Implantable Hypoglossal Nerve Stimulation for the Treatment of Obstructive Sleep Apnea

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DESCRIPTION

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. OSA is associated with a heterogeneous group of anatomic variants producing obstruction. In patients with OSA, the normal pharyngeal narrowing may be accentuated by anatomic factors, such as a short, fat "bull" neck, elongated palate, and uvula, and large tonsillar pillars with redundant lateral pharyngeal wall mucosa. In addition, OSA is associated with obesity. OSA may also be associated with craniofacial abnormalities, including micrognathia, retrognathia or maxillary hypoplasia. Obstruction anywhere along the upper airway can result in apnea.

Untreated OSA has many potential consequences and adverse clinical associations, including excessive daytime sleepiness, impaired daytime function, metabolic

dysfunction, and an increased risk of cardiovascular disease and mortality. The goals of OSA therapy are to resolve signs and symptoms of OSA, improve sleep quality, and normalize the apnea hypopnea index (AHI) and oxyhemoglobin saturation levels. OSA should be approached as a chronic disease that requires long term, multidisciplinary management.

Continuous positive airway pressure (CPAP) is the preferred treatment option for most patients with OSA. In patients who prefer not to use positive airway pressure (PAP) or who fail to respond to it, oral appliances, or surgery to correct anatomic structures in the upper airway are additional treatment alternatives. Evidence is lacking related to upper airway surgery long term effectiveness. Therefore, new approaches to the treatment of OSA is desired and the use of implanted hypoglossal nerve stimulation has been studied as a potential treatment option for the treatment of OSA.

Clinical Context and Therapy Purpose
Obstructive sleep apnea (OSA) is associated with a heterogeneous group of anatomic variants producing obstruction. The normal pharyngeal narrowing may be accentuated by anatomic factors, such as a short, fat "bull" neck, elongated palate and uvula, and large tonsillar pillars with redundant lateral pharyngeal wall mucosa. In addition, OSA is associated with obesity. OSA may also be associated with craniofacial abnormalities, including micrognathia, retrognathia, or maxillary hypoplasia. Obstruction anywhere along the upper airway can result in apnea. The severity and type of obstruction may be described with the Friedman staging system. Nonsurgical treatment for OSA or upper airway resistance syndrome includes continuous positive airway pressure (CPAP) or mandibular repositioning devices. Patients who fail conservative therapy may be evaluated for surgical treatment of OSA.

Traditional surgeries for obstructive sleep apnea (OSA) or upper airway resistance syndrome include uvulopalatopharyngoplasty (UPPP) and a variety of maxillofacial surgeries such as mandibular-maxillary advancement. UPPP involves surgical resection of the mucosa and submucosa of the soft palate, tonsillar fossa, and the lateral aspect of the uvula. The first-line treatment in children is usually adenotonsillectomy. Minimally invasive surgical approaches are being evaluated for OSA in adults.

Patients
The population of interest is patients with OSA who have failed or are intolerant to positive airway pressure (PAP) therapy.

Interventions
The intervention addressed in this review is implantable hypoglossal nerve stimulation.

Stimulation of the hypoglossal nerve causes tongue protrusion and stiffening of the anterior pharyngeal wall, potentially decreasing apneic events.

Comparators
For patients with mild OSA who are intolerant of CPAP, the comparator would be oral appliances or an established upper airway surgical procedure.

For patients with moderate-to-severe OSA who have failed CPAP or are intolerant of CPAP, the comparator would be conventional surgical procedures such as maxillofacial surgeries that may include UPPP, hyoid suspensions, maxillary and mandibular osteotomies, and modification of the tongue. UPPP alone has limited efficacy. UPPP may be modified or combined with a tongue base procedure such as uvulopalatopharyngoglossoplasty, depending on the location of the obstruction. UPPP variants would not be the most appropriate comparator for hypoglossal nerve stimulation (HNS) since the procedures address different sources of obstruction.

Outcomes
Established surgical procedures are associated with adverse events such as dysphagia. In addition, the surgical procedures are irreversible should an adverse event occur. Therefore, an improvement in effectiveness and/or a decrease in adverse events compared with standard surgical procedures would be the most important outcomes.

The outcomes measure used to evaluate treatment success are a decrease in Apnea/Hypopnea Index (AHI) and Oxygen Desaturation Index on polysomnography (PSG) and improvement in a measure of sleepiness such as the Epworth Sleepiness Scale (ESS) or Functional Outcomes of Sleep Questionnaire (FOSQ).

Health Outcome Measures Relevant to Obstructive Sleep Apnea (OSA)

Outcome	**Measure (units)**	**Description**	**Clinically Meaningful Difference (If Known)**
Change in AHI	AHI	Mean change in AHI from baseline to post-treatment	Change from severe to moderate or mild OSA
AHI success	Percentage of patients achieving success.	Studies may use different definitions of success; the most common definition of AHI success is the Sher criteria	Sher criteria is a decrease in ≥50% AHI and an AHI < 20 Alternative measure of success may be AHI <15, <10, or <5
Oxygen Desaturation Index	Oxygen levels in blood during sleep	The number of times per hour of sleep that the blood oxygen level drops by ≥4 percentage points	More than 5 events per hours

Snoring	10-point visual analog score	Filled out by the bed partner to assess snoring intensity or frequency	There is no standard for goal outcomes. Studies have used 50% decrease in VAS or final VAS of <5 or <3
Epworth Sleepiness Score (ESS)	Scale from 0 to 24	The ESS is a short, self-administered questionnaire that asks patients how likely they are to fall asleep in 8 different situations such as watching TV, sitting quietly in a car, or sitting and talking to someone	An ESS of ≥10 is considered excessively sleepy
Functional outcome of sleep questionnaire	30 questions	Disease-specific quality of life questionnaire that evaluates functional status related to excessive sleepiness	A score of ≥18 is the threshold for normal sleep related functioning a change of ≥2 points is considered to be clinically meaningful improvement
OSA-18	18 item survey graded from 1 to 7	Validated survey to assess quality of life in children	Change score of 0.5 to 0.9 is a small change, 1.0 to 1.4 a moderate change, and 1.5 a large change

The effect of surgical treatment of OSA should be observed on follow-up polysomnography (PSG) that would be performed from weeks to months after the implantable hypoglossal nerve stimulation procedure. Longer term follow-up over 2 years is also needed to determine whether the effects of the procedure are durable or change over time.

Implantable Hypoglossal Nerve Stimulation

Implantable hypoglossal nerve stimulation has been evaluated as way to relieve upper airway obstruction. The hypoglossal nerve stimulation system being evaluated is the Inspire II Upper Airway Stimulation device (Inspire Medical). The Inspire II Upper Airway Stimulation therapy is intended to treat moderate to severe obstructive sleep apnea (OSA). The device is designed for use in patients who are unable or unwilling to use CPAP device. Inspires construction and implantation are similar to those of a pacemaker: a surgeon implants the device containing a neurostimulator subcutaneously in

the patient's chest with one lead attached to the patient's hypoglossal nerve (cranial nerve XII) at the base of the tongue and one lead implanted in the patient's chest. The lead in the chest consists of a pressure sensor that detects breathing. Information about the respiration rate is relayed to the device, which stimulates the hypoglossal nerve in the tongue. When stimulated, the tongue moves forward, thus opening the airway. The patient can operate the device by remote control, which the patient activates before going to sleep. The device turns on after 20 minutes to minimize disrupting the patient's sleep onset; the device is turned off via remote when the patient wakes up.

In 2021, Huntley et.al. compared patients with moderate-severe obstructive sleep apnea (OSA) undergoing traditional single and multilevel sleep surgery to those undergoing upper airway stimulation (UAS). This case control study compared a retrospective cohort of patients undergoing traditional sleep surgery to patients undergoing UAS enrolled in the ADHERE registry. There were 233 patients undergoing prior single or multilevel traditional sleep surgery and meeting study inclusion criteria and were compared to 465 patients from the ADHERE registry who underwent UAS. They compared preoperative and postoperative demographic, quality of life, and polysomnographic data and also evaluated treatment response rates. he pre and postoperative apnea hypopnea index (AHI) was 33.5 and 15 in the traditional sleep surgery group and 32 and 10 in the UAS group. The postoperative AHI in the UAS group was significantly lower. The pre and postoperative Epworth sleepiness scores (ESS) were 12 and 6 in both the traditional sleep surgery and UAS groups. Subgroup analysis evaluated those patients undergoing single level palate and multilevel palate and tongue base traditional sleep surgeries. The UAS group had a significantly lower post-operative AHI than both traditional sleep surgery subgroups. The UAS group had a higher percentage of patients reaching surgical success, defined as a postoperative AHI <20 with a 50% reduction from preoperative severity. The authors concluded UAS offers significantly better control of AHI severity than traditional sleep surgery. Quality life improvements were similar between groups.

In 2020, Thaler et.al. reported on the result of the ADHERE upper airway stimulation registry and predictors of therapy efficacy. The ADHERE Registry is a multicenter prospective observational study following outcomes of upper airway stimulation (UAS) therapy in patients who have failed continuous positive airway pressure therapy for obstructive sleep apnea (OSA). The aim of this registry and purpose of this article were to examine the outcomes of patients receiving UAS for treatment of OSA. Demographic and sleep study data collection occurred at baseline, implantation visit, post-titration (6 months), and final visit (12 months). Patient and physician reported outcomes were also collected. Post hoc univariate and multivariate analysis was used to identify predictors of therapy response, defined as ≥50% decrease in Apnea-Hypopnea Index (AHI) and AHI ≤20 at the 12-month visit. The registry has enrolled 1,017 patients from October 2016 through February 2019. Thus far, 640 patients have completed their 6-month follow-up and 382 have completed the 12-month follow-up. After 12 months, median AHI was reduced from 32.8 (interquartile range [IQR], 23.6-45.0) to 9.5 (IQR, 4.0-18.5); mean, 35.8 ± 15.4 to 14.2 ± 15.0, P < .0001. Epworth Sleepiness Scale was similarly improved from 11.0 (IQR, 7-16) to 7.0 (IQR, 4-11); mean, 11.4 ± 5.6 to 7.2 ± 4.8, P < .0001.

Therapy usage was 5.6 ± 2.1 hours per night after 12 months. In a multivariate model, only female sex and lower baseline body mass index remained as significant predictors of therapy response. The authors concluded across a multi-institutional study, UAS therapy continues to show significant improvement in subjective and objective OSA outcomes. This analysis shows that the therapy effect is durable, and adherence is high.
In 2019, Kent et. al. examined the association of hypoglossal nerve stimulation with obstructive sleep apnea severity, daytime sleepiness, and sleep-related quality of life. Patient-level data were pooled from 3 prospective cohorts and 1 retrospective observational cohort comprising 584 adults with moderate to severe obstructive sleep apnea unable to tolerate or benefit from continuous positive airway pressure. The data were gathered from the Stimulation Therapy for Apnea Reduction Trial; a post-market approval study conducted in Germany; the multicenter, international Adherence and Outcome of Upper Airway Stimulation for OSA Registry; and a retrospective cohort study from 2 sites in the United States. Of the 584 patients included in the study, 472 were men (80.8%); mean (SD) age was 58.5 (11.0) years. Greater improvement in the postoperative AHI was associated with a higher preoperative AHI (-0.74 events/h; 95% CI, -0.82 to -0.67), older patient age (-0.10 events/h; 95% CI, -0.20 to -0.00), and lower body mass index (0.52; 95% CI, 0.22-0.83). After adjusting for these variables and considering all patients in the analysis, the AHI was statistically higher at 12 months than at 6 months (3.24 events/hour: 95% CI, 1.67-4.82 events/hour). The authors concluded hypoglossal nerve stimulation demonstrated clinically significant improvements in obstructive sleep apnea severity, daytime sleepiness, and sleep-related quality of life in this pooled cohort of patient-level results. Age, body mass index, and preoperative AHI appeared to be associated with treatment outcomes, and these variables may explain some of the difference between 2- to 6-month and 12-month outcomes.

