Advancements in the Treatment of Paediatric Sleep-disordered Breathing Using Hypoglossal Nerve Stimulation

Anahita Shiva[1] and Taylor B Teplitzky[2]

1. University of Maryland School of Medicine, Baltimore, MD, USA; 2. Department of Surgery, Division of Pediatric Otolaryngology, Nemours Children's Hospital of Delaware, Wilmington, DE, USA

Sleep-disordered breathing (SDB) encompasses upper airway dysfunction during sleep caused by increased upper airway resistance and pharyngeal collapsibility. It is estimated that SDB affects up to 4% of children worldwide. Paediatric obstructive sleep apnoea (OSA) is characterized by periods of apnoea and hypopnoea and is diagnosed using overnight polysomnography. The first-line treatment for OSA in most children is adenotonsillectomy. However, those with persistent OSA require additional therapies. Hypoglossal nerve stimulation (HGNS) has been shown to be safe and effective in appropriate patients with OSA, where stimulation of the genioglossus maintains airway patency during sleep. This article aims to explore the literature on paediatric OSA management, and new utilization of HGNS.

Keywords

Down syndrome, hypoglossal nerve stimulation, obstructive sleep apnoea, paediatrics, paediatric sleep apnea, persistent sleep apnea, severe sleep apnea, sleep-disordered breathing

Disclosures: Anahita Shiva and Taylor B Teplitzky have no financial or non-financial relationships or activities to declare in relation to this article.

Review process: Double-blind peer review.

Compliance with ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the writing of this article.

Authorship: The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given the final approval for the version to be published.

Received: 28 September 2023

Accepted: 5 January 2024

Citation: *touchREVIEWS in Respiratory & Pulmonary Diseases.* 2024;9(1):Online ahead of journal publication

Corresponding author: Dr Taylor B Teplitzky, Department of Surgery, Division of Pediatric Otolaryngology, Nemours Children's Hospital of Delaware, 1600 Rockland Road, Wilmington, 19808, DE, USA.
E: taylor.teplitzky@nemours.org

Support: No funding was received in the publication of this article.

Paediatric sleep-disordered breathing

Sleep-disordered breathing (SDB) is defined as the disruption of normal respiration and ventilation while asleep.[1] SDB encompasses multiple sleep disturbances, ranging from mild snoring to obstructive sleep apnoea (OSA).[1,2] OSA is characterized by episodic partial or complete obstruction of the upper airway, with associated desaturations, awakenings or arousals from sleep.[3] Common symptoms include snoring, nocturnal gasping, witnessed apnoeas and daytime somnolence.[4,5] OSA affects 1–4% of children worldwide, with incidence increasing over time.[6–8] When untreated, paediatric OSA is known to negatively affect outcomes and quality of life.[9] OSA has been linked with neurocognitive and behavioural disturbances in paediatric patients, including learning difficulties, attention disorders, poor school performance, hyperactivity, aggression, moodiness and antisocial behaviours.[10–14] Paediatric OSA may also be associated with cardiovascular disease and hypertension.[1,8,15–17]

Evaluation and diagnosis of paediatric obstructive sleep apnoea

The gold standard for the diagnosis of OSA in children is in-laboratory overnight polysomnography (PSG).[3] However, current research efforts are in place to determine the efficacy of less invasive, more readily accessible diagnostic methods in the paediatric population.[2,18] The American Academy of Sleep Medicine defines paediatric obstructive apnoea events as a reduction in peak airflow by ≥90% of pre-event baseline with an associated respiratory effort.[19] A hypopnoea event is defined as a decrease in the peak signal by ≥30% from baseline nasal pressure for at least two breaths in association with either a ≥3% oxygen desaturation or an arousal.[19] OSA is diagnosed using the apnoea–hypopnoea index (AHI), which is the average number of apnoeas and hypopnoeas per hour of sleep.[19] The most commonly accepted definition of OSA severity is mild OSA corresponds to an AHI ≥1 and <5, moderate with an AHI of 5–10 and severe with an AHI of ≥10.[3,8,20]

Pathophysiology

Lymphoid tissue in Waldeyer's ring serves as part of the immune system, positioned in the oropharynx and nasopharynx to initiate immune responses towards antigens entering the body.[20,21] This tissue is most active between 3 and 10 years of age, leading to an associated peak in size during this period with subsequent age-related involution.[20,22] To date, there have been no studies demonstrating a significant impact on immune function after the removal of the adenoids and/or tonsils to manage SDB.[23]

Certain populations are at a higher risk of developing OSA than others. In the USA, upwards of 60% of children with obesity have comorbid OSA.[24,25] The aetiology of this relationship is likely multifactorial, but the co-occurrence of obesity and adenotonsillar hypertrophy may have a cumulative effect on narrowing the oropharyngeal airway.[26,27] Other risk factors for paediatric OSA include craniofacial anomalies and neuromuscular disorders.[8,28,29]

Trisomy 21: An at-risk population

A well-studied, unique population with high rates of OSA is patients with Down syndrome (DS).[30] Overall, 55–80% of children with DS have OSA.[31,32] Hill et al. found that 14% of children with DS had moderate-to-severe OSA and 59% had mild-to-moderate OSA.[33] Some characteristic features of DS, such as obesity, baseline hypotonia and altered craniofacial anatomy, including midface hypoplasia and macroglossia, place them at a higher risk of the disease.[33,34] OSA may be associated with severe ramifications in this population. Breslin et al. identified an association between OSA, reduced cognition and lower verbal intelligence quotient in a paediatric DS cohort.[35] Due to the high incidence of OSA in these patients, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) recommends screening all children with DS for OSA by overnight PSG before 4 years of age.[20] Unfortunately, patients with DS are more likely to have disease persistence after initial therapy with adenotonsillectomy (AT).[36–38] Reasons for this are discussed later in this article.

Treatments

Adenotonsillectomy

In children, the most common cause of OSA oropharyngeal obstruction is adenotonsillar hypertrophy.[1,20] The AAO-HNS guidelines support surgical management via AT as the first-line treatment for appropriate children with OSA diagnosed using PSG.[20] AT is also indicated for children who demonstrate signs of obstructive SDB with adenotonsillar hypertrophy and clinical signs of comorbid conditions, such as growth retardation, enuresis and school/behavioural issues, which may improve after surgery.[20]

Surgical removal of the adenoids and palatine tonsils often results in significant improvements in respiratory parameters, including the AHI, obstructive apnoea and hypopnoea indices and minimum oxygen saturation.[39] Success rates of AT approaches 80% in certain populations.[40–42] AT has also been associated with improvements in behaviours, such as aggression, attention and hyperactivity, and in the quality of life.[9,43]

While highly efficacious in developmentally typical children, AT has lower efficacy in children with DS.[36] The literature suggests that 30–50% of children with DS have persistent OSA after AT.[44] In addition, these children suffer higher complication rates post-operatively. Cottrell et al. demonstrated that 78/251 (31.5%) of children suffered a post-operative complication needing medical attention, most commonly respiratory issues (53.8%), poor oral intake (37.2%) and bleeding (17.9%).[45] These findings were echoed by Goldstein et al.[46] In this setting, additional or alternate therapies may be considered.

Continuous positive airway pressure

Continuous positive airway pressure (CPAP) is the mainstay of treatment for adult patients with OSA and is an option for children who are not appropriate surgical candidates for AT.[47] It can also be considered in children with persistent OSA after AT.[47,48] CPAP is delivered nasally or oronasally via a mask and stabilizes the upper airway by providing positive pressure that exceeds the pressure of the collapsing intraluminal oropharyngeal space.[49] Studies have highlighted the benefits of positive airway pressure (PAP) therapy in managing SDB.[50,51] However, adherence to PAP is a barrier to its efficacy in both adult and paediatric populations, leading to persistent, untreated disease.[52,53] PAP adherence is not as well defined in children as in adults.[54] However, the most common definition of PAP adherence utilized for children is the adult definition: use of PAP ≥4 hours per night for 70% of nights during 30 consecutive days.[55]

Weiss et al. found that less than half of the children with OSA were using CPAP for >4 hours a night.[56] Children with caregiver support show improved compliance, and the medical team's engagement via family-based education programmes on CPAP improves adherence.[54,57] Additionally, it has been found that younger children (primary school age versus middle/high school age), those with higher baseline AHI and those with neurocognitive disorders better tolerate PAP.[58]

Notably, non-invasive ventilation, including PAP, is an option for children with DS who have persistent OSA after AT or who are not candidates for surgical management.[48,59] However, PAP is less effective in children with DS than in developmentally typical children.[60] Despite improved adherence to PAP, children with DS have poorer clinical outcomes compared with non-DS counterparts, namely persistent AHI elevations and mask leaks.[60,61] Therefore, it is important to continue re-evaluating these children to ensure appropriate treatment responses. If the result is unsatisfactory, other treatments may be required.

Non-positive airway pressure upper airway approaches in obstructive sleep apnoea

There are additional non-surgical and surgical options for the management of persistent OSA. Non-surgical approaches work to expand the oropharyngeal airway to reduce obstruction. Common options include rapid maxillary expansion and oral appliances providing maxillary advancement.[62–65] Although individual studies have shown promise, the data are lacking to definitively comment on these options in children.[66] Surgical alternatives also aim to increase the size of the oropharyngeal airway. These include oromaxillofacial procedures, namely maxillomandibular advancements and mandibular distraction osteogenesis, or neurosurgical procedures, such as fronto-facial monobloc advancement.[63,67–69] Tongue base reduction and lingual tonsillectomy can be considered in cases with obstruction at these sites.[70,71] Expansion sphincter pharyngoplasty is another procedure aimed at improving oropharyngeal obstruction in children with persistent OSA.[72,73]

The only cure for persistent OSA is a tracheostomy, typically performed by otolaryngology or paediatric surgery physicians.[48,74] Discussion on which of these treatments are most appropriate requires a multidisciplinary sleep medicine team and shared decision-making between the team and the caregivers.[63] Further details about these treatments are outside the scope of this article. A list of the mentioned options and their efficacy can be found in *Table 1*.[40–42,44,48,54,67–69,71,72,74–79]

Hypoglossal nerve stimulation

The upper airway consists of 23 pairs of muscles that are state-dependent, exhibiting reduced activity upon sleep onset.[80–82] Of these, the genioglossus is readily accessible, and its role in OSA has, thus, been extensively studied.[83] The genioglossus is an extrinsic muscle of the tongue, originating from the superior mental spine and inserting at the tip and dorsum of the tongue and into the body of the hyoid bone.[84] It is innervated by cranial nerve 12 and supplied by the lingual arteries. Importantly, the genioglossus works to maintain airway patency by stabilizing the upper respiratory tract.[85,86]

Efforts to increase the upper airway muscular output, such as myofunctional therapy and playing woodwind instruments, for the treatment of OSA have been attempted.[87,88] These therapies target the

Table 1: Comparison of paediatric hypoglossal nerve stimulation with other obstructive sleep apnoea treatment modalities[40–42,44,48,54,67–69,71,72,74–79]

Procedure/device	Success rate
Paediatric HGNS	At least 50% reduction in AHI in paediatric patients[75]
AT	• As high as 80% in certain populations[40–42] • 30–50% of children with DS have persistent OSA after AT[44]
Continuous positive airway pressure	• 90% in most patients, but 50% compliance[54] • Syndromic children: 86.2% success rate[76]
Oral appliances	May have efficacy; data are lacking in children[77,78]
Maxillomandibular advancement	*Surgical success rate: 85.5%; surgical cure rate: 38.5%[67]
Mandibular distraction osteogenesis	• Average AHI improvement of 33.9%[68] • Successful treatment of airway obstruction: 89.3% of children[69]
Tongue base reduction	48.5% reduction in AHI[71]
Lingual tonsillectomy	AHI <1, success rate 17%; AHI <5, success rate 51%[79]
Expansion sphincter pharyngoplasty	Cure rates: AHI <1, 64%, AHI <2, 72% and AHI <5, 60%[72]
Tracheostomy	Considered curative[48,74]

**Data are derived from adult populations.*
AHI = apnoea–hypopnoea index; AT = adenotonsillectomy; DS = Down syndrome; HGNS = hypoglossal nerve stimulation; OSA = obstructive sleep apnoea.

oral cavity and oropharyngeal structures to strengthen dilator muscles of the upper airway, which relax during sleep and thus result in soft tissue collapse in the throat. Patency of the pharyngeal airway, which lacks intrinsic support, may be improved with oropharyngeal exercise.[88,89]

Proof of concept

Despite varying therapeutic success rates of oropharyngeal exercises on OSA resolution, they provided the rationale for the hypoglossal nerve stimulation (HGNS) device. Studies in both animal models and humans were performed to test this idea.

Animal models served as a proof of concept for hypoglossal stimulation for the treatment of OSA.[90,91] Stimulation of the hypoglossal nerve decreased upper airway collapsibility via contraction of musculature, leading to improved patency and dilation. Schwartz et al. found that stimulation of the proximal trunk of the hypoglossal nerve, which primarily innervates the genioglossus, reduced pharyngeal collapsibility.[91] Stimulation of the hypoglossal nerve, via activation of the genioglossus muscle, was more effective than stimulation of the strap muscles and other lingual muscles.[92] Later, it was determined that action by both tongue protrudor muscles (genioglossus) and retractors (styloglossus and hyoglossus) occurs when respiratory drive increases, supporting co-stimulation of both muscle groups to stabilize the airway during sleep.[93,94]

Simultaneously, various forms of stimulation were attempted in humans. Miki et al. placed percutaneous electrodes into the genioglossus muscle in six patients during overnight PSG.[95] The authors noted that the stimulation of this muscle significantly decreased the incidence of apnoea episodes, promoted deeper sleep and did not have any serious side effects.[95] Schwartz et al. used transoral intramuscular electrodes to stimulate the hyoglossus, styloglossus and genioglossus muscles, noting the different effects on airway patency by each muscle group.[96] Some authors similarly used fine-wire electrodes directly into the genioglossus, while others developed methods for stimulating the nerve directly.[97,98] This allowed for the activation of both the protrudor and retractor muscles for best outcomes. As data accumulated, both in animal and in human studies, there was strong evidence for direct HGNS in support of airway adequacy during sleep.[99]

Implantation trials

Prior to its approval by theUS Food and Drug Administration (FDA), several studies were conducted to evaluate the feasibility and efficacy of fully implanted HGNS devices. The initial studies were performed in adults. In 2001, Schwartz et al. implanted a tripolar cuff electrode for HGNS.[100] The device was placed in eight adults, confirming the feasibility of the procedure and therapeutic benefits in OSA via stimulation of the entire distal nerve.[100] The authors noted reduced AHI and oxyhaemoglobin desaturations after intervention with unilateral hypoglossal activation.[100] Subsequently, a similar study was performed with more patients, finding comparable results lasting for at least 1 year.[101]

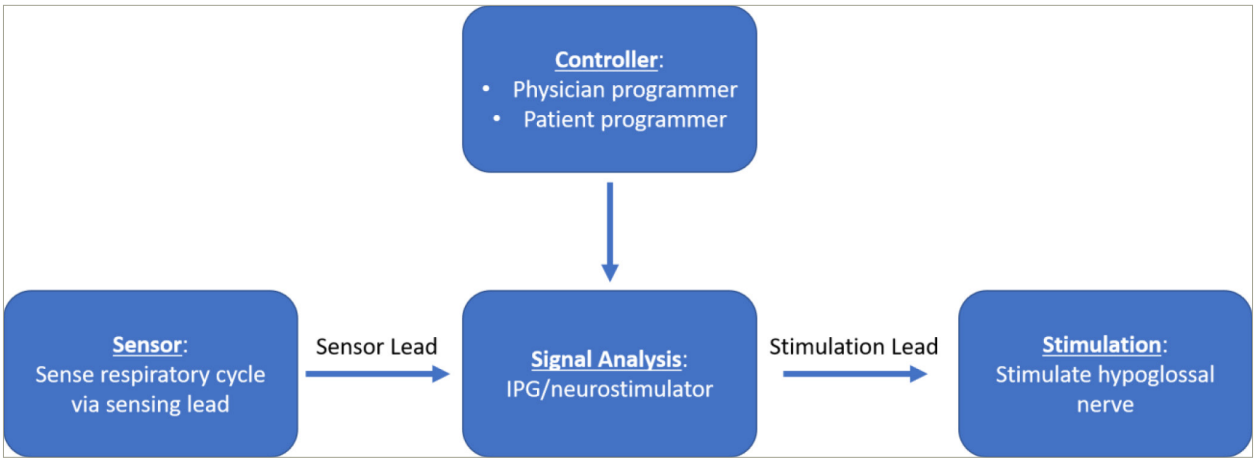
With the knowledge that branches of the hypoglossal nerve could be directly isolated and stimulated to move the genioglossus and improve airway obstruction, technology and techniques advanced to place the cuff electrode more distally, thereby targeting the protrudor muscles.[97,102] This adjustment was supported in multiple studies, demonstrating similar efficacy.[103–106]

Several issues with these devices were appreciated. Eastwood et al. noted that 71% of participants experienced one or more adverse events from the implantation surgery, including numbness, pain or skin irritation at the incision site.[104] In addition, 67% of participants experienced therapy-related complications, including abrasions on the tongue surface and tongue muscle fatigue.[104] However, these events were of short duration and resolved in all cases.[104] Most studies cite low rates of similar complications.[99] Overall, the pilot studies suggested that implantation was well tolerated with therapeutic efficacy for the management of OSA. Therefore, definitive trials were warranted.

Clinical trials

The Stimulation Therapy for Apnea Reduction Trial (STAR; ClinicalTrials.gov identifier: NCT01161420) was pivotal in assessing the outcomes of unilateral HGNS in adult patients with OSA.[107] This was a multicentre, prospective, single-group cohort study of patients with OSA intolerant to CPAP. The primary outcome measures were AHI and oxygen desaturation index (ODI) changes with implantation. Secondary outcomes included quality-of-life assessments as well as percentage of sleep time with oxygen saturation <90%. Inclusion criteria were patients 22 years or older who were intolerant to CPAP with a body mass index (BMI) of 32 kg/m^2 or less and AHI between 20 and 50 events per hour. Exclusion criteria were tonsillar hypertrophy and collapse of palatal tissues on pre-operative drug-induced sleep endoscopy (DISE). The study included 126 patients, 66% of whom saw a reduction of at least 50% in baseline AHI at 1 year. The authors noted that at the 12-month follow-up, repeat PSG revealed a median AHI reduction of 68% and an ODI reduction of 70% from baseline. In addition, 23 patients were selected for randomized therapy withdrawal, thereby serving as their own controls. These patients had return of their OSA despite a reduction in AHI the week prior, during the use of the device, further confirming its efficacy. Patients also reported improvement in secondary outcomes, namely quality of life, snoring and daytime sleepiness.[107] Treatment responses were sustained at 3 and 5 years

Figure 1: Flow diagram of the mechanism of action of the hypoglossal nerve stimulation[114]



Reproduced with permission from Vanderveken et al.[114] (http://creativecommons.org/licenses/by-nc/4.0).
IPG = implantable pulse generator.

after implantation with minimal risk.[102,108] A subsequent meta-analysis found that all available devices performed similarly, indicating equivalent treatment success as well as potential generalizability of the aforementioned results.[109]

Three medical device companies have conducted human trials with hypoglossal nerve stimulators. The Inspire® Upper Airway Stimulation system (P130008/S039; Inspire Medical Systems, Inc., Maple Grove, MN, USA) received FDA approval in 2014, with post-market trials using the device.[110,111] The long-term safety of the Genio® system (Nyxoah SA, Mont-Saint-Guibert, Belgium) in adult patients with OSA will soon be assessed in a clinical trial (A prospective, open-label, multicentric extension study to assess the long-term safety of the Genio® system in study subjects who have been implanted with the Genio® implantable stimulator [IS] for the treatment of OSA in adult patients; ClinicalTrials.gov identifier: NCT05939141).[112]

Procedure

By maintaining a stiffened tongue and tongue protrusion, the HGNS device opens the airway and reduces airway collapse during sleep.[113] The Inspire® Upper Airway Stimulation system is composed of a respiratory sensing lead, impulse generator (IPG) and stimulation lead. The device is controlled by an external remote control. The respiratory-sensing lead detects the respiratory cycle phase and activates the impulse generator upon inspiration; the impulse generator then sends an electrical impulse to the stimulation lead on the hypoglossal nerve, causing tongue protrusion.[83 107,114] Figure 1 provides a flow diagram of this process.[114]

The HGNS device was originally introduced as a right-sided, three-incision approach to limit noise from the cardiovascular system and accommodate existing cardiac implantation devices.[115–117] This strategy involved one incision for the stimulator lead midway in the right submandibular region, a second incision for the IPG at the right anterior chest wall and a third incision for the respiratory-sensing lead along the fifth or sixth intercostal space at the lateral chest.[115] Kent et al. eliminated the need for the third incision site by placing the respiratory sensory electrode behind the IPG.[118] Due to the reduced intraoperative time and post-operative pain, the FDA approved the two-incision, right-sided implantation in March 2021.[116,119] The two-incision technique has also been successfully conducted in left-sided implantation and should be considered if right-sided implantation is contraindicated.[120]

Devices are typically activated 1 month following placement. Patients are required to repeat a PSG to optimize the voltage settings for upper airway patency throughout sleep several months after surgery, with additional routine follow-up to ensure treatment success.[110]

Hypoglossal nerve stimulation in children

As mentioned previously, patients with DS are uniquely at risk for OSA, and disease persistence, after initial treatment. A majority (55–80%) of children with DS have OSA.[31,32] In this population, the pathophysiology is multifactorial and related to several anatomic features, including generalized hypotonia, macroglossia, midface hypoplasia, small tracheal calibre and lingual tonsil hypertrophy.[121] It is estimated that only 16–33% of children with DS and OSA have resolution of their OSA after AT.[121,122] Oftentimes, the site of residual obstruction is at the base of the tongue or may be due to pharyngeal collapse and oropharyngeal crowding associated with concomitant obesity and/or lingual tonsillar hypertrophy.[121] It has also been shown that 63% of patients with DS and persistent OSA have obstruction from glossoptosis, a feature that can be improved with HGNS. Therefore, this technology was applied specifically to children with DS in the setting of CPAP intolerance.[36]

Several case reports have shown the success of HGNS in adults with DS, suggesting expanded indications for the device. Van de Perck et al. reported a case of an adult patient with DS, severe OSA and CPAP intolerance who underwent HGNS.[123] They were found to have a 63% decrease in AHI and a 77% decrease in ODI 6 months after HGNS device implantation, with an average device usage of 9.4 hours per night.[123] A case series of three adults with DS and OSA showed strong adherence to the use of HGNS at an average of 57.3 hours per week and overall reductions in the titrated AHI.[124]

With these studies in mind, implantation was then attempted in children with DS. Diercks et al. implanted the first six paediatric HGNS devices in 2018.[125] Participants (aged 12–18 years) had DS and severe OSA (AHI >10 events/hour) despite prior AT.[125] In all patients, the implant was well tolerated and effective in significantly improving their OSA.[125] At 1-year follow-up, patients showed an 85% reduction in AHI, with four children having an AHI <5 events/hour and two children with AHI <10 events/hour.[125] The authors also reported a significant improvement in quality of life with the use of the HGNS device in these patients, as measured by the OSA-18 questionnaire.[125] Caloway et al. evaluated the safety and

Table 2: US Food and Drug Administration inclusion criteria for hypoglossal nerve stimulation[129–131]

	2014[130,131]	2023[129]		
Parameter				
Age	>18 years	22+ years	18–21 years	13–18 years with DS
AHI	15 ≤ AHI ≤ 65 events/hour	15 ≤ AHI ≤ 100 events/hour		10 ≤ AHI ≤ 50 events/hour
BMI	<32 kg/m^2	<40 kg/m^2		
Central/mixed apnoeas	<25% of total events	<25% of total events		
DISE findings	No complete concentric collapse at the palate	No complete concentric collapse at the palate		
Failed PAP	Yes	Yes	Yes	
Other			• Not candidates for AT • Have been considered for all other standard-of-care treatment options	

Central or mixed apnoeas must comprise <25% of the total AHI score.
AHI = apnoea– hypopnoea index; AT = adenotonsillectomy; BMI = body mass index; DISE = drug-induced sleep endoscopy; DS = Down syndrome; PAP = positive airway pressure.

efficacy of HGNS in 20 nonobese children and adolescents (aged 10–21 years) with DS and severe OSA.[126] These patients had prior intolerance to CPAP after previous AT.[126] The authors found that HGNS therapy was both safe and effective, with a median percentage reduction in titration AHI of 85% and a change in OSA-18 scores by 1.15 points, indicating a moderate clinical change in the quality of life.[126] A systematic review and meta-analysis of efficacy and adverse effects of HGNS in adolescents with OSA and DS identified nine studies, with a total of 106 patients.[127] This study found that HGNS significantly reduces the AHI as well as improves the quality of life in patients undergoing the procedure.[127] At this time, there is an ongoing clinical trial (Effects of hypoglossal nerve stimulation on cognition and language in Down syndrome and obstructive sleep apnea; ClinicalTrials.gov identifier: NCT04801771) involving 57 adolescents and young adults (aged 10–21 years) with DS and moderate-to-severe sleep apnoea post-AT for 12 months after HGNS device implantation.[128] The study will evaluate changes in cognition and language after therapy with the HGNS device.

Clinical indications

FDA approval for the Inspire® Upper Airway Stimulation system (P130008/S039) was originally granted in May 2014.[111,129] In 2023, FDA approval expanded and now includes (1) people with moderate-to-severe OSA (15 ≤ AHI ≤ 100) aged 22 years and older who cannot tolerate PAP or bi-level PAP and who do not have complete blockage of the soft palate; (2) people aged 18–21 years with moderate-to-severe OSA (15 ≤ AHI ≤ 100) and (3) people aged 13–18 years with DS and severe OSA (10 ≤ AHI ≤ 50) who are not AT candidates and have been considered for all alternative treatments.[111,129] *Table 2* provides the complete FDA inclusion criteria for HGNS.[129–131] To date, there are limited studies in children as the device was only recently approved.[129–131] It is expected that there will be a growing body of literature on children, which likely will result in further expansions for the indications and patient eligibility.

Complications

Overall, HGNS therapy is well tolerated. The STAR trial reported no serious complications, rehospitalizations or infections from the procedure.[107] Two participants required repositioning of the neurostimulator due to discomfort. Less serious adverse events related to tongue discomfort resolved with continued use of the HGNS device.[107] No long-term complications were reported in a cohort of 600 patients followed for 1 year after implantation.[132] It should be noted that patients with HGNS undergoing external electrical cardioversion should be counselled on potential device malfunction.[133] Additionally, patients with chronic lower respiratory diseases may be at an increased risk of intraoperative pneumothorax and pleural effusion and must be counselled accordingly.[134]

Paediatric trials parallel adult trials in their low complication rates. Diercks et al. reported that two patients experienced perioperative adverse events, including irritation of the chest incision and poor pain control, which were addressed with antibiotics and improved pain regimens.[75,125] Jayawardena et al. indicated no major complications among 23 patients implanted with the HGNS device.[135] Other cited complications include tongue or oral pain/discomfort, oral ulcers, surgical-site rash/cellulitis and cheek swelling.[127]

Some unique paediatric considerations include the potential for device displacement during puberty, the need for battery replacement every 10 years and the potential benefit of adjustments in surgical technique.[75,135] Further research is needed to fully evaluate these possibilities.

Hypoglossal nerve stimulation outcomes

To date, the success rate for HGNS is best established in adults, with a quoted rate of 66%.[107] Factors contributing to surgical success are being further elucidated. Ong et al. found that patients with complete anterior–posterior or lateral soft palate and/or epiglottic collapse are at risk of HGNS failure.[136] Complete concentric collapse at the velum is a known contraindication for implantation, and in this study, patients with this pattern were excluded from implantation.[129,136] Chao et al. noted lateral oropharyngeal collapse and significantly elevated preoperative AHI (49.4 ± 19.6 versus 36.9 ± 18.8, p=0.05) as risk factors for poor surgical success.[137] Xiao et al., interestingly, did not find any association between DISE patterns of collapse, but instead noted Mallampati III/IV and Friedman Tongue Position IV as factors that led to mildly decreased response.[138] Lee et al. noted that patients with lower pre-operative PAP requirements (<8 cm H_2O) had a greater response rate to HGNS.[139] Seay et al. similarly found that lower PAPs during a DISE were associated with HGNS responders when compared with non-responders.[140]

Researchers and surgeons are expanding the use of HGNS outside of the FDA approval criteria (*Table 2*). Sarber et al. reported the implantation in such patients with a success rate of 67%, which is similar to the 1-year STAR trial results at 66%.[141] The need to better characterize appropriate patients for this procedure, with additional data points outside of the FDA approval, is currently being investigated.[130]

Summary

OSA is common in the paediatric population, with higher rates in at-risk groups. AT is the first-line treatment for the majority of children, and management of persistent OSA after AT is nuanced. HGNS has recently expanded therapeutic options for patients with refractory OSA, including children and adolescents with DS. To date, this procedure has proven effective and well tolerated across multiple clinical trials. Continued

studies will likely expand eligible paediatric, and adult, candidates for HGNS. ❑

1. Gipson K, Lu M, Kinane TB. Sleep-disordered breathing in children. *Pediatr Rev*. 2019;40:3–13. DOI: 10.1542/pir.2018-0142.
2. Teplitzky TB, Zauher AJ, Isaiah A. Alternatives to polysomnography for the diagnosis of paediatric obstructive sleep apnea. *Diagnostics*. 1956;13:1956. DOI: 10.3390/diagnostