https://doi.org/10.5664/jcsm.9542

JCSM | Journal of Clinical Sleep Medicine

SPECIAL ARTICLES

Improving outcomes of hypoglossal nerve stimulation therapy: current practice, future directions, and research gaps. Proceedings of the 2019 International Sleep Surgery Society Research Forum

Maria V. Suurna, MD[1]; Ofer Jacobowitz, MD, PhD[2]; Jolie Chang, MD[3]; Ioannis Koutsourelakis, MD[4]; David Smith, MD, PhD[5,6]; Uri Alkan, MD[7]; Mark D'Agostino, MD[8]; Maurits Boon, MD[9]; Clemens Heiser, MD[10]; Paul Hoff, MD[11]; Colin Huntley, MD[9]; David Kent, MD[12]; Alan Kominsky, MD[13]; Richard Lewis, MD[14]; Joachim T. Maurer, MD[15]; Madeline J. Ravesloot, MD[16]; Ryan Soose, MD[17]; Armin Steffen, MD[18]; Edward M. Weaver, MD[19]; Amy M. Williams, PhD[20]; Tucker Woodson, MD[21]; Kathleen Yaremchuk, MD[20]; Stacey L. Ishman, MD[5,6]

[1]Division of Sleep Surgery, Department of Otolaryngology–Head and Neck Surgery, Weill Cornell Medicine/New York Presbyterian Hospital, New York, New York; [2]ENT and Allergy Associates, New York, New York; [3]Division of Sleep Surgery, Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco, California; [4]Mideterraneo Hospital, Athens, Greece; [5]Divisions of Pediatric Otolaryngology, Pulmonary Medicine, and the Sleep Center, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [6]Department of Otolaryngology–Head and Neck Surgery of University of Cincinnati College of Medicine, Cincinnati, Ohio; [7]Department of Otorhinolaryngology, Head and Neck Surgery, Rabin Medical Center, Beilinson Hospital, Petach Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [8]Southern New England Ear, Nose, Throat and Facial Plastic Surgery Group and Middlesex Hospital, Middletown, Connecticut; [9]Otolaryngology–Head and Neck Surgery, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; [10]Department of Otorhinolaryngology, Head and Neck Surgery, Technische Universität München, Munich, Germany; [11]Department of Otolaryngology, University of Michigan, Ann Arbor, Michigan; [12]Department of Otolaryngology, Vanderbilt University Medical Center, Nashville, Tennessee; [13]Head and Neck Institute, Cleveland Clinic, Cleveland, Ohio; [14]Perth Head and Neck Surgery, Hollywood Medical Centre, Nedlands, Australia; [15]Division of Sleep Medicine, Department of Otorhinolaryngology, Head and Neck Surgery, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [16]Department of Ear, Nose and Throat, OLVG, Amsterdam, Netherlands; [17]Division of Sleep Surgery, Department of Otolaryngology, Pittsburgh School of Medicine, UPMC Mercy, University of Pittsburgh, Pittsburgh, Pennsylvania; [18]Department of Otorhinolaryngology, University of Lübeck, Lübeck, Germany; [19]Department of Otolaryngology–Head and Neck Surgery, University of Washington, Surgery Service, Seattle Veterans Affairs Medical Center; Harborview Medical Center, Seattle, Washington; [20]Department of Otolaryngology–Head and Neck Surgery of Henry Ford Health System, Detroit, Michigan; [21]Division of Sleep Medicine and Sleep Surgery, Department of Otolaryngology and Human Communication of Medical College of Wisconsin, Milwaukee, Wisconsin

Hypoglossal nerve stimulation (HGNS) has evolved as a novel and effective therapy for patients with moderate-to-severe obstructive sleep apnea. Despite positive published outcomes of HGNS, there exist uncertainties regarding proper patient selection, surgical technique, and the reporting of outcomes and individual factors that impact therapy effectiveness. According to current guidelines, this therapy is indicated for select patients, and recommendations are based on the Stimulation Therapy for Apnea Reduction or STAR trial. Ongoing research and physician experiences continuously improve methods to optimize the therapy. An understanding of the way in which airway anatomy, obstructive sleep apnea phenotypes, individual health status, psychological conditions, and comorbid sleep disorders influence the effectiveness of HGNS is essential to improve outcomes and expand therapy indications. This article presents discussions on current evidence, future directions, and research gaps for HGNS therapy from the 10th International Surgical Sleep Society expert research panel.

Keywords: hypoglossal nerve stimulation, OSA, neurostimulation, OSA treatment, upper airway stimulation, sleep surgery outcomes, upper airway surgery, sleep apnea

Citation: Suurna MV, Jacobowitz O, Chang J, et al. Improving outcomes of hypoglossal nerve stimulation therapy: current practice, future directions and research gaps. Proceedings of the 2019 International Sleep Surgery Society Research Forum. *J Clin Sleep Med*. 2021;17(12):2477–2487.

INTRODUCTION

Implantable hypoglossal nerve stimulation (HGNS) has emerged as an effective treatment to increase the patency of the upper airway during sleep for patients with moderate-to-severe obstructive sleep apnea (OSA) who are intolerant to positive airway pressure (PAP) therapy. In the Stimulation Therapy for Apnea Reduction (STAR) trial, HGNS use resulted in substantial reductions in the apnea-hypopnea index (AHI) and in the number of oxygen desaturations, as well as improvements in sleep quality.[1] These results have proven to be reproducible across centers and stable over time.[2,3] Currently, the only commercially available HGNS system available in the United States (Inspire Medical, Minneapolis, MN) consists of an implanted electrical stimulation cuff placed around the hypoglossal nerve (HGN), an implanted pulse generator in the infraclavicular space, and an implanted sensor lead in the intercostal space. The implanted pulse generator delivers electrical stimulation to the select HGN fibers within the cuff, which is coordinated with respiration as detected by the sensor lead. This results in activation of the tongue muscles and opening of the upper airway.[4,5] As the use of this therapy expands, questions arise pertaining to therapy effectiveness, patient selection, and health benefits outcomes. Several expert research panels were invited to

discuss current evidence, future therapy directions, and research gaps at the 10th International Surgical Sleep Society held on May 9–11, 2019 in New York City. The panelists were the meeting participants who have established expertise and published on hypoglossal nerve stimulation therapy. These panels focused on 3 main topics: (1) current evidence for HGNS therapy for OSA, (2) anatomic and clinical considerations for HGNS therapy optimization, and (3) Individual Factors in the Management of HGNS. This article summarizes those presentations and discussions.

CURRENT EVIDENCE FOR HGNS THERAPY FOR OSA

Defining outcome measures

Treatment outcomes for OSA include health outcomes, treatment adherence (where applicable), patient-reported outcomes, and adverse effects. This is true for HGNS therapy as well as for other standard treatments.

Health outcomes include hypertension, cardiovascular disease, and mortality, among others.[6] Because measurement of most long-term health outcomes is not practical in clinical practice, short-term surrogate measures of health outcomes are typically used to follow patients and for outcomes assessment. Sleep study measures are an example of a health outcome surrogate, with the apnea-hypopnea index most commonly reported; however, this measure is replete with challenges.[7–9] Results of all night therapy measured by full night polysomnography or home sleep apnea test utilizing 4% hypopnea scoring criteria are currently recommended to assess treatment outcomes. Alternatively, the apnea index, oxygen desaturation index, and hypoxemic burden are metrics that can be more reliably measured and are important to long-term health.[9–12]

While treatment effect is more important than an arbitrary cutoff for success,[13] clinical epidemiological precedent[12] suggests that a 50% decrease in the 4% oxygen desaturation index may serve as 1 success criterion. In order to assess real-world treatment effectiveness (rather than in-lab efficacy alone), treatment adherence must be accounted for in any measure that is taken only when using the treatment.[14,15] Furthermore, the sleep study outcome must be measured at the prescribed setting for an entire night rather than extracting selected data obtained during a titration study.