Woodson et. al. (2018) conducted a multicenter prospective cohort study to describe the 5- year outcomes of hypoglossal cranial nerve upper airway stimulation for obstructive sleep apnea: the STAR trial. From a cohort of 126 patients, 97 completed protocols, and 71 consented to a voluntary polysomnogram. Those having continuous positive airway pressure failure with moderate to severe OSA, body mass index <32 kg/m^2, and no unfavorable collapse on drug-induced sleep endoscopy were enrolled in a phase 3 trial. Prospective outcomes included apnea-hypopnea index (AHI), oxygen desaturation index, and adverse events, as well as measures of sleepiness, quality of life, and snoring. Patients who did and did not complete the protocol differed in baseline AHI, oxygen desaturation index, and Functional Outcomes of Sleep Questionnaire scores but not in any other demographics or treatment response measures. Improvement in sleepiness (Epworth Sleepiness Scale) and quality of life was observed, with normalization of scores increasing from 33% to 78% and 15% to 67%, respectively. AHI response rate (AHI <20 events per hour and >50% reduction) was 75% (n = 71). When a last observation carried forward analysis was applied, the responder rate was 63% at 5 years. Serious device-related events all related to lead/device adjustments were reported in 6% of patients. The authors concluded, improvements in sleepiness, quality of life, and respiratory outcomes are observed with 5 years of upper airway stimulation (UAS). Serious adverse events are uncommon. UAS is a nonanatomic surgical treatment with long-term benefit for

individuals with moderate to severe OSA who have failed nasal continuous positive airway pressure.

Kompelli et. al. (2018) performed a meta-analysis of available hypoglossal nerve stimulator (HSN) studies investigating treatment of OSA to analyze objective and subjective outcomes and side effects. Studies with objective and subjective endpoints in sleep were included for analysis. Adverse events from trials were also recorded. Across 16 studies, 381 patients were analyzed. At 6 months ($p = 0.008$), mean SAQLI improved by 3.1 (95% CI, 2.6-3.7). At 12 months ($p < 0.0001$), mean AHI was reduced by 21.1 (95% CI, 16.9-25.3), mean ODI was reduced by 15.0 (95% CI, 12.7-17.4), mean ESS was reduced by 5.0 (95%CI, 4.2-5.8), mean FOSQ improved by 3.1 (95% CI, 2.6-3.4). Pain (6.2%:0.7-16.6), tongue abrasion (11.0%:1.2-28.7), and internal (3.0%:0.3-8.4)/external device (5.8%:0.3-17.4) malfunction were common adverse events. The authors concluded, HNS is a safe and effective treatment for CPAP refractory OSA. HNS is associated with high compliance and significantly improves subjective and objective outcomes of sleep. Complications are generally uncommon and benign. Further study comparing HNS to other therapies, such as airway surgery, is required.

In 2019, Yu et.al., performed a retrospective chart review comparing transoral robotic (TORS) surgery versus upper airway stimulation (UAS) in select obstructive sleep apnea patients by a single surgeon between 2011 and 2016. Transoral robotic surgery (TORS) has been used to treat obstructive sleep apnea (OSA) since 2009, with a recent meta-analysis showing an average reduction of apnea-hypopnea index (AHI) from 44.3 to 17.0.

In 2014, upper airway stimulation surgery (UAS) was approved for OSA treatment, with results showing an average AHI reduction from 32.0 to 15.3. Given there was a period when TORS was available and UAS was not, the authors looked at a subset of patients treated with TORS but who could have qualified for UAS and compared their outcomes to patients who received UAS. Inclusion criteria were a body mass index less than 35 and AHI between 20 and 65 consistent with criteria for UAS implantation. Patients who received TORS and met the inclusion criteria had their preoperative drug-induced sleep endoscopy recordings re-evaluated. Patients with anteroposterior retropalatal collapse that would have qualified them for UAS had their outcomes compared to patients who received UAS. Results between TORS and UAS showed an average AHI reduction of 12.7 and 33.3, respectively. Overall cure rate, defined as AHI < 5, was 10.0% and 70.3%, respectively. The authors concluded results of this study indicate that, when met with criteria for both TORS and UAS, patients receiving UAS had greater improvement in several objective measures of OSA.

In 2017, Gillespie et. al. assessed patient- based outcomes of participants in a multi-center prospective cohort study – the STAR trial (Stimulation for Apnea Reduction) 48 months after implantation with an upper airway stimulation system for moderate to severe obstructive sleep apnea. Participants (n=91) at 48 months from a cohort of 126 implanted participants. Patient reported outcomes at 48 months, including Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), and

snoring level were completed with preimplantation baseline. A total of 91 subjects completed the 48- month visit. Daytime sleepiness as measured by ESS was significantly reduced (P=.01) and sleep related quality of life as measured by FOSQ significantly improved (P=.01) when compared with baseline. Soft to no snoring was reported by 85% of bed partners. Two patients required additional surgery without complication for lead malfunction. The authors concluded upper airway stimulation maintained a sustained benefit on patient reported outcomes (ESS, FOSQ, snoring) at 48 months in select patients with moderate to severe obstructive sleep apnea. The limitations are the same as the original study, the lack of control group limits the validity of the results of this study.

Woodson et. al. (2016) conducted a multicenter prospective cohort study to describe the three -year outcomes of hypoglossal cranial nerve upper airway stimulation for obstructive sleep apnea: the STAR trial. The participants were enrolled in a prospective phase III trial evaluating the efficacy of UAS for moderate to severe OSA. Prospective outcomes included apnea-hypopnea index, oxygen desaturation index, other PSG measures, self-reported measures of sleepiness, sleep related quality of life and snoring. Of the 126 participants enrolled 116 completed 36- month follow up evaluation per protocol: 98 participants agreed to a voluntary 36- month PSG. Self-reported daily device usage was 81%. In the PSG group, 74% met the priori definition of success with the primary outcomes of apnea-hypopnea index, reduced from the median value of 28.2 events per hour at baseline to 8.7 and 6.2 at 12 and 36 months. Similarly, self-reported outcomes improved from baseline to 12 months and were maintained at 36 months. Soft or no snoring reported by bed partner increased from 17% at baseline to 80% at 36 months. Serious device related adverse events were rare. The authors concluded this study provides prospective results at 3 years and indicates substantial use and clinical improvement in individuals who have moderate to severe OSA, who have failed conventional therapy, and who met favorable inclusion criteria. There were 3 -year improvements in objective respiratory and subjective quality of life outcome measures that were maintained. Adverse events were uncommon. However, weakness of the current report included a potential selection bias in the group agreeing to have sleep studies and the lack of a control group. The lack of a control group limits the validity of the results of this study.

In 2015, Strollo et. al. evaluated the stability of improvement in polysomnographic measures of sleep disordered breathing, patient reported outcomes, the durability of hypoglossal nerve recruitment and safety at 18 months in the Stimulation Treatment for Apnea Reduction (STAR) trial participants. Prospective multicenter single group trial with participants serving as their own controls. Primary outcome measures were the apnea-hypopnea index (AHI) and the 4% oxygen desaturation index (ODI). Secondary outcome measures were the Epworth Sleepiness Scale (ESS), the Functional Outcomes of Sleep Questionnaire (FOSQ), and oxygen saturation percent time < 90% during sleep. Stimulation level of each participant was collected at three predefined thresholds during awake testing. The median AHI was reduced by 67.4% from baseline of 29.3 to 9.7/h at 18 months. The median ODI was reduced by 67.5% from 25.4 to 8.6/h at 18 months. The FOSQ and ESS improved significantly at 18 months compared to baseline values. The

functional threshold was unchanged from baseline at 18 months. Two participants experienced a serious device related adverse event requiring neurostimulator repositioning and fixation. No tongue weakness was reported at 18months.The authors concluded upper airway stimulation via the hypoglossal nerve maintained a durable effect of improving airway stability during sleep and improved patient reported outcomes (Epworth Sleepiness Scale and Functional Outcomes of Sleep Questionnaire) without an increase of the stimulation thresholds or tongue injury at 18 months of follow-up. The limitations are the same as the original study, the lack of control group limits the validity of the results of this study. This study was funded by Inspire Medical Systems.

Certal et al. (2015) conducted a systematic review of the evidence regarding the efficacy and safety of hypoglossal nerve stimulation as an alternative therapy in the treatment of OSA. Studies were included that evaluated the efficacy of hypoglossal nerve stimulation to treat OSA in adults with outcomes of apnea-hypopnea (AHI), oxygen desaturation index (ODI), and effect on daytime sleepiness (Epworth Sleepiness Scale [ESS]). Tests for heterogeneity and subgroup analysis were performed. A total of six prospective studies with 200 patients were included in this review. At 12 months, the pooled fixed effects analysis demonstrated statistically significant reductions in AHI, ODI, and ESS mean difference of -17.51 (95% CI: -20.69 to -14.34); -13.73 (95% CI: -16.87 to -10.58), and -4.42 (95% CI: -5.39 to -3.44), respectively. Similar significant reductions were observed at 3 and 6 months. Overall, the AHI was reduced between 50% and 57%, and the ODI was reduced between 48% and 52%. Despite using different hypoglossal nerve stimulators in each subgroup analysis, no significant heterogeneity was found in any of the comparisons, suggesting equivalent efficacy regardless of the system in use. The authors reported that further studies comparing hypoglossal nerve stimulation with conventional therapies are needed to definitively evaluate outcomes.

The primary study for this device is the Stimulation Therapy for Apnea Reduction (STAR) trial, Strollo et. al. (2014) evaluated the clinical safety and effectiveness of upper airway stimulation at 12 months for the treatment of moderate to severe obstructive sleep apnea (OSA). Using a multicenter, prospective, single-group, cohort design, an upper airway stimulation device was surgically implanted in patients with obstructive sleep apnea who had difficulty either accepting or adhering to CPAP therapy. The primary outcome measures were the apnea-hypopnea index (AHI; the number of apnea or hypopnea events per hour, with a score of $\geq$ 15 indicating moderate to severe apnea) and the oxygen desaturation index (ODI: the number of times per hour, with a score of $\geq$ 4 percentage points from baseline. Secondary outcome measures were the Epworth Sleepiness Scale, the Functional Outcomes of Sleep Questionnaire (FOSQ), and the percentage of sleep time with the oxygen saturation less than 90%. Consecutive participants with a response were included in a randomized, controlled therapy-withdrawal trial. The study included 126 participants; 83% were men. The mean age was 54.5 years and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 28.4. The median AHI score at 12 months decreased 68% from 29.3 events per hour to 9.0 events per hour ($P<0.001$); the ODI score decreased 70%, from 25.4 events per hour to 7.4 events per hour ($P<0.001$). Secondary outcome

measures showed a reduction in the effects of sleep apnea and improved quality of life. In the randomized phase, the mean AHI score did not differ significantly from the 12-month score in the nonrandomized phase among the 23 participants in the therapy maintenance group (8.9 and 7.2 events per hour, respectively) among the 23 participants in the therapy-withdrawal group (25.8 vs. 7.6 events per hour, P<0.001). The ODI results followed a similar pattern. The rate of procedure related serious adverse events was less than 2%. The authors concluded in this uncontrolled cohort study, upper-airway stimulation led to significant improvements in objective and subjective measurements of the severity of obstructive sleep apnea. This study was funded by Inspire Medical Systems; STAR Clinical Trials NCT01161420. The lack of control group limits the validity of the results of this study.

In a subgroup analysis of the STAR trial, Woodson et. al (2014) assessed the efficacy and durability of the upper airway stimulation via the hypoglossal nerve on obstructive sleep apnea (OSA) severity including objective and subjective clinical outcome measures. The study included a consecutive cohort of 46 responders at 12 months from a prospective phase III trial of 126 implanted participants. Participants were randomized to either therapy maintenance ("ON") group or therapy withdrawal ("OFF") group for a minimum of 1 week. Short-term withdrawal effect as well as durability at 18 months of primary (apnea hypopnea index and oxygen desaturation index) and secondary measures (arousal index, oxygen desaturation metrics, Epworth Sleepiness Scale, Functional Outcomes of Sleep Questionnaire, snoring and blood pressure) were assessed. Both the therapy withdrawal group and the maintenance group demonstrated significant improvements in outcomes at 12 months compar3ed to study baseline. In the randomized assessment, therapy withdrawal group returned to baseline, and therapy maintenance group demonstrated no change. At 18 months with therapy on in both groups, all objective respiratory and subjective outcomes measures showed sustained improvement similar to those observed at 12 months. The authors concluded that withdrawal of therapeutic upper airway stimulation results in worsening of both objective and subjective measures of sleep and breathing, which when resumed results in sustained effect at 18 months. The authors state that reduction of obstructive sleep apnea severity and improvement of quality of life were attributed directly to the effects of the electrical stimulation of the hypoglossal nerve. The author-reported limitations of this study to include selection bias

In a small prospective uncontrolled study, Vanderveken et. al. (2013) evaluated the possible predictive value of drug induced sleep endoscopy (DISE) in assessing therapeutic response to implanted upper airway stimulation (UAS) for obstructive sleep apnea (OSA). The authors reported on the correlation between DISE results and therapy response in 21 OSA patients (apnea-hypopnea index [AHI] 38.5 to 11.8/h; body mass index [BMI] 28.2 kg/m^2; age 55 and 11 y; 20 males and 1 female) who underwent DISE before implantation of a UAS system. Statistical analysis revealed a significantly better outcome with UAS in patients (n=16) without palatal complete concentric collapse (CCC), reducing AHI from 37.6 to 11.4/h at baseline to 11.1 to 12.0/h with UAS (p<0.001). No statistical difference was noted in AHI or BMI at baseline between the patients with and without palatal CCC. In addition, no predictive value was found for the

other DISE collapse patterns documented. The authors concluded based on the results of the reported study, drug induced sleep endoscopy (DISE) can be recommended as a patient selection tool for implanted UAS to treat OSA. Further analysis of predictive value of DISE in assessing therapeutic response to UAS therapy needs to be performed in larger multicenter trials that are currently ongoing. This study was funded by Inspire Medical Systems.

In 2012, Mwenge et. al. studied targeted hypoglossal neurostimulation (THN) therapy with the aura6000 System. The primary objective was to improve the polysomnographically determined apnea/hypopnea index (AHI) at 3 months and maintain the improvement after 12 months of treatment. Thirteen out of fourteen operated patients were successfully implanted. At 12 months, AHI decreased from 45 to 18 to 21 to 17, a 53% reduction ($p<0.001$). The 4% oxygen desaturation index fell from 29 to 20 to 15 to 16 and the arousal index from 37 to 13 to 25 to 14, both $p<0.001$. The Epworth Sleepiness Scale decreased from 11 to 7 to 8 to 4 ($p=0.09$). THN was neither painful nor awakened patients, who all complied with therapy. There were two transient tongue paresis. The authors concluded that THN is safe and effective to treat OSA in patients not compliant with CPAP. The small sample size and lack of a control group compromises the validity of the results of this study.

In a prospective uncontrolled study, Van de Heyning et. al. (2012) examined the safety and preliminary effectiveness of a second-generation device, the Upper Airway Stimulation (UAS) system, and identified baseline predictors for therapy success. UAS systems were implanted in patients with moderate to severe OSA who failed or were intolerant of continuous positive airway pressure (CPAP). The study was conducted in 2 parts. In part 1, patients were enrolled with broad selection criteria. Apnea hypopnea index (AHI) was collected using laboratory-based polysomnography at pre-implant and post-implant visits. Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ) were also collected. In part 2, patients were enrolled using selection criteria derived with the experience in part 1. In part 1, 20 of 22 enrolled patients (two exited the study) were examined for factors predictive of therapy response. Responders had both a body mass index $\leq$ 32 and AHI $\leq$ 50 and did not have complete concentric palatal collapse. Part 2 patients (n=8) were selected using responder criteria and showed an improvement on AHI from baseline, from 38.9 to 9.8 to 10.0 to 11.0 at 6 months post-implant. Both ESS and FOSQ improved significantly in part 1 and 2 subjects. According to the authors, the study demonstrated that therapy with upper airway stimulation is safe and efficacious is a select group of patients with moderate to severe OSA who cannot or will not use CPAP as primary treatment. Limitations of this study included lack of control group and small sample size. The investigators acknowledge that the different implantation techniques and eligibility criteria in the 2 parts of the study hampered interpretation of the study results. The study was funded by Inspire Medical Systems.

Clinical Input

In 2018, BlueCross BlueShield Association (BCBSA) obtained clinical input regarding the published evidence regarding hypoglossal nerve stimulation (HNS) for the treatment of obstructive sleep apnea (OSA). The clinical input indicates that hypoglossal nerve stimulation (HNS) leads to meaningful improvement in net health outcomes in appropriately selected adult patients with a favorable pattern of non-concentric palatal collapse. The alternative treatment for this anatomical endotype is maxilla-mandibular advancement (MMA), which is associated with greater morbidity and lower patient acceptance than hypoglossal nerve stimulation (HNS). The improvement in AHI (apnea-hypopnea index) with HNS, as shown in the STAR trial, is similar to the improvement in AHI following MMA. Clinical input also supports that HNS results in a meaningful improvement in health outcomes in appropriately selected adolescents with OSA and Down's syndrome who have difficulty in using CPAP (age 10 to 21 years with prior T&A; BMI < 95th percentile; severe OSA with AHI between 10 and 50 (< 25% central events); unable to tolerate CPAP or tracheostomy dependent at night; and need for future head MRI). The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes based on information from clinical study populations, clinical expert opinion and the FDA approval for the Inspire II Upper Airway Stimulation device.

In 2017, Diercks et. al. conducted a case series of 6 adolescents with Down's Syndrome (DS) to determine whether hypoglossal nerve stimulation is safe and effective in children with DS with moderate to severe obstructive sleep apnea (OSA). Obstructive sleep apnea (OSA) affects up to 60% of children with Down Syndrome (DS) and may persist in half of patients after adenotonsillectomy. Children with DS who have persistent OSA often do not tolerate treatment with positive pressure airway support devices or tracheotomy for their residual moderate to severe OSA. The hypoglossal nerve stimulator is an implantable device that delivers an electrical impulse to anterior branches of the hypoglossal nerve in response to respiratory variation, resulting in tongue base protrusion that alleviates upper airway obstruction in adults. Participants were 6 children and adolescents (12-18 years) with DS and severe OSA (apnea hypopnea index [AHI] > 10 events/hour) despite prior adenotonsillectomy. The Inspire hypoglossal nerve stimulator was implanted. Patients were monitored for adverse events. Adherence to therapy was measured by hours of use recorded by the device. Efficacy was evaluated by comparing AHI and OSA-18, a validated quality-of-life instrument, scores at baseline and follow-up. In 6 patients (4 male, 2 females; aged 12-18 years), hypoglossal nerve stimulator therapy was well tolerated (mean use, 5.6-10.0 hours/night) and effective, resulting in significant improvement in OSA. At 6 to 12-month follow-up, patients demonstrated a 56% to 85% reduction in AHI, with an overall AHI of less than 5 events/hour in 4 children and less than 10 events/hour in 2 children. Children also demonstrated a clinically significant improvement (mean [SD] overall change score, 1.5 [0.6]; range, 0.9-2.3) on the OSA-18, a validated quality-of-life instrument. Limitations related to this study, in patients who completed 1 year pilot study, voltage settings were relatively stable; however, a further

long- term study is needed to determine whether effectiveness, particularly through other measures of gas exchange, and stimulation parameters remain stable over a longer period in this patient population. For this pilot study older children and adolescents for implantation were chosen due to concern about the size of the impulse generator device, as well as the potential for growth during puberty to displace the device's stimulation and sensing leads. In addition, the battery of the impulse generator will need to be replaced approximately every 10 years due to limitations in battery capacity, which raises additional safety concerns. The ideal age for implantation in the pediatric population has not been established. Additionally, it remains unclear whether hypoglossal nerve stimulation may represent a treatment option for pediatric patients without DS who demonstrate persistent OSA after T&A. The risks and benefits of implantation, as well as long-term follow-up, will need to be considered as more data are collected on initial pediatric implant recipients. The authors concluded hypoglossal nerve stimulation was well tolerated and effective in the study population, representing a potential therapeutic option for patients with DS and refractory OSA after adenotonsillectomy who are unable to tolerate positive pressure airway devices.

In 2020, Caloway et. al., in a case series evaluated hypoglossal nerve stimulation (HNS) in children with Down Syndrome (DS). The efficacy and safety in children with Down Syndrome (DS), was previously reported in a preliminary case series of six adolescents. Twenty nonobese children and adolescents (aged 10-21 years) with DS and severe OSA (apnea-hypopnea index [AHI] >10 and <50 events/hour) despite prior adenotonsillectomy were enrolled. Participants had failed a trial of continuous positive airway pressure (CPAP) therapy and underwent sleep endoscopy confirming surgical candidacy. The primary outcome was to assess safety and monitor for adverse events. Secondary outcomes included efficacy in reducing AHI (% reduction in AHI), adherence to therapy, and change in a validated quality-of-life instrument, the OSA-18 survey. All 20 children (median age = 16.0 years [interquartile range = 13-17 years], 13 male) were implanted with no long-term complications. We report two interval adverse events, both of which were corrected with revision surgery. Twenty participants completed the 2-month polysomnogram, with median percent reduction in titration AHI of 85% (interquartile range = 75%-92%). The median nightly usage for these children was 9.21 hours/night. There was a median change in the OSA-18 score of 1.15, indicating a moderate, yet significant, clinical change. The authors concluded HGN stimulation was safe and effective in the study population. Two minor surgical complications were corrected surgically. Overall, these data suggest that pediatric HGN stimulation appears to be a safe and effective therapy for children with DS and refractory severe OSA.

A study in a larger population of children with Down Syndrome (DS) is ongoing (NCT02344108).

Summary of Evidence

For individuals who have obstructive sleep apnea (OSA) who receive hypoglossal nerve stimulation (HNS), the evidence includes case series and a multicenter, prospective, single-group, cohort design study (STAR) of 126 participants that were surgically implanted with an upper airway stimulation device with obstructive sleep apnea who had

difficulty either accepting or adhering to CPAP therapy and were followed for 5 years. Hypoglossal nerve stimulation (HNS) has shown improved outcomes in this single arm study when used in a very select group of patients. For the patients that met the inclusion criteria for AHI, BMI and favorable pattern for palatal collapse about two-thirds met the study definition of success. Woodson et. al. (2018) conducted a multicenter prospective cohort study to describe the 5- year outcomes of hypoglossal cranial nerve upper airway stimulation for obstructive sleep apnea: the STAR trial. When the last observation carried forward analysis was applied, the responder rate was 63% at 5 years. Serious device-related events all related to lead/device adjustments were reported in 6% of patients. The authors concluded, improvements in sleepiness, quality of life (QOL) and respiratory outcomes were observed with 5 years of upper airway stimulation (UAS). Upper airway stimulation is a nonanatomic surgical treatment with long-term benefit for individuals with moderate to severe OSA who have failed continuous positive airway pressure. In 2018, BlueCross BlueShield Association (BCBSA) obtained clinical input regarding the published evidence regarding hypoglossal nerve stimulation for the treatment of obstructive sleep apnea (OSA). The clinical input indicates that hypoglossal nerve stimulation (HNS) leads to meaningful improvement in net health outcomes in appropriately selected patients with a favorable pattern of non-concentric palatal collapse. Clinical input also supports that HNS results in a meaningful improvement in net health outcomes in appropriately selected adolescents with OSA and Down's syndrome with a prior T&A, who have difficulty in using CPAP. The evidence includes a safety study with 20 patients who were treated at tertiary care centers. The success rate was 70% with 2 adverse events of the leads, which were resolved with further surgery. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes for patients meeting the policy criteria below which is based on information from clinical study populations, clinical expert opinion, and the FDA approval for the Inspire II Upper Airway Stimulation device. All other indications would be considered investigational as the safety and efficacy for all other indications has not been established in the peer reviewed medical literature. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Practice Guidelines and Position Statements

American Academy of Otolaryngology Head and Neck Surgery
In 2019, the American Academy of Otolaryngology Head and Neck Surgery updated the position statement on hypoglossal nerve stimulation for treatment of obstructive sleep apnea (OSA) which states "The American Academy of Otolaryngology Head and Neck Surgery considers upper airway stimulation (UAS) via the hypoglossal nerve for the treatment of adult obstructive sleep apnea syndrome to be an effective second-line treatment of moderate to severe obstructive sleep apnea in patient who are intolerant or unable to achieve benefit with positive pressure therapy (PAP)."

National Institute for Health and Clinical Excellence (NICE)
In 2017, National Institute for Health and Clinical Excellence (NICE) issued an interventional procedure guidance (IPG598) which states: "Current evidence on the

safety and efficacy of hypoglossal nerve stimulation for moderate to severe obstructive sleep apnea is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit for research."

Regulatory Status
In May 2014, The Inspire II Upper Airway Stimulator (Inspire Medical Systems, Inc, Maple Grove, MN) received FDA approval. The device is used to treat a subset of patients with moderate to severe obstructive sleep apnea (OSA) (apnea hypopnea index (AHI) of greater or equal to 20 and less than or equal to 65). Inspire Upper Airway System is used in adult patients 22 years of age and older who have confirmed to fail or cannot tolerate positive airway pressure (PAP) treatments (such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BPAP) machines) and who do not have a complete concentric collapse of the soft palate level. PAP failure is defined as an inability to eliminate OSA (AHI of greater than 20 despite PAP usage) and PAP tolerance is defined as 1) inability to use PAP (greater than 5 nights per week of usage; usage defined as greater than 4 hours of use per night); or 2) unwillingness to use PAP (for example, a patient returns the PAP system after attempting to use it).

The Inspire Upper Airway Stimulator is contraindicated for:

- Central + mixed apneas greater than 25% of the total AHI
- Any anatomical finding that would affect the performance of upper airway stimulation, such as the presence of complete concentric collapse of the soft palate
- Any condition or procedure that would affect neurological control of the upper airway
- Patients who are unable or do not have the necessary assistance to operate the sleep remote
- Patients who are pregnant or plan to become pregnant
- Patients who will require magnetic resonance imaging (MRI)
- Patients with an implantable device that may have unintended interactions with the Inspire system

PRIOR APPROVAL

Not applicable.

POLICY

Implantable hypoglossal nerve stimulation may be considered **medically necessary** in an adult individual with moderate to severe obstructive sleep apnea (OSA) when **ALL** of the following criteria are met:

- 22 years of age or older; **AND**
- Body mass index (BMI) $\leq$ 34 kg/m^2; **AND**
- A polysomnography (PSG) (sleep study) is performed within 24 months of first consultation for the inspire implant; **AND**

- The individual has predominately obstructive events defined as:
    - Central and mixed apneas less than 25% of total AHI (apnea-hypopnea index) and apnea-hypopnea index (AHI) is $\geq$ 15 to 65 events per hour; **AND**
- The individual has a minimum of one month of PAP monitoring documentation that demonstrates PAP failure defined as at least one of the following:
    - AHI greater than 15 despite regular PAP usage; **OR**
    - PAP therapy intolerance, defined as less than 4 hours per night, 5 nights per week; **OR**
    - A documented unwillingness to use PAP therapy; **AND**
- Absence of complete concentric collapse at the soft palate level as seen on a drug-induced sleep endoscopy (DISE) procedure; **AND**
- No other anatomical findings that would compromise performance of the device (e.g., tonsil size 3 or 4 per tonsillar hypertrophy grading scale).

Implantable hypoglossal nerve stimulation may be considered **medically necessary** in adolescents or young adults with Down Syndrome (DS) with moderate to severe obstructive sleep apnea (OSA) when **ALL** of the following criteria are met:

- 10 through 21 years of age; **AND**
- Body mass index (BMI) < 95th percentile ages 10 through 17; **OR**
- Body mass index (BMI) $\leq$ 35 kg/m^2 age 18 through 21; **AND**
- A polysomnography (PSG) (sleep study) is performed within 24 months of first consultation of the inspire implant; **AND**
- The individual has predominately obstructive events after a prior adenotonsillectomy defined as:
    - Central and mixed apneas less than 25% of total AHI (apnea-hypopnea index); **AND** one of the following:
        - AHI 5 or greater for ages 10 through 17; **OR**
        - AHI $\geq$ 15 to 65 events per hour age 18 through 21; **AND**
- The individual has a tracheotomy or has a minimum of one month of PAP monitoring documentation that demonstrates PAP failure, defined as at least one of the following:
    - Noncompliance; **OR**
    - Discomfort; **OR**
    - Undesirable side effects; **OR**
    - Persistent symptoms despite compliant use; **OR**
    - A documented unwillingness or refusal to use PAP therapy; **OR**
- The patient has absence of complete concentric collapse at the soft palate level as seen on a drug-induced sleep endoscopy (DISE) procedure.

A replacement or revision of an implantable hypoglossal nerve stimulation (generator, leads and/or battery) may be considered **medically necessary** for an individual who meets **ALL** of the above criteria, and the existing device is no longer under warranty and cannot be repaired.

Implantable hypoglossal nerve stimulation not meeting the above criteria would be considered **not medically necessary**.

Implantable hypoglossal nerve stimulation **is** considered **investigational** for all other indications as the safety and efficacy for all other indications has not been established in the peer reviewed medical literature. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Policy Guidelines

Drug Induced Sleep Endoscopy (DISE)
Drug-induced sleep endoscopy (DISE) replicates sleep with an infusion of propofol. DISE will suggest either a flat, anterior-posterior collapse or complete circumferential oropharyngeal collapse. Concentric collapse decreases the success of hypoglossal nerve stimulation and is an exclusion criterion from the U.S. Food and Drug Administration.

Terminology and Definitions for Obstructive Sleep Apnea (OSA)

Terms	**Definitions**
Respiratory Event	
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 4% arterial oxygen desaturation or an arousal. Hypopneas in children are scored by a ≥50% drop in nasal pressure and either a ≥3% decrease in oxygen saturation or an associated arousal
RERA	Respiratory event-related arousal is defined as an event lasting at least 10 seconds associated with flattening of the nasal pressure waveform and/or evidence of increasing respiratory effort, terminating in an arousal but not

	otherwise meeting criteria for apnea or hypopnea
Respiratory Event Reporting	
Apnea/Hypopnea Index (AHI)	The average number of apneas or hypopneas per hour of sleep
Respiratory Disturbance Index (RDI)	The respiratory disturbance index is the number of apneas, hypopneas, or respiratory event-related arousals per hour of sleep time. RDI is often used synonymously with the AHI
Respiratory Event Index (REI)	The respiratory event index is the number of events per hour of monitoring time. Used as an alternative to AHI or RDI in home sleep studies when actual sleep time from EEG is not available
Diagnosis	
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	AHI of 15 to < 30. Children: AHI of > 5 to 10
Severe OSA	Adults: AHI ≥30. Children: AHI of >10
Treatment	
Positive airway pressure (PAP)	Positive airway pressure may be continuous (CPAP) or auto-adjusting (APAP) or Bi-level (Bi-PAP).
Pap Failure	Usually defined as an AHI greater than 20 events per hour while using PAP
Pap Intolerance	PAP 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

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 64568 Open implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator

- 64582 Open implantation of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electode array
- 64583 Revision or replacement of hypoglossal nerve neurostimulator array and distal respiratory sensor electrode or electrode array, including connection to existing pulse generator
- 64584 Removal of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electrode array
- C1767 Generator neurostimulator (implantable) non-rechargeable
- C1778 Lead, neurostimulator
- C1787 Patient programmer, neurostimulator
- C1816 Receiver and/or transmitter neurostimulator (implantable)
- C1820 Generator, neurostimulator (implantable), non-high frequency with rechargeable battery and charging system
- C1822 Generator, neurostimulator (implantable), high frequency with rechargeable battery and charging system
- C1897 Lead neurostimulator test kit (implantable)
- L8679 Implantable neurostimulator pulse generator any type
- L8680 Implantable neurostimulator electrode, each
- L8681 Patient programmer (external) for use with implantable programmable neurostimulator pulse generator
- L8682 Implantable neurostimulator radiofrequency receiver
- L8683 Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
- L8685 Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
- L8686 Implantable neurostimulator pulse generator, single array, nonrechargeable includes extension
- L8687 Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
- L8688 Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension
- L8689 External recharging system for battery (internal) for use with implantable neurostimulator, replacement only
- 95970 Electronic analysis of implanted neurostimulation pulse generator system/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycle, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter without programming
- 95976 Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and

passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional

- 95977 Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex cranial nerve neurostimulator pulse generator/transmitter programming by Yuphysician or other qualified health care professional

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POLICY HISTORY

Date	Reason	Action
April 2022	Annual Review	Policy Revised
April 2021	Annual Review	Policy Revised
April 2020	Annual Review	Policy Revised
April 2019	Annual Review	Policy Renewed
January 2019	Interim Review	Policy Revised
April 2018	Annual Review	Policy Revised
April 2017	Annual Review	Policy Revised
April 2016	Annual Review	Policy Revised
May 2015		New Policy Created

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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