2020)[33]					
HNS	33.7 (13.4)	14.7 (13.8)		12.3 (5.5)	7.2 (4.8)
No HNS	34.9 (16.4)	26.8 (17.6)		10.9 (5.4)	12.8 (5.2)
p-value	0.95	<0.001		0.06	<0.001
Yu (2019)[21]		Average AHI Reduction	% Cure Rate	Change in SaO2 <90%	
HNS		33.3	70.4%	14.1	
TORS		12.7	10.0%	1.3	
p-value		0.002	<0.001	0.02	
Shah (2018)[20]					
HNS	38.9 (12.5)	4.5 (4.8)[b]	20 (100%)	13 (4.7)	8 (5.0)[b]
UPPP	40.3 (12.4)	28.8 (25.4)[a]	8 (40%)	11 (4.9)	7 (3.4)[b]
Huntley (2018)[19]					
HNS	36.8 (20.7)	7.3 (11.2)	86.7	11.2 (4.2)	5.4 (3.4)
ESP	26.7 (20.3)	13.5 (19.0)	63.6	10.7 (4.5)	7.0 (6.0)
p	0.003	0.003	0.008	0.565	*NS*

AHI: Apnea/Hypopnea Index; ESP: expansion sphincter pharyngoplasty; HNS: hypoglossal nerve stimulation; NS: not significant; Sher criteria: 50% decrease in AHI and final AHI <20; SD; standard deviation; UPPP: uvulopalatopharyngoplasty.
[a] Baseline vs posttreatment p<0.05.
[b] Baseline vs posttreatment p<0.001.

Table 4. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Huntley (2021)[17]	4. Study populations not comparable				1. The timing of follow-up was different (173 days after surgery and 383 days after HNS)
Mehra (2020)[33]	4. Study populations not comparable		3. Hours of use on the test night was not reported. This may not represent the normal use of the device.		1. The timing of follow-up was different
Yu (2019)[21]					1, 2. Duration of follow-up unclear
Shah (2018)[20]			2. UPPP may not be preferred treatment for patients with primarily lingual obstruction		

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Huntley (2018)[19]	4. Study populations not comparable		1. Not clearly defined, few ESP patients had follow-up PSG		
Steffen (2018)[27]			2.No comparator		
STAR trial[23-26, 34, 35]			2.No comparator		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. ESP: expansion sphincter pharyngoplasty; PSG: polysomnography; STAR: Stimulation Therapy for Apnea Reduction; UPPP: uvulopalatopharyngoplasty.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Gaps

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[d]	Power[d]	Statistical[f]
Huntley (2021)[17]	1. Not randomized (retrospective)	1.-3. No blinding				
Mehra (2020)[33]	1. Not randomized	1.-3. No blinding			1. Power calculations not reported	
Yu (2019)[21]	1. Not randomized (retrospective)					
Shah (2018)[20]	1. Not randomized (retrospective) 4. Inadequate control for selection bias	1.-3. No blinding				4. Comparative treatment effects not calculated
Huntley (2018)[19]	1. Not randomized (retrospective)	1.-3. No blinding				
Steffen (2018)[27]	1. Not randomized	1.-3. No blinding				
STAR trial[23-26, 34, 35]	1. Not randomized	1.-3. No blinding				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. STAR: Stimulation Therapy for Apnea Reduction.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Prospective Single Arm Studies

Results of prospective single-arm studies show success rates in 66% to 68% of patients who had moderate-to-severe sleep apnea and a favorable pattern of palatal collapse (see Tables 6 and 7). Mean AHI was 31 to 32 at baseline, decreasing to 14 to 15 at 12 months. ESS scores decreased to 6.5 to 7.0. All improvements were maintained through five years of follow-up. Discomfort due to the electrical stimulation and tongue abrasion were initially common but were decreased when stimulation levels were reduced (see Table 8). In the post-market study, a normal ESS score (<10) was obtained in 73% of patients. A FOSQ score of at least 19 was observed in 59% of patients compared to 13% at baseline. At the 12- month follow-up, 8% of bed partners regularly left the room due to snoring, compared to 75% of bed partners at baseline. The average use was 5.6 + 2.1 h per night. Use was correlated with the subjective outcomes but not with AHI response. Two- and three-year follow-ups of this study were reported by Steffen (2020)[36], but the percentage of patients at follow-up was only 68% at two years and 63% at three years, limiting conclusions about the longer-term efficacy of the procedure. A comparison of the populations who had 12-month versus two- or three-year results showed several differences between the patients who followed up and those who dropped out, including higher baseline AHI, higher baseline ODI, and trends towards lower usage per night and a lower responder rate at 12 months.

Table 6. Summary of Prospective Single-Arm Study Characteristics

Study	Country	Participants	Treatment Delivery	Follow-Up
STAR trial[23-26, 34, 35]	EU, US	126 patients with AHI >20 and <50, BMI ≤32 kg/m^2, failed CPAP, favorable pattern of palatal collapse[a]	Stimulation parameters titrated with full PSG	5 y
Postmarket studies: Heiser (2017)[28] Steffen (2018, 2020)[27, 36] Hasselbacher (2018)[37] Withrow (2019)[38]	3 sites in Germany Thirteen US hospitals and 3 German hospitals	60 patients with AHI ≥15 and ≤65 on home sleep study, BMI ≤35 kg/m^2, failed CPAP; favorable pattern of palatal collapse[a] 600 adults with moderate to severe OSA (AHI, 15-65), <25% central and mixed apneas, CPAP nonadherence or intolerance, absence of concentric collapse		12 mo 12 mo

AHI: apnea/hypopnea index; BMI: body mass index; CPAP: continuous positive airway pressure; STAR: Stimulation Therapy for Apnea Reduction.
[a] A favorable pattern of palatal collapse is non-concentric retropalatal obstruction on drug-induced sleep endoscopy.

Table 7. Summary of Prospective Single-Arm Study Results

Study	N	Percent of Patients with AHI Success (Sher criteria)	Mean AHI Score (SD)	Mean ODI Score (SD)	FOSQ Score (SD)	ESS Score (SD)
STAR trial[23-26, 34, 35]						
Baseline	126		32.0 (11.8)	28.9 (12.0)	14.3 (3.2)	11.6 (5.0)
12 months	124	66%	15.3 (16.1)[d]	13.9 (15.7)[d]	17.3 (2.9)[d]	7.0 (4.2)[d]
3 years	116[a]	65%	14.2 (15.9)	9.1 (11.7)	17.4 (3.5)[b]	7.0 (5.0)[b]
5 years	97[c]	63%	12.4 (16.3)	9.9 (14.5)	18.0 (2.2)	6.9 (4.7)
Postmarket studies: Heiser (2017)[28] Steffen (2018, 2020)[27, 36] Hasselbacher (2018)[37]						
Baseline	60		31.2 (13.2)	27.6 (16.4)	13.7 (3.6)	12.8 (5.3)
12 months	56[f]	68%	13.8 (14.8)[e]	13.7 (14.9)[e]	17.5 (3)[e]	6.5 (4.5)[e]
2 years	41	76%[h]				
3 years	38	68%[h]				
Withrow (2019)[38]						
age < 65	365					
Baseline			36.2 (34.6-37.8)[f]			12.3 (11.7-12.9)[f]
12 months			11.9 (9.9-13.9)[f]			7.1 (6.4-7.8)
age ≥ 65	235					
Baseline			36.1 (34.2-38.0)[f]			10.7 (9.9-11.5)[f]
12 months			7.6 (6.1-9.1)[f]			6.3 (5.4-7.2)[f]

AHI: Apnea/Hypopnea Index; ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; ODI: Oxygen Desaturation Index; PSG: polysomnography; SD: standard deviation; STAR: Stimulation Therapy for Apnea Reduction.

[a] Ninety-eight participants agreed to undergo PSG at 36 months, of the 17 participants who did not undergo PSG at 36 months, 54% were nonresponders and their PSG results at 12 or 18 months were carried forward.

[b] The change from baseline was significant at p<0.001.

[c] Seventy-one participants agreed to a PSG.

[d] p<0.001.

[e] p< 0.05.

[f] Four patients lost to follow-up were analyzed as treatment failures.

[g] Range

[h] defined as AHI below 15/h

Table 8. Device-Related Adverse Events from Prospective Single-Arm Studies

Header Row	N	Discomfort due to Electrical Stimulation[a]	Tongue Abrasion	Dry Mouth	Mechanical Pain from Device	Internal Device Usability	External Device Usability
STAR trial[26]							

Header Row	N	Discomfort due to Electrical Stimulation[a]	Tongue Abrasion	Dry Mouth	Mechanical Pain from Device	Internal Device Usability	External Device Usability
0 to 12 months	126	81	28	10	7	12	11
12 to 24 months	124	23	12	5	2	8	11
24 to 36 months	116	26	4	2	3	1	8
36 to 48 months	97	7	3	0	1	3	9
> 48 months		5	3	3	1	1	6
Participants with event, n of 126 (%)		76 (60.3)	34 (27.0)	19 (15.1)	14 (11.1)	21 (16.7)	33 (26.2)

STAR: Stimulation Therapy for Apnea Reduction.

[a] Stimulation levels were adjusted to reduce discomfort

Down Syndrome

Liu (2022) published a systematic review investigating HNS in adolescents with Down Syndrome and OSA.[39] A total of nine studies were included with a follow up period ranging from two to 58 months; six studies had sample sizes fewer than 10 patients. The largest of the included studies was a prospective cohort study published by Yu (2022), which is summarized below. In an analysis that included 104 patients, AHI scores were significantly reduced in patients after HNS (mean AHI reduction, 17.43 events/h; 95% CI, 13.98 to 20.88 events/h; p<0.001). Similarly, in an analysis that included 88 patients, OSA-18 survey scores were significantly reduced after HNS (mean OSA-18 reduction, 1.67; 95% CI, 1.27 to 2.08; p<0.001).

Yu (2022) reported on the safety and effectiveness of HNS in 42 adolescents with Down Syndrome and severe OSA (AHI of 10 events/h or greater).[40] This was a single-group, multicenter, cohort study with a one-year follow-up that included non-obese (BMI <95%) children and adolescents aged 10 to 21 years who were refractory to adenotonsillectomy and unable to tolerate CPAP. Patients who were included had an AHI between 10 and 50 on baseline PSG; the mean baseline AHI was 23.5 (SD, 9.7). All patients included tolerated HNS without any intraoperative complications. The most common complication was tongue or oral discomfort or pain, which occurred in 5 (11.9%) patients and was temporary, lasting weeks or rarely, months. Four patients (9.5%) had device extrusion resulting in readmissions to replace the extruded device. At 12 months, there was a mean decrease in AHI of 12.9 (SD, 13.2) events per hour (95% CI, -17.0 to -8.7 events/h). At the 12-month PSG, 30 of 41 patients (73.2%) had an AHI of less than 10 events/h, 14/41 patients (34.1%) had an AHI of less than five events/h, and 3/41 patients (7.3%) had an AHI of less than two events/h. There was also a significant improvement in quality-of-life outcomes. The mean improvement in the OSA-18 total score was 34.8 (SD, 20.3; 95% CI, -42.1 to -27.5) and the ESS improved by 5.1 (SD, ,6.9; 95% CI, -7.4 to -2.8).