Patient-reported outcomes include symptoms, daily function, quality of life and productivity. Moreover, assessing changes in a patient's chief concern is paramount, and the definition of success for each patient should incorporate meaningful improvement in that patient's chief concern. However, this is a variable definition of success that hinders comparison across studies or patients, and sleep testing surrogate measures do not correlate with patient-reported outcomes.[16] Thus, patient-reported outcomes should be measured directly, preferably with validated, reliable, and responsive instruments when available. Well established instruments include snoring scales, the Epworth Sleepiness Scale (sleep propensity), the Functional Outcomes of Sleep Questionnaire (function), and the Symptoms of Nocturnal Obstruction and Related Events (SNORE-25) instrument (quality of life), where measurement of treatment effect is preferred to a binary definition of success.[13]

Adverse effects are specific to each treatment and patient and should be included in any assessment of individual and cohort therapy outcomes.

HGNS candidacy

HGNS implantation was approved by the US Food and Drug Administration (FDA) in 2014. The criteria put forth were largely based on the previously mentioned STAR Trial.[1] The FDA criteria are based on both physical parameters and on the results of drug-induced sleep endoscopy (DISE) (**Table 1**).

As with any surgical intervention for OSA, HGNS is a second-line therapy for those patients who have failed PAP. Though the first-generation Inspire HGNS device on the market was not magnetic resonance imaging-compatible, the second-generation device is conditionally approved for magnetic resonance imaging scans of the head and extremities with a 1.5-Tesla magnet.

Effectiveness of the HGNS beyond the FDA indications is unclear. For example, the presence of palatal complete concentric collapse (CCC) is currently a contraindication to implantation; however, the number of patients who were implanted during the preapproval stage with palatal CCC on DISE was very small.[17] This is an opportunity for investigation. Implantation and treatment of patients with an AHI > 65 events/h is another area where further evidence is needed. This is especially true if we assume that there is a relationship between AHI and comorbidities, in which case any reduction in AHI would be beneficial, and significant reduction of the AHI may be an acceptable goal, particularly when other treatment options are not tolerated (ie, PAP). Likewise, body mass index (BMI) is not a strict criterion. A BMI of <32 kg/m^2 is recommended by the FDA, whereas a BMI of 35 kg/m^2 is the recommended limit in Europe. Sarber et al[18] published results of a small series of patients with BMI >32 kg/m^2 and promising outcomes.

Neuroanatomy

The anatomy of the human tongue and its innervating nerve fibers is very complex, and understanding it is essential for successful surgical implantation of the HGNS system. Electrode cuff placement on the proper distal branches of the HGN plays

Table 1—FDA criteria for hypoglossal nerve stimulation implant.

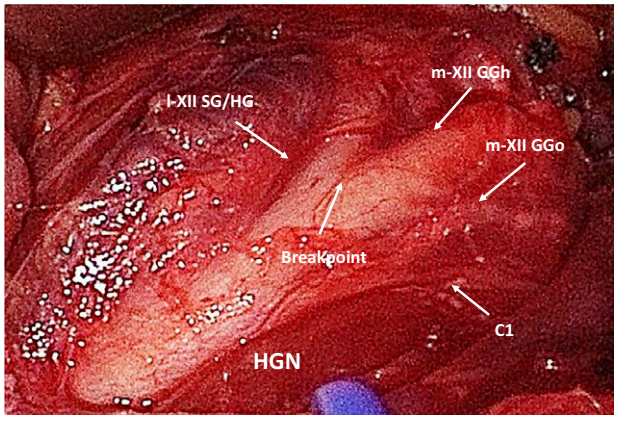
Parameter	HGNS Criteria
Age	18 years or older
AHI	15–65 events/h
BMI	< 32 kg/m^2
Central apneas	< 25% of total events
DISE findings	No palatal complete concentric collapse
Failed continuous PAP use	Yes

AHI = apnea-hypopnea index, BMI = body mass index, DISE = drug-induced sleep endoscopy, FDA = Food and Drug Administration, HGNS= hypoglossal nerve stimulation, PAP = positive airway pressure.

a crucial role in optimizing the clinical outcome.[19] The genioglossus (GG) and geniohyoid (GH) muscles are the main airway dilators, while the hyoglossus and styloglossus muscles cause tongue retrusion. Therefore, identification of the breakpoint between the medial and lateral branches of the HGN and proper placement of the cuff around the protrusor and intrinsic muscle nerve branches is essential[20] (**Figure 1**). The aim of the stimulation is to achieve an "unhindered protrusion of the stiffened tongue" and to additionally attain the opening of the soft palate by the palatoglossus coupling, a muscle which runs in the anterior pillar of the soft palate into the side of the tongue.[21] The intraoperative nerve integrity monitoring can help to identify and differentiate HGN branches; however, it does not always allow for clear identification of all individual branches. Electromyography needles are inserted directly into GG and Styloglossus (SG)/Hyoglossus (HG) muscles to measure responses to nerve branch stimulation. It is important to not just rely on the quantity of the electromyography signal channels but to also focus on the quality of the signal. Therefore, intraoperative analysis of the electromyography wave signal is essential. Other additional techniques, such as muscle contraction during stimulation, tongue movement during intraoperative testing, and knowledge of the anatomy of the HGN are needed to identify the boundary between branches to the transverse/vertical intrinsic tongue muscles and the final hyoglossus muscle branch, which needs to be excluded.[20]

The first cervical nerve (C1), which innervates the GH muscle, plays an important role in opening the pharynx during sleep. This muscle moves the hyoid bone forward superiorly and anteriorly during contraction.[22] Activity of the GH combined with the GG reduces the resistance of the upper airway.[22,23] In 1 clinical trial the effect of C1 on the tongue movement and clinical outcomes investigated with ultrasound were analyzed. The study found that active or passive activation of the GH can be easily detected with ultrasound.[21] It has been shown that patients with obstructions at the level of the epiglottis particularly benefit from the inclusion of C1 in the cuff.[24] In one third of the cases it is difficult to detect the C1 branch during surgery due to its highly variable anatomic patterns,[20] or when the nerve has a sharp takeoff and needs to be transposed to be included in the electrode cuff.[25] C1 seems to play a crucial role in the opening of the lower pharynx during HGNS, and its inclusion in the electrode cuff is important when possible. Further research is needed to understand in which patients C1 stimulation plays a key role in treatment outcome.

Figure 1—Intraoperative HGN anatomy.



Lateral division styloglossus/hyoglossus (l-XII SG/HG), medial division genioglossus horizontal (m-XII GGh) and genioglossus oblique (m-XII GGo), cervical nerve 1 (C1), breakpoint between lateral and medial divisions. HGN = hypoglossal nerve.

Implant titration and programming

Postimplant therapy management will play an increasingly important role in the successful longitudinal care of HGNS patients, particularly as this treatment modality gains acceptance and begins to be used more widely around the world. Although many HGNS patients are either straightforward therapy responders or distinct nonresponders, there is a substantial population subset with suboptimal clinical response and outcomes but without the indications of clear nonresponders. This patient profile is similar to that reported with PAP or other medical device treatments. Some patients achieve adequate AHI reduction and symptomatic response but struggle with inadequate adherence or comfort with therapy. Other patients demonstrate excellent therapy adherence but fail to achieve adequate disease control with residual AHI elevation and/or OSA-related symptoms.

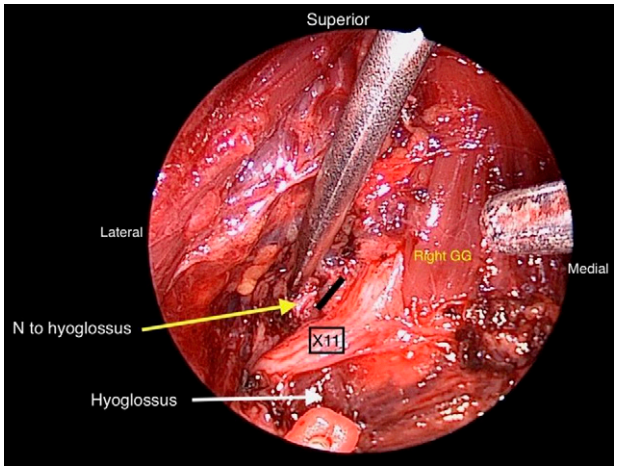
Advanced electrical programming (eg, amplitude, pulse width, rate, electrode configuration) can be systematically analyzed and modified in the outpatient setting, with or without concurrent upper airway endoscopy, to improve long-term outcomes. As clinically indicated, the addition of positional therapy, weight management, lowering of nasal resistance, mandibular repositioning, upper airway surgery, and other adjunctive measures may also provide an opportunity to further strengthen HGNS outcomes. Thus, for HGNS patients with partial but incomplete response, a standardized best-practice approach to therapy troubleshooting and modifications could make a significant difference in long-term outcomes.

Bilateral neurostimulation

Bilateral simulation of the hypoglossal nerve could potentially provide enhanced stimulation of the airway during sleep, compared to unilateral stimulation. Therefore, this is an area being actively studied in human trials.

The bilateral nerve implant is a system with bipolar electrodes inserted on both HGNs via a submental incision. Each bipolar electrode is placed over the hypoglossal nerve immediately prior to the insertion of the terminal branches into the GG muscle (**Figure 2**). Intraoperative nerve monitoring of both the GG and SG/HG is performed to ensure optimal placement of the device. Energy is delivered to the device via an activation chip attached to a disposable adhesive patch that is placed beneath the chin in the midline of the neck. The chip is programmed via a Bluetooth connection during an overnight polysomnography in the lab. The stimulation is not timed with the respiratory cycle, but instead operates on a regular duty cycle. Clinical experience has shown that the duty cycle stimulation effectively covers most of the

Figure 2—Intraoperative nerve anatomy for bilateral nerve implantation showing the view of the right side.



Cranial nerve XII, genioglossus (GG) muscle.

respiratory cycle. Three parameters can be titrated to optimize the clinical effect: (1) the length of the stimulus train, (2) the amplitude of the stimulation, and (3) the pulse frequency of the individual pulses making up each stimulus train.

The first clinical trial (BiLAteral Hypoglossal Nerve Stimulation for Treatment of Obstructive Sleep Apnoea (BLAST OSA); ClinicalTrials.gov: NCT03048604) was a safety and efficacy trial of 27 patients. Patients treated per protocol experienced a mean decrease in AHI from 22 to 11 events/h. The mean per protocol decrease in oxygen desaturation index was 18 to 8 events/h. The Epworth Sleepiness Score decreased from a mean of 11 to 8, and scores for the Functional Outcomes of Sleep Questionnaire increased from 15.3 to 17.2. The apnea index, hypopnea index, arousal index, and time spent with a $SaO_2 < 90\%$ significantly decreased (all $P < .05$).[26] Based on these results, a new larger trial (BilatEral Hypoglossal Nerve StimulaTion for TreatmEnt of ObstRuctive SLEEP Apnoea With and Without Complete Concentric Collapse (BETTER SLEEP); ClinicalTrials.gov: NCT03763682) was started in February 2019 in Australia. This trial will include 2 treatment groups, 20 patients with CCC on DISE and 20 patients without CCC, and should be completed by early 2020. Clinical trials have started in Germany and in the United States.

ANATOMIC AND CLINICAL CONSIDERATIONS FOR HGNS THERAPY OPTIMIZATION

The role of the nose and route of breathing

Mouth opening and nasal obstruction may be major contributors to HGNS clinical outcomes, although with our current understanding of mechanisms of airway collapse and limited clinical data, their roles are unclear. However, mouth opening has been negatively associated with outcomes of other sleep surgeries.[27,28]

Nasal airway structure has the potential to impact HGNS via several mechanisms. First, increased nasal resistance augments downstream negative pressures through a Starling resistor mechanism.[29] This may increase collapsibility through direct shear stress and negative pressure on the pharyngeal wall, and increased collapsibility makes airway stiffening and opening more challenging. Second, decreases in nasal airflow decrease nasally mediated afferent sensory stimulation, which reduces baseline levels of upper airway muscle tone.[30] Since baseline muscle tone is the major determinant of the degree of activation created by a fixed neurostimulation, a lower baseline resting muscle tone could reduce the effectiveness of airway opening for any given level of HGNS. Third, and likely most important, mouth opening has marked detrimental effects on pharyngeal collapse.

Mouth opening has multiple effects on upper airway anatomy.[31–33] It is associated with collapse of the retropalatal and retroglossal airways and with increased pharyngeal length along with decreases in retropalatal and retroglossal cross-sectional areas. Additionally, independent of changes in fixed airway resistance, mouth opening has been associated with increased collapsibility of the airway during midazolam sedation.[34] These studies did not evaluate the mechanism of increased collapsibility, but observation suggests that it is likely due to changes in lateral wall compliance with mouth opening. Since increased lateral wall compliance is a mechanism contributing to CCC during DISE, mouth opening is potentially a major negative predictor of HGNS clinical outcomes.

The impact of the nasal route of breathing on pharyngeal collapse independent of mouth opening has also been studied. In a model where mouth opening was kept constant, a nasal route of breathing was associated with a distal pharynx significantly less collapsible compared to mouth breathing.[35]

Increases in nasal resistance, loss of nasal afferents, mouth breathing, and mouth opening all increase pharyngeal collapsibility. Such increases in collapsibility likely worsen outcomes for any mechanical/structural treatment for sleep apnea. Given the importance of lateral wall tension on HGNS outcomes, these mechanisms may be important modulators of clinical effectiveness for this therapy. Mouth opening is likely a major unfavorable variable for current methods of nerve stimulation. Assessing this effect should be a major focus of research, because while the effects of nasal resistance and nasal afferents on HGNS are possible, their clinical magnitude is uncertain.

The role of the soft palate

There is a growing number of studies assessing the effect of soft palate surgery on HGNS outcomes. About 20% of the implanted patients in larger cohort reports underwent uvulopalatopharyngoplasty.[1,36,37] Early data are conflicting regarding the odds ratio between responders with previous soft palate surgery at 0.13[3] and those without previous surgery at 3.167,[36] while more recent and larger cohorts found no difference in responder rate based on previous soft palate surgery status.[38,39]

CCC during DISE is an exclusion criterion for HGNS therapy. This obstruction pattern can be seen in 23%–25% of otherwise eligible OSA patients.[40,41] The prevalence of CCC is dependent on previous soft palate surgery,[41] as CCC was

observed more frequently among candidates without previous soft palate surgery at 38%. Furthermore, CCC could be changed into a non-CCC pattern by performing a soft palate surgery.[42] Outcomes of 29 consecutive patients with HGNS implants were compared based on whether they had undergone palatal surgery or not.[43] The groups with no soft palate surgery or soft palate surgery before implantation had lower AHI, oxygen desaturation index, and BMI compared to groups who underwent soft palate surgery after implantation. However, those in the latter group had higher AHI, oxygen desaturation index, and BMI at baseline.[43] At a 2-year post-implantation follow up assessment, there was no clinically significant difference in treatment AHI between these groups.

The role of DISE and BMI

The role of BMI is generally felt to be an important element in selecting patients for HGNS therapy. The therapy is typically offered to patients with a BMI below 32 kg/m^2. Several studies have shown that with increasing BMI the upper airway obstruction changes from single-level to multilevel.[44] Increasing BMI has been found to be associated with a higher probability of CCC of the palate and lateral oropharyngeal collapse.[44–46] In addition, base of tongue collapse (anterior to posterior) is more common in patients with lower BMIs. Using HGNS, Goding et al[47] examined airway changes under fluoroscopy. He found that the ability of HGNS to open the retrolingual area was not affected by BMI; however, the ability to produce a retropalatal airway opening trended toward correlation with the BMI. In the ADHERE Registry Study, Heiser et al[37] showed that for each 1 unit increase of BMI there was a 9% reduced odds of treatment success. BMI was also a predictor for lower HGNS adherence. On the other hand, while Steffen et al[48] found that higher BMIs and AHI values were predictive of CCC, more than 50% of patients in that study with BMIs > 32kg/m^2 did not have CCC of the palate. Thus, excluding all overweight candidates may not be appropriate. This raises the question whether BMI < 32 kg/m^2 or the absence of CCC is crucial for success. It is likely that BMI and CCC may not be the best means of assessing the impact of body weight on success, and perhaps neck circumference or waist-to-hip ratios could be more appropriate; however, further studies are needed to evaluate this concept.

The role of sex and age

Little has been written about the impact of sex on outcomes for HGNS. In the first study of predictors of treatment effectiveness in the ADHERE registry, there was some suggestion that females had better results compared to males, but this was not a significant difference.[37] Another study by Patel et al found that sex did not influence outcomes.[49] However, in the latest update of the ADHERE registry study, which included 1017 HGNS patients, female sex appeared as a significant predictor of therapy response.[50]

It should be noted that given the limited morbidity associated with this therapy, HGNS may represent a very reasonable option for consideration in the aging population. However, as with BMI, age has shown conflicting outcomes. In the study of predictors of treatment effectiveness in the ADHERE registry, for every 1 year increase in age there was a 4% increase in odds of treatment success.[37] On the other hand, in the previously quoted study by Patel et al,[49] patients above the age of 65 years had a decreased treatment response compared to their younger counterparts. Certainly, further study is warranted with regard to the ideal age for implantation.

Role of imaging and craniofacial anatomy

While most sleep surgeons feel that craniofacial anatomy and its analysis is important in the assessment of a patient's HGNS candidacy, little has been described on this topic. Since FDA approval of HGNS therapy, there has been an ongoing "postmarket" trial (Inspire® Upper Airway Stimulation System (UAS): Post-Approval Study Protocol Number 2014-001; ClinicalTrials.gov: NCT02413970) that has included the assessment of facial characteristics (eg, facial profile and Angle's classification of malocclusion) as a means of assessing the impact of craniofacial anatomy on both candidacy for HGS therapy and treatment efficacy. However, the results of this trial have not yet been published, thus the question remains unanswered.

We also have limited data to support the use of preoperative imaging with HGNS therapy. Studies have assessed the utility of cephalometry for identifying candidates for oral appliance therapy. However, the published studies have conflicting information. Limitations of cephalometry include the static nature of the image and the fact that it only analyzes the airway in a lateral view, thus limiting the ability to identify lateral wall pathology. Findings to date indicate that isolated cephalometric parameters cannot be used to reliably predict treatment outcomes of oral appliances and surgical methods for treating OSA.[51]

The only published study to date that specifically used imaging in the assessment of HGNS was published by Schwab et al in 2018.[52] Responders to therapy had smaller baseline soft palate volume, greater increase in retroglossal airway size with stimulation, and increased shortening of the mandible hyoid distance with stimulation. This study was limited in that it included only White males and had a small sample size (6 patients).[52] Further study would be warranted to evaluate imaging as a preoperative predictor of candidacy for HGNS therapy.

Position/positional therapy and adjunct therapies to improve HGNS outcomes

In approximately 56%–75% of patients with OSA, the frequency and duration of apneas are influenced by body position.[53–58] In 26%–38% of OSA patients and in 36%–54% of positional OSA patients, respiratory disturbances normalize in the nonsupine position.[54,58,59] After upper airway sleep surgery, studies report that 42%–75% of nonpositional patients improve compared to less severe positional patients.[60–67] The effect of upper airway surgery is suggested to be greater in the lateral than the supine position, resulting in residual OSA in the supine position. In case of HGNS, positional patients are more difficult to titrate and often need a different stimulation amplitude in the supine and nonsupine sleeping positions. The latter will also be dependent on the individual tolerance threshold. Steffen et al[68] evaluated the impact of preoperative positionality on surgical success in patients undergoing HGNS and found no difference between positional patients and nonpositional patients but did

find that positional patients were more likely to achieve an AHI < 5 events/h. Considerations when interpreting these results include the small study population and the fact that positional patients are younger, slimmer, and have less severe disease. As these parameters are also predictors of surgical success, they were potential confounders of the study.

Patients with residual positional OSA after upper airway surgery can benefit from additional positional therapy. Benoist et al[69] reported an increase in overall therapeutic effectiveness by improving the median mean disease alleviation from 39.5% (effect of surgery alone) to 65.6% (effect of surgery and positional therapy in combination). To the best of our knowledge no studies have been performed evaluating the additional role of positional therapy in HGNS nonresponders, nor is this the case concerning oral appliance therapy or hypopharyngeal surgery, such as lingual tonsillectomy or epiglottopexy. Although hypopharyngeal surgery also aims to treat base-of-tongue obstruction, indications are different. One study reported improved outcomes, shorter length of stay, and lower readmissions when comparing HGNS and transoral robotic base of tongue resection.[70]

INDIVIDUAL FACTORS IN THE MANAGEMENT OF HGNS

OSA phenotypes and individual factors

Significant progress has been made in the last decade in understanding the contribution of various pathophysiologic mechanisms to the development of OSA. Several nonanatomic factors, such as high loop gain (respiratory system instability) and low arousal threshold act as destabilizing factors, tipping the balance toward more frequent obstructive disease in patients with susceptible airways. Muscle responsiveness of the upper airway dilator muscles affects an individual's ability to maintain pharyngeal patency through increasingly negative inspiratory pressures. The era of neurostimulation has ushered in a better understanding and management option for patients with poor muscle tone. However, the physiology of sleep as a tool to predict outcomes has only recently been brought to the forefront.

Critical airway pressure

The critical closing pressure of the airway (Pcrit) has been identified as a key pathophysiologic factor in the development of OSA.[71] It is a measure of the intrinsic collapsibility of an individual's pharyngeal airway and represents the lowest pressure at which the pharynx resists collapse. As such, lower Pcrit values represent a less collapsible pharynx.

Experiments in a cohort of 75 participants demonstrated that all those with Pcrit < –5 cm H_2O do not have OSA, all those with Pcrit > +2 cm H_2O have severe OSA, and those with Pcrit of intermediate value may have OSA depending on other nonanatomic vulnerabilities. Factors such as anatomic configuration, presence of anatomic vulnerabilities (eg, lymphoid hypertrophy), pharyngeal muscle tone, tracheal traction, weight, age, and degree of arousal all affect collapsibility.[72–77]

In addition, estimates of Pcrit, as predicted by positive airway pressure titration during laboratory polysomnography, may predict response to HGNS, with patients requiring < 8 cm H_2O experiencing significantly higher success rates than those with higher pressures (92% vs 44%, $P < .01$).[78] Conversely, experiments have demonstrated that GG stimulation significantly decreased mean Pcrit from –1.32 ± 1.97 to –5.30 ± 3.30 cm H_2O ($P < .05$) in 14 participants.[79]

Loop gain

Stability of the ventilatory system is defined by loop gain, a ratio of the response to stimulus (ventilatory response/ventilatory disturbance). A number of investigators have looked at loop gain in patients with OSA as a predictor of treatment success or failure. In a landmark 2001 study, Younes et al[80] investigated the role of chemical control instability in the pathogenesis of OSA. These authors concluded that the chemical control system (loop gain) is more unstable in patients with severe OSA than in patients with milder OSA and may contribute to the severity of OSA in some patients. Joosten et al[81] investigated whether loop gain predicts the response to upper airway surgery in patients with OSA and found that responders to multilevel surgery had a lower loop gain and were younger than nonresponders. A stable ventilator control system (low loop gain) was a predictor of successful upper airway surgery, and a high baseline loop gain was predictive of surgical failure.[81]

Changes in arousal threshold

Respiratory arousal threshold is defined as the level of inspiratory effort at which obstructive events terminate, usually with an arousal from sleep. It is measured by the esophageal pressure. A polysomnograph characterized by prolonged and severe desaturations is consistent with a high respiratory arousal threshold, especially in patients with severe AHI. In a large prospective cohort, Butler et al[82] characterized respiratory event duration, a heritable measure which is a marker for arousal threshold. They reported that after correcting for AHI, smoking, and demographics, the patients with low respiratory arousal threshold characterized by the shortest duration of obstructive events had significantly higher (hazard ratio = 1.31) all-cause mortality than did those with higher respiratory arousal threshold. Short duration of obstructive events preceding arousals increase respiratory instability (loop gain), which increases adrenergic output and associated long term morbidity. Thus, apnea event duration, which is readily available from routine polysomnography, may help to identify subgroups with low arousal threshold who are at higher risk for adverse outcomes.

Integrating anatomic and nonanatomic physiologic data is the future of patient selection for sleep surgery. Important questions still stand as we learn more about successes and failures of HGNS.

HGNS for individuals with congenital, neurologic, and medical disorders

Apart from the impact of CCC, there is little literature regarding the impact of anatomy on the success of HGNS implantation. Anatomic risk factors that likely merit evaluation include the role of the nose, palate position, adenotonsillar hypertrophy, macroglossia, lateral pharyngeal wall thickening, and the parapharyngeal fat pad. These factors along with pathophysiologic

considerations are discussed by Sistla et al[83] and should be considered for further research.

With regard to neurologic impairment, it was recommended that assessment of its impact be based on the literature evaluating upper airway neurogenic changes in OSA to establish positive and negative predictors of success. Sabiosky et al[84] review the mechanisms through which OSA causes neural injury—primarily resulting from hypoxia and vibration trauma—which leads to airway muscle remodeling. In light of this, assessment of motor or sensory function of the muscles of the upper airway may impact HGNS success[84] and may be useful for preoperative assessment. In addition, Cobo et al[85] reviewed the changes noted in upper airway nerves and muscles in patients with OSA and noted that motor nerve fibers and motor endplates along with the potential role of sensory nerve impairment has not been adequately investigated in OSA, as the current literature regarding this is heterogeneous and contradictory.

In patients with Down syndrome, who have both anatomic and neurologic impairment, there are a few case series and reports of the impact of HGNS. The first described a single 23-year-old who had a 63%–81% decrease in the apnea-hypopnea index and a 77% decrease in the oxygen desaturation index with the device.[86] A separate report of 3 adults noted improvements in the obstructive apnea hypopnea index from 40 to 12, 28 to 6.8, and 37.4 to 0.6 events/h with weekly adherence between 45 and 70 hours a week.[87] The last series documented 20 children with Down syndrome with a median age of 16 (range 13–17) and a median decrease in AHI from 24 to 3 events/h with median adherence rates of 9.2 hours/night.[88]

Psychosocial factors to consider for candidates of HGNS

The concept of psychological readiness for surgery is common in bariatric surgery, organ transplantation, and spinal procedures, including spinal cord stimulator implantation. Psychological readiness is often mandated by governing organizations (eg, United Network for Organ Sharing) or by insurance companies prior to elective procedures and is assessed by a trained health psychologist or psychiatrist. A clinical interview is critical for assessing appropriateness for surgery and for enhancing likelihood of success and postoperative adjustment.

The core components of the clinical interview include: (1) reasons for seeking surgery; (2) understanding the surgical procedure, expected outcomes, and associated lifestyle changes; (3) social support; and (4) current and historical psychiatric symptoms and substance abuse, including sleep disturbance.[89,90] The overarching goal of these assessments is to ensure that the patient understands that surgery is a "tool," rather than a "magic cure" and is motivated to adhere to recommendations that will increase the chances of good outcomes following surgery.[90] In fact, a large review of presurgical psychosocial evaluations in spinal cord stimulator implantation demonstrated that psychological tests were the scientific equivalent of medical tests. This study also identified exclusionary (eg, danger to self/others, psychosis, drug abuse, severe psychopathology) and cautionary (eg, moderate depression, anxiety/anger, pervasive pain, limited pain tolerance, catastrophizing, conflict with medical team) risk factors for poor outcomes.[91,92] Similar risk factors have been identified for bariatric surgery and organ transplantation.

Psychological readiness for surgery testing is not typically carried out prior to HGNS implantation. Additionally, little is known of psychosocial contributors to poor postsurgical outcomes, despite the fact that psychopathology has been frequently identified in patients with OSA. The 5-year prevalence of major depressive disorder in patients with OSA is 3–7 times higher than in the general population.[93] Further, depression has been found in 21%–41% of patients presenting to sleep clinics, compared to 8%–18% in the general population.[93] In research examining personality characteristics in patients with OSA, characteristics such as general dissatisfaction with life, vague nonspecific somatic complaints, avoidant coping, and the physical expression of psychological distress were found.[94,95] Given the large amounts of research supporting the importance of presurgical psychosocial assessment in other elective surgeries that require postsurgical lifestyle changes, there is justification for similar presurgical evaluations of psychological readiness as part of a presurgical workup for patients with OSA presenting for HGNS implantation.

The role of insomnia and other sleep disorders in use/noncompliance of HGNS

About 39%–55% of patients with OSA complain of insomnia symptoms, and OSA has been postulated to cause or exacerbate insomnia.[96–98] In light of these findings, it is likely that a significant number of patients implanted with a HGNS system experience insomnia. Those patients who experience comorbid insomnia and sleep apnea (COMISA) have a greater degree of cumulative morbidity, increased daytime sleepiness, and poorer sleep quality compared to patients with OSA alone.[99] Moreover, COMISA patients are significantly more prone to fail PAP therapy compared to other OSA patients.[100] Additionally COMISA patients are less likely to accept and continue using PAP therapy in order to treat the OSA component,[101] typically due to hyperarousability. Complicating this issue, sedative and hypnotic medications used to treat the insomnia component may reduce upper airway muscle tone and impair control of respiratory drive, thus exacerbating OSA. Combined treatment with hypnotic medications and PAP therapy for OSA reduces middle-of-the-night awakenings[102] and Cognitive Behavioral Therapy for Insomnia (CBT-I) improves insomnia in patients with OSA.[96] Guilleminault et al[103] found that soft palate and tongue base surgery improved OSA and insomnia symptoms in COMISA patients.

HGNS has not been assessed in patients with COMISA to date, although the authors are hopeful that it might be useful in combination with CBT-I. We encountered a case of a woman with COMISA who complained that she could feel the stimulation and, therefore, could not fall asleep nor stay asleep over the course of the night with HGNS therapy. She never successfully used the device. This sensation of tongue stiffening may be especially problematic while trying to fall asleep, and patients with COMISA are likely more prone to low adherence than patients with OSA. However, information is limited, as COMISA patients were excluded from the major selective HGNS prospective trials such as the STAR trial[1] and the German post-

market study.[36] In addition, the ADHERE registry has not yet systematically assessed insomnia, although there is recommendation for its inclusion in research regarding effectiveness in patients with COMISA, along with understanding the prevalence of COMISA and its impact on HGNS adherence.[50]

CONCLUSIONS

HGNS is an effective and evolving second-line therapy for OSA. Multiple factors can influence therapy outcomes, compliance, and long-term success. Further research is needed to establish criteria for outcomes assessment, patient candidacy, predictors of treatment success, and evaluation for combination therapy to eliminate OSA and address other associated comorbidities.

Future research topics

1. Define best measures of objective success of HGNS therapy
2. Is complete concentric collapse a contraindication to HGNS therapy?
3. Utility of DISE for preoperative screening of candidates for HGNS
4. What anatomical factors predict therapy success?
5. Outcomes of bilateral HGNS therapy
6. Mechanism and impact of nasal resistance and mouth breathing on therapy outcomes
7. How does positional OSA affect outcomes of HGNS?
8. Is loop gain a practical measure that can be used with polysomnography to predict surgical success of HGNS?
9. Can arousal threshold be used to stratify risk for patients considering HGNS treatment of OSA?
10. Can neurostimulation be used to correct ventilatory instability (loop gain) and improve surgical outcomes – lower loop gain?
11. Can neurostimulation increase arousal threshold, and thereby improve all-cause mortality?
12. Role of psychosocial factors on HGNS therapy outcomes
13. Should patients considering HGNS therapy undergo psychological readiness for surgery assessment?
14. How to assess and manage insomnia in conjunction with HGNS therapy for OSA?
15. What is the impact of insomnia on outcomes of HGNS?

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
C1, first cervical nerve
CCC, palatal complete concentric collapse
COMISA, comorbid insomnia and sleep apnea
DISE, drug-induced sleep endoscopy
FDA, US Food and Drug Administration
GG, genioglossus
GH, geniohyoid
HGN, hypoglossal nerve
HGNS, hypoglossal nerve stimulation
OSA, obstructive sleep apnea
PAP, positive airway pressure
Pcrit, critical closing pressure of the airway

REFERENCES

1. Strollo PJ Jr, Soose RJ, Maurer JT, et al; STAR Trial Group. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med.* 2014;370(2):139–149.
2. Woodson BT, Soose RJ, Gillespie MB, et al; STAR Trial Investigators. Three-year outcomes of cranial nerve stimulation for obstructive sleep apnea: the STAR trial. *Otolaryngol Head Neck Surg.* 2016;154(1):181–188.
3. Woodson BT, Strohl KP, Soose RJ, et al. Upper airway stimulation for obstructive sleep apnea: 5-Year outcomes. *Otolaryngol Head Neck Surg.* 2018; 159(1):194–202.
4. Maurer JT, Van de Heyning P, Lin HS, et al. Operative technique of upper airway stimulation-an implantable treatment of obstructive sleep apnea. *Operative Techniques in Otolaryngology Head and Neck Surgery.* 2012;23(3):227–233.
5. Heiser C, Thaler E, Boon M, Soose RJ, Woodson BT. Updates of operative techniques for upper airway stimulation. *Laryngoscope.* 2016;126(Suppl 7): S12–S16.
6. Balk EM, Moorthy D, Obadan NO, et al. *Diagnosis and Treatment of Obstructive Sleep Apnea in Adults.* Rockville, MD: Agency for Healthcare Research and Quality; 2011.
7. Redline S, Sanders M. Hypopnea, a floating metric: implications for prevalence, morbidity estimates, and case finding. *Sleep.* 1997;20(12):1209–1217.
8. Manser RL, Rochford P, Pierce RJ, Byrnes GB, Campbell DA. Impact of different criteria for defining hypopneas in the apnea-hypopnea index. *Chest.* 2001;120(3): 909–914.
9. Punjabi NM, Newman AB, Young TB, Resnick HE, Sanders MH. Sleep-disordered breathing and cardiovascular disease: an outcome-based definition of hypopneas. *Am J Respir Crit Care Med.* 2008;177(10):1150–1155.
10. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA.* 2011; 306(6):613–619.
11. Campos-Rodriguez F, Martinez-Garcia MA, Martinez M, et al; Spanish Sleep Network. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. *Am J Respir Crit Care Med.* 2013;187(1): 99–105.
12. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. *Am J Respir Crit Care Med.* 2002;166(2):159–165.
13. Weaver EM. Judging sleep apnea surgery. *Sleep Med Rev.* 2010;14(5):283–285.
14. Ravesloot MJ, de Vries N. Reliable calculation of the efficacy of non-surgical and surgical treatment of obstructive sleep apnea revisited. *Sleep.* 2011;34(1): 105–110.
15. Stuck BA, Leitzbach S, Maurer JT. Effects of continuous positive airway pressure on apnea-hypopnea index in obstructive sleep apnea based on long-term compliance. *Sleep Breath.* 2012;16(2):467–471.
16. Weaver EM, Woodson BT, Steward DL. Polysomnography indexes are discordant with quality of life, symptoms, and reaction times in sleep apnea patients. *Otolaryngol Head Neck Surg.* 2005;132(2):255–262.
17. Vanderveken OM, Maurer JT, Hohenhorst W, et al. Evaluation of drug-induced sleep endoscopy as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea. *J Clin Sleep Med.* 2013;9(5): 433–438.
18. Sarber KM, Chang KW, Ishman SL, Epperson MV, Dhanda PR. Hypoglossal nerve stimulator outcomes for patients outside the U.S. FDA recommendations. *Laryngoscope.* 2020;130(4):866–872
19. Heiser C, Maurer JT, Steffen A. Functional outcome of tongue motions with selective hypoglossal nerve stimulation in patients with obstructive sleep apnea. *Sleep Breath.* 2016;20(2):553–560.

20. Heiser C, Knopf A, Hofauer B. Surgical anatomy of the hypoglossal nerve: A new classification system for selective upper airway stimulation. *Head Neck.* 2017;39(12):2371–2380.
21. Heiser C, Edenharter G, Bas M, Wirth M, Hofauer B. Palatoglossus coupling in selective upper airway stimulation. *Laryngoscope.* 2017;127(10):E378–E383.
22. Bassiri Gharb B, Tadisina KK, Rampazzo A, et al. Microsurgical anatomy of the terminal hypoglossal nerve relevant for neurostimulation in obstructive sleep apnea. *Neuromodulation.* 2015;18(8):721–728.
23. Pengo MF, Steier J. Emerging technology: electrical stimulation in obstructive sleep apnoea. *J Thorac Dis.* 2015;7(8):1286–1297.
24. Heiser C. Advanced titration to treat a floppy epiglottis in selective upper airway stimulation. *Laryngoscope.* 2016;126(Suppl 7):S22–S24.
25. Heiser C, Hofauer B, Lozier L, Woodson BT, Stark T. Nerve monitoring-guided selective hypoglossal nerve stimulation in obstructive sleep apnea patients. *Laryngoscope.* 2016;126(12):2852–2858.
26. Eastwood PR, Barnes M, MacKay SG, et al. Bilateral hypoglossal nerve stimulation for treatment of adult obstructive sleep apnoea. *Eur Respir J.* 2020; 55(1):1901320.
27. Ramaswamy AT, Li C, Suurna MV. A case of hypoglossal nerve stimulator-resistant obstructive sleep apnea cured with the addition of a chin strap. *Laryngoscope.* 2018;128(7):1727–1729.
28. Lee CH, Mo JH, Seo BS, Kim DY, Yoon IY, Kim JW. Mouth opening during sleep may be a critical predictor of surgical outcome after uvulopalatopharyngoplasty for obstructive sleep apnea. *J Clin Sleep Med.* 2010;6(2):157–162.
29. Le TB, Moghaddam MG, Woodson BT, Garcia GJM. Airflow limitation in a collapsible model of the human pharynx: physical mechanisms studied with fluid-structure interaction simulations and experiments. *Physiol Rep.* 2019;7(10): e14099.
30. McNicholas WT, Coffey M, Boyle T. Effects of nasal airflow on breathing during sleep in normal humans. *Am Rev Respir Dis.* 1993;147(3):620–623.
31. Kim EJ, Choi JH, Kim KW, et al. The impacts of open-mouth breathing on upper airway space in obstructive sleep apnea: 3-D MDCT analysis. *Eur Arch Otorhinolaryngol.* 2011;268(4):533–539.
32. Hu B, Ye J, Yin G, Zhang Y. The influential factors on the morphological changes of upper airway associated with mouth opening. *Laryngoscope.* 2018;128(12): 2902–2909.
33. Lee SH, Choi JH, Shin C, Lee HM, Kwon SY, Lee SH. How does open-mouth breathing influence upper airway anatomy? *Laryngoscope.* 2007;117(6): 1102–1106.
34. Ayuse T, Inazawa T, Kurata S, et al. Mouth-opening increases upper-airway collapsibility without changing resistance during midazolam sedation. *J Dent Res.* 2004;83(9):718–722.
35. Wang W, Verin E, Sériès F. Influences of the breathing route on upper airway dynamics properties in normal awake subjects with constant mouth opening. *Clin Sci (Lond).* 2006;111(5):349–355.
36. Steffen A, Sommer JU, Hofauer B, Maurer JT, Hasselbacher K, Heiser C. Outcome after one year of upper airway stimulation for obstructive sleep apnea in a multicenter German post-market study. *Laryngoscope.* 2018;128(2):509–515.
37. Heiser C, Steffen A, Boon M, et al; ADHERE Registry Investigators. Post-approval upper airway stimulation predictors of treatment effectiveness in the ADHERE registry. *Eur Respir J.* 2019;53(1):1801405.
38. Kezirian EJ, Heiser C, Steffen A, et al. Previous surgery and hypoglossal nerve stimulation for obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2019; 161(5):897–903.
39. Huntley C, Vasconcellos A, Doghramji K, Hofauer B, Heiser C, Boon M. Upper Airway stimulation in patients who have undergone unsuccessful prior palate surgery: an initial evaluation. *Otolaryngol Head Neck Surg.* 2018;159(5): 938–940.
40. Ong AA, Murphey AW, Nguyen SA, et al. Efficacy of upper airway stimulation on collapse patterns observed during drug-induced sedation endoscopy. *Otolaryngol Head Neck Surg.* 2016;154(5):970–977.
41. Hasselbacher K, Bruchhage KL, Abrams N, Steffen A. [Sleep endoscopy and complete concentric collapse in CPAP failure]. *HNO.* 2018;66(11): 837–842.
42. Hasselbacher K, Seitz A, Abrams N, Wollenberg B, Steffen A. Complete concentric collapse at the soft palate in sleep endoscopy: what change is possible after UPPP in patients with CPAP failure? *Sleep Breath.* 2018;22(4): 933–938.
43. Steffen A, Abrams N, Suurna MV, Wollenberg B, Hasselbacher K. Upper-airway stimulation before, after, or without uvulopalatopharyngoplasty: a two-year perspective. *Laryngoscope.* 2019;129(2):514–518.
44. Vroegop AV, Vanderveken OM, Boudewyns AN, et al. Drug-induced sleep endoscopy in sleep-disordered breathing: report on 1,249 cases. *Laryngoscope.* 2014;124(3):797–802.
45. Lan MC, Liu SY, Lan MY, Modi R, Capasso R. Lateral pharyngeal wall collapse associated with hypoxemia in obstructive sleep apnea. *Laryngoscope.* 2015; 125(10):2408–2412.
46. Ravesloot MJ, de Vries N. One hundred consecutive patients undergoing drug-induced sleep endoscopy: results and evaluation. *Laryngoscope.* 2011; 121(12):2710–2716.
47. Goding GS Jr, Tesfayesus W, Kezirian EJ. Hypoglossal nerve stimulation and airway changes under fluoroscopy. *Otolaryngol Head Neck Surg.* 2012;146(6): 1017–1022.
48. Steffen A, Frenzel H, Wollenberg B, König IR. Patient selection for upper airway stimulation: is concentric collapse in sleep endoscopy predictable? *Sleep Breath.* 2015;19(4):1373–1376.
49. Patel J, Daniels K, Bogdan L, Huntley C, Boon M. Effect of gender, age, and profound disease on upper airway stimulation outcomes. *Ann Otol Rhinol Laryngol.* 2020;129(8):772–780.
50. Thaler E, Schwab R, Maurer J, et al. Results of the ADHERE upper airway stimulation registry and predictors of therapy efficacy. *Laryngoscope.* 2020; 130(5):1333–1338.
51. Hong S, Won T, Kim J, Lee C, Rhee C. Upper airway evaluation in patients with obstructive sleep apnea. *Sleep Med Res.* 2016;7(1):1–9.
52. Schwab RJ, Wang SH, Verbraecken J, et al. Anatomic predictors of response and mechanism of action of upper airway stimulation therapy in patients with obstructive sleep apnea. *Sleep.* 2018;41(4):zsy021.
53. Ravesloot MJ, van Maanen JP, Dun L, de Vries N. The undervalued potential of positional therapy in position-dependent snoring and obstructive sleep apnea–a review of the literature. *Sleep Breath.* 2013;17:39–49.
54. Ravesloot MJ, Frank MH, van Maanen JP, Verhagen EA, de Lange J, de Vries N. Positional OSA part 2: retrospective cohort analysis with a new classification system (APOC). *Sleep Breath.* 2016;20(2):881–888.
55. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep.* 1984;7(2): 110–114.
56. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest.* 1997;112(3):629–639.
57. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N. The role of sleep position in obstructive sleep apnea syndrome. European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology. *Head Neck Surg.* 2006;263(10):946–950.
58. Heinzer R, Petitpierre NJ, Marti-Soler H, Haba-Rubio J. Prevalence and characteristics of positional sleep apnea in the HypnoLaus population-based cohort. *Sleep Med.* 2018;48:157–162.
59. Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJ. Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest.* 2005; 128(4):2130–2137.
60. Katsantonis GP, Miyazaki S, Walsh JK. Effects of uvulopalatopharyngoplasty on sleep architecture and patterns of obstructed breathing. *Laryngoscope.* 1990; 100(10):1068–1072.
61. Lee CH, Kim S-W, Han K, et al. Effect of uvulopalatopharyngoplasty on positional dependency in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg.* 2011; 137(7):675–679.
62. van Maanen JP, Ravesloot MJ, Witte BI, Grijseels M, de Vries N. Exploration of the relationship between sleep position and isolated tongue base or multilevel surgery in obstructive sleep apnea. *Eur Arch Otorhinolaryngol.* 2012;269(9): 2129–2136.

63. Lee YC, Eun YG, Shin SY, Kim SW. Change in position dependency in non-responders after multilevel surgery for obstructive sleep apnea: analysis of polysomnographic parameters. *Eur Arch Otorhinolaryngol.* 2014;271(5):1081–1085.
64. Li H-Y, Cheng W-N, Chuang L-P, et al. Positional dependency and surgical success of relocation pharyngoplasty among patients with severe obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2013;149(3):506–512.
65. Van Maanen JP, Witte BI, de Vries N. Theoretical approach towards increasing effectiveness of palatal surgery in obstructive sleep apnea: role for concomitant positional therapy? *Sleep Breath.* 2014;18(2):341–349.
66. Kastoer C, Benoist LBL, Dieltjens M, et al. Comparison of upper airway collapse patterns and its clinical significance: drug-induced sleep endoscopy in patients without obstructive sleep apnea, positional and non-positional obstructive sleep apnea. *Sleep Breath.* 2018;22(4):939–948.
67. Benoist LB, de Ruiter MH, de Lange J, de Vries N. Residual POSA after maxillomandibular advancement in patients with severe OSA. In: de Vries N, Ravesloot M, van Maanen J, eds. *Positional Therapy in Obstructive Sleep Apnea.* Springer International Publishing, Switzerland; 2015:321–329.
68. Steffen A, Hartmann JT, König IR, Ravesloot MJL, Hofauer B, Heiser C. Evaluation of body position in upper airway stimulation for obstructive sleep apnea—is continuous voltage sufficient enough? *Sleep Breath.* 2018;22(4):1207–1212.
69. Benoist LBL, Verhagen M, Torensma B, van Maanen JP, de Vries N. Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery. *Sleep Breath.* 2017;21(2):279–288.
70. Huntley C, Topf MC, Christopher V, Doghramji K, Curry J, Boon M. Comparing upper airway stimulation to transoral robotic base of tongue resection for treatment of obstructive sleep apnea. *Laryngoscope.* 2019;129(4):1010–1013.
71. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am J Respir Crit Care Med.* 2013;188(8):996–1004.
72. Appleton SL, Vakulin A, McEvoy RD, et al. Undiagnosed obstructive sleep apnea is independently associated with reductions in quality of life in middle-aged, but not elderly men of a population cohort. *Sleep Breath.* 2015;19(4):1309–1316.
73. Eastwood PR, Szollosi I, Platt PR, Hillman DR. Comparison of upper airway collapse during general anaesthesia and sleep. *Lancet.* 2002;359(9313):1207–1209.
74. Isono S, Remmers JE, Tanaka A, Sho Y, Sato J, Nishino T. Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. *J Appl Physiol 1985.* 1997;82(4):1319–1326.
75. Kirkness JP, Schwartz AR, Schneider H, et al. Contribution of male sex, age, and obesity to mechanical instability of the upper airway during sleep. *J Appl Physiol 1985.* 2008;104(6):1618–1624.
76. Schwartz AR, Gold AR, Schubert N, et al. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis.* 1991;144(3 pt 1):494–498.
77. Gleadhill IC, Schwartz AR, Schubert N, Wise RA, Permutt S, Smith PL. Upper airway collapsibility in snorers and in patients with obstructive hypopnea and apnea. *Am Rev Respir Dis.* 1991;143(6):1300–1303.
78. Lee CH, Seay EG, Walters BK, Scalzitti NJ, Dedhia RC. Therapeutic positive airway pressure level predicts response to hypoglossal nerve stimulation for obstructive sleep apnea. *J Clin Sleep Med.* 2019;15(8):1165–1172.
79. Oliven A, O'Hearn DJ, Boudewyns A, et al. Upper airway response to electrical stimulation of the genioglossus in obstructive sleep apnea. *J Appl Physiol 1985.* 2003;95(5):2023–2029.
80. Younes M, Ostrowski M, Thompson W, Leslie C, Shewchuk W. Chemical control stability in patients with obstructive sleep apnea. *Am J Respir Crit Care Med.* 2001;163(5):1181–1190.
81. Joosten SA, Leong P, Landry SA, et al. Loop gain predicts the response to upper airway surgery in patients with obstructive sleep apnea. *Sleep.* 2017;40(7).
82. Butler MP, Emch JT, Rueschman M, et al. Apnea-hypopnea event duration predicts mortality in men and women in the sleep heart health study. *Am J Respir Crit Care Med.* 2019;199(7):903–912.
83. Sistla SK, Paramasivan VK, Agrawal V. Anatomic and pathophysiologic considerations in surgical treatment of obstructive sleep apnea. *Sleep Med Clin.* 2019;14(1):21–31.
84. Saboisky JP, Butler JE, Gandevia SC, Eckert DJ. Functional role of neural injury in obstructive sleep apnea. *Front Neurol.* 2012;3:95.
85. Cobo T, Macías E, Álvarez C, et al. Nerve and Muscle Changes in the Upper Airways of Subjects with Obstructive Sleep Apnea: Structural Basis for the Neurogenic Theory; 2017. https://www.intechopen.com/chapters/53037. Accessed December 1, 2019.
86. Van de Perck E, Beyers J, Dieltjens M, et al. Successful upper airway stimulation therapy in an adult Down syndrome patient with severe obstructive sleep apnea. *Sleep Breath.* 2019;23(3):879–883.
87. Li C, Boon M, Ishman SL, Suurna MV. Hypoglossal nerve stimulation in three adults with down syndrome and severe obstructive sleep apnea. *Laryngoscope.* 2019;129(11):E402–E406.
88. Caloway CL, Diercks GR, Keamy D, et al. Update on hypoglossal nerve stimulation in children with down syndrome and obstructive sleep apnea. *Laryngoscope.* 2020;130(4):E263–E267.
89. Snyder AG. Psychological assessment of the patient undergoing bariatric surgery. *Ochsner J.* 2009;9(3):144–148.
90. Sogg S, Lauretti J, West-Smith L. Recommendations for the presurgical psychosocial evaluation of bariatric surgery patients. *Surg Obes Relat Dis.* 2016;12(4):731–749.
91. Campbell CM, Jamison RN, Edwards RR. Psychological screening/phenotyping as predictors for spinal cord stimulation. *Curr Pain Headache Rep.* 2013;17(1):307.
92. Bruns D, Disorbio JM. Evaluating Candidates for Spinal Cord Stimulation, Spinal Surgery, and Intrathecal Pumps. https://healthpsych.com/scs_glossary.pdf. Accessed September 30, 2019
93. Schröder CM, O'Hara R. Depression and obstructive sleep apnea (OSA). *Ann Gen Psychiatry.* 2005;4:13.
94. Ekici A, Ekici M, Oğuztürk O, Karaboğa I, Cimen D, Senturk E. Personality profiles in patients with obstructive sleep apnea. *Sleep Breath.* 2013;17(1):305–310.
95. Aikens JE, Caruana-Montaldo B, Vanable PA, Tadimeti L, Mendelson WB. MMPI correlates of sleep and respiratory disturbance in obstructive sleep apnea. *Sleep.* 1999;22(3):362–369.
96. Bahr K, Cámara RJA, Gouveris H, Tuin I. Current treatment of comorbid insomnia and obstructive sleep apnea with CBTI and PAP-therapy: a systematic review. *Front Neurol.* 2018;9:804.
97. Lam AS, Collop NA, Bliwise DL, Dedhia RC. Validated measures of insomnia, function, sleepiness, and nasal obstruction in a CPAP alternatives clinic population. *J Clin Sleep Med.* 2017;13(8):949–957.
98. Philip P, Bioulac S, Altena E, et al. Specific insomnia symptoms and self-efficacy explain CPAP compliance in a sample of OSAS patients. *PLoS One.* 2018;13(4):e0195343.
99. Krakow B, Melendrez D, Ferreira E, et al. Prevalence of insomnia symptoms in patients with sleep-disordered breathing. *Chest.* 2001;120(6):1923–1929.
100. Nguyên XL, Chaskalovic J, Rakotonanahary D, Fleury B. Insomnia symptoms and CPAP compliance in OSAS patients: a descriptive study using data mining methods. *Sleep Med.* 2010;11(8):777–784.
101. Luyster FS, Buysse DJ, Strollo PJ Jr. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. *J Clin Sleep Med.* 2010;6(2):196–204.
102. Sweetman AM, Lack LC, Catcheside PG, et al. Developing a successful treatment for co-morbid insomnia and sleep apnoea. *Sleep Med Rev.* 2017;33:28–38.
103. Guilleminault C, Davis K, Huynh NT. Prospective randomized study of patients with insomnia and mild sleep disordered breathing. *Sleep.* 2008;31(11):1527–1533.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication February 11, 2021
Submitted in final revised form July 4, 2021
Accepted for publication July 6, 2021

Address correspondence to: Maria V. Suurna, MD, Weill Cornell Medicine, 2135 Broadway, New York, NY 10024; Tel: (646) 962-9135; Fax (646) 962-0162; Email: mas9390@med.cornell.edu

DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Maria Suurna has received honoraria and research support from Inspire Medical and is a consultant for Medtronic; Ofer Jacobowitz is a consultant to LivaNova and Nyxoah Medical; Mark D'Agostino is a Chief Medical Advisor for Alaxo USA; Maurits Boon has received research support and is a consultant for Inspire Medical; Clemens Heiser has received a research grant, travel support, and consulting honoraria from Inspire Medical; Colin Huntley has received research support from Inspire Medical; Alan Kominsky is a consultant for Enhale Medical; Joachim Maurer received honoraria from ImThera Medical, is a consultant and received honoraria from Inspire Medical, is a consultant and received honoraria from Nyxoah Medical, and has received honoraria and travel reimbursement from Neuwirth Medical Products; Ryan Soose received research support from Inspire Medical, is a consultant for Smith & Nephew, Cryosa Inc., Invicta Medical, Inspire Medical, Galvani Bioelectronics, and Enhale Medical; Armin Steffen has received honoraria and covered travel expenses for invited talks on behalf of Inspire Medical and is a consultant for Merz Pharmaceuticals and Respicardia; Tucker Woodson received research support from Inspire Medical and Linguaflex and is a consultant for Inspire Medical, Linguaflex, Medtronic, Medrobitics, Cook Medical, and Siesta Medical; Stacey Ishman was a consultant for Inspire Medical. Dr. Weaver's effort was supported by resources from the VA Puget Sound Health Care System, Seattle, Washington. The contents do not represent views of the US Department of Veterans Affairs or US government. The other authors report no conflicts of interest.