Caloway (2020) reported a safety study of HNS in 20 children with Down Syndrome and severe OSA (AHI of 10 or greater) treated at three tertiary care centers.[41] Included were non-obese (BMI < 95%) children and adolescents aged 10 to 21 years who were refractory to tonsillectomy and either unable to tolerate CPAP or dependent on a tracheostomy. Patients who were included had an AHI between 10 and 50 on baseline PSG; the median baseline AHI

was 24.15 (interquartile range [IQR] of 19.88 to 35.10). All of the patients tolerated the stimulation, and at two months after implantation, the median AHI was 3.56 (IQR 2.61 to 4.40). Success, defined as an AHI of 5 or less (mild) with HNS, was achieved in 14 of 20 patients (70%). The median percent reduction in AHI was 85% with a median usage of 9.21 h (IQR: 8.29 to 9.50) per night. The OSA-18 score improved by 1.15 (IQR: 0.02 to 1.97), indicating a moderate but clinically significant change. There were two adverse events related to extrusion or connectivity of the stimulation or sensation leads, which were both corrected with wound exploration surgery. Study in a larger population of children with Down Syndrome is ongoing.

Registry

Bentan (2024) published a retrospective review of the US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database, a publicly available reporting system.[42] This review analyzed adverse events associated with hypoglossal nerve stimulator implantation, for treating OSA, from 1,178 reports from May 2014 to December 2023. 1,312 adverse events were identified. Common adverse events included infection (24.0%), pain (19.7%), and hematoma/seroma (10.2%). Approximately 83.1% of these adverse events necessitated medical and/or surgical intervention. The most frequent procedures included explantation (29.4%) and device repositioning (15.8%). Pneumothorax was reported in 50 cases, with 41 (82.0%) requiring a chest tube to be inserted. Three adverse events described overstimulation in the setting of magnetic resonance imaging (MRI) despite the implantation of MRI-compatible second-generation internal pulse generators.

A retrospective review of the US FDA MAUDE database, a publicly available voluntary reporting system, was published by Bellamkonda in 2021.[43] This search was specific to the Inspire system and for adverse events reported between May 2014 and September 2019. Over the five-year period, 132 patient reports containing 134 adverse events were identified, including 32 device revision procedures and 17 device explantations. Complications noted to have not been reported in large-scale clinical trials included pneumothorax, pleural effusion, and lead migration into the pleural space.

Kent (2019) pooled data from the ADHERE registry plus data from three other studies to evaluate factors predicting success.[44] Over 80% of the 584 patients were men, and most were overweight. Seventy-seven percent of patients achieved treatment success, defined as a decrease in AHI by at least 50% and below 20 events/per hour. AHI decreased to below 5 in 41.8% of patients. Greater efficacy was observed in patients with a higher preoperative AHI, older patient age, and lower BMI. A report of data from the ADHERE registry by Thaler (2020) included 640 patients with six-month follow-up and 382 with 12-month follow-up.[45] AHI was reduced from 35.8 at baseline to 14.2 at 12 months ($p<0.001$), although the number of hours of use during the sleep test was not reported and home sleep studies may underestimate AHI. ESS was reduced from 11.4 at baseline to 7.2 at 12 months ($p<0.001$), and patient satisfaction was high. In a multivariate model, only female sex (odds ratio: 3.634, $p=0.004$) and lower BMI (odds ratio: 0.913, $p=0.011$) were significant predictors of response according to the Sher criteria. In sensitivity analysis, higher baseline AHI was also found to be a negative predictor of success.

Boon (2018) reported results from 301 patients in the multicenter Adherence and Outcome of Upper Airway Stimulation for OSA International Registry (ADHERE).[46] The ADHERE registry included both retrospective and prospectively collected data from the U.S. and Germany between October 2016 and September 2017. Data were collected from PSG prior to implantation and between two and six months after implantation, or from home sleep tests

which were often performed at six and 12 months after implantation as part of routine care. Mean AHI decreased from 35.6 (SD: 15.3) to 10.2 (SD: 12.9) post-titration with 48% of patients achieving an AHI of 5 or less. ESS decreased from 11.9 (5.5) to 7.5 (4.7) ($p < 0.001$).

Body Mass Index

A publication by Sarber (2020) reported on outcomes of 18 patients implanted with HNS as a salvage procedure despite being outside of FDA trial data.[47] Of these patients, 12 had a BMI >32 kg/m^2 (range 32.1 to 39.1). Positive outcomes across the 18 subjects were found, with (83.3%) patients achieving surgical success (decrease in AHI >50% and AHI <20 events/hour). This study is limited by the retrospective design and very small sample size. In addition, a retrospective analysis by Huntley (2018) found patients with a BMI of greater than 32 (n=40) did not have lower success rates than patients with a BMI less than 32 (n=113).[18] Only patients who had palpable cervical landmarks and carried most of their weight in the waist and hips were offered HNS.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF OTOLARYNGOLOGY - HEAD AND NECK SURGERY

In a position statement, the American Academy of Otolaryngology - Head and Neck Surgery (2019) supported hypoglossal nerve stimulation as an effective second-line treatment of moderate-to-severe obstructive sleep apnea in patients who are intolerant or unable to achieve benefit with positive pressure therapy.[48]

AMERICAN ACADEMY OF SLEEP MEDICINE

The American Academy of Sleep Medicine (AASM, 2021) published practice guidelines on when to refer patients for surgical modifications of the upper airway for OSA.[49] These guidelines replaced the 2010 practice parameters for surgical modifications.[50] The AASM guidelines note that positive airway pressure (PAP) is the most efficacious treatment for OSA, but effectiveness can be compromised when patients are unable to adhere to therapy or obtain adequate benefit, which is when surgical management may be indicated. The AASM guideline recommendations are based on a systematic review and meta-analysis of 274 studies of surgical interventions, including procedures such as uvulopalatopharyngoplasty (UPPP), modified UPPP, MMA, tongue base suspension, and hypoglossal nerve stimulation.[51] The systematic review deemed most included data of low quality, consisting of mostly observational data. The AASM strongly recommend that clinicians discuss referral to a sleep surgeon with adults with OSA and body mass index (BMI) <40 kg/m^2 who are intolerant or unaccepting of PAP. Clinically meaningful and beneficial differences in nearly all critical outcomes, including decrease in excessive sleepiness, improved quality of life (QOL), improved Apnea/Hypopnea Index (AHI) or respiratory disturbance index (RDI), and sleep quality, were demonstrated with surgical management in patients who are intolerant or unaccepting of PAP. The AASM makes a conditional recommendation that clinicians discuss referral to a sleep surgeon with adults with OSA, BMI <40 kg/m^2, and persistent inadequate PAP adherence due to pressure-related side effects, as available data (very low-quality) suggests that upper airway surgery has a moderate effect in reducing minimum therapeutic PAP level and increasing PAP adherence. In adults with OSA and obesity (class II/III, BMI >35) who are intolerant or unaccepting of PAP, the AASM strongly recommends discussion of referral to a bariatric surgeon, along with other weight loss strategies.

SUMMARY

There is enough research to show that hypoglossal nerve stimulation (HNS) improves health outcomes for individuals with obstructive sleep apnea (OSA). Evidence-based clinical practice guidelines recommend HNS as an effective second-line treatment for individuals with OSA who cannot tolerate positive airway pressure (PAP) therapy. Therefore, hypoglossal nerve stimulation may be considered medically necessary for some patients with OSA when policy criteria are met.

A hypoglossal nerve stimulation device may require revision after it has been placed. In these cases, revision may be medically appropriate to allow for the proper functioning of the device. Therefore, revision(s) to an existing hypoglossal nerve stimulation device may be considered medically necessary after the device has been placed.

In certain situations, a hypoglossal nerve stimulation device may no longer be able to perform its basic function due to damage or wear. When a stimulator is out of its warranty period and cannot be repaired adequately to meet the patient's medical needs, replacement of the device may be medically appropriate. Therefore, replacement of all or part of a hypoglossal nerve stimulation device and/or generator may be considered medically necessary when device replacement Criteria are met.

When a hypoglossal nerve stimulation device is in its warranty period or can be repaired or adapted adequately to meet the patient's medical needs, replacement of the device is not medically appropriate. Therefore, replacement of all or part of a hypoglossal nerve stimulation device and/or generator is considered not medically necessary when device replacement Criteria are not met.

Clinical practice guidelines recommend positive airway pressure (PAP) as the most efficacious treatment for obstructive sleep apnea (OSA) and hypoglossal nerve stimulation (HNS) may be considered in some patients who are unable to adhere to therapy or obtain adequate benefit. Therefore, HNS is considered not medically necessary when there is PAP therapy refusal in adults with OSA.

There is not enough research to know if or how well hypoglossal nerve stimulation (HNS) works to treat people when policy criteria are not met. This does not mean that it does not work, but more research is needed to know. No clinical guidelines based on research address HNS for indications other than for those listed in the policy criteria. Therefore, hypoglossal nerve stimulation is considered investigational when policy criteria are not met.

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CODES

Codes	Number	Description
CPT	64568	Open implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
	64582	Hypoglossal nerve neurostimulator implantation; open
	64583	Hypoglossal nerve neurostimulator revision or replacement
	64584	Hypoglossal nerve neurostimulator removal
HCPCS	C1767	Generator, neurostimulator (implantable), nonrechargeable
	C8007	Open implantation of hypoglossal nerve neurostimulator array and pulse generator, not requiring insertion of a separate distal respiratory sensor electrode or electrode array
	C8008	Revision or replacement of hypoglossal nerve neurostimulator array including connection to existing pulse generator
	C8009	Removal of hypoglossal nerve neurostimulator array and pulse generator
	C8011	Open implantation of hypoglossal nerve(s) neurostimulator electrode array(s) and receiver, including external power source and all system components
	C8012	Revision or replacement of hypoglossal nerve(s) neurostimulator electrode array(s) and receiver
	C8013	Removal of hypoglossal nerve(s) neurostimulator electrode array(s) and receiver

Date of Origin: *June 2019*

Appendix A: BMI Percentiles for Age for Females with Down Syndrome, Aged 2 to 20 Years[5]

Age	95th Percentile BMI
2.0	20.0
2.5	20.2
3.0	20.4
3.5	20.5
4.0	20.8
4.5	21.0
5.0	21.3
5.5	21.7
6.0	22.0
6.5	22.5
7.0	23.0
7.5	23.6
8.0	24.2
8.5	24.9
9.0	25.6
9.5	26.4
10.0	27.2
10.5	28.1
11.0	29.0
11.5	29.9
12.0	30.9
12.5	31.8
13.0	32.8
13.5	33.7
14.0	34.7
14.5	35.6
15.0	36.5
15.5	37.5
16.0	38.4
16.5	39.3
17.0	40.2
17.5	41.0
18.0	41.9
18.5	42.7
19.0	43.5
19.5	44.2
20.0	45.0

Appendix B. BMI Percentiles for Age for Males with Down Syndrome, Aged 2 to 20 years[5]

Age	95th Percentile BMI
2.0	13.8
2.5	14.8
3.0	15.7
3.5	16.7
4.0	17.9
4.5	19.3
5.0	21.1
5.5	23.1
6.0	25.1
6.5	27.3
7.0	29.5
7.5	31.9
8.0	34.6
8.5	37.4
9.0	40.3
9.5	43.3
10.0	46.4
10.5	49.6
11.0	53.1
11.5	57.0
12.0	61.1
12.5	65.5
13.0	70.1
13.5	74.5
14.0	78.6
14.5	81.9
15.0	84.5
15.5	86.5
16.0	88.1
16.5	89.5
17.0	90.5
17.5	91.4
18.0	92.0
18.5	92.5
19.0	92.8
19.5	93.0
20.0	93.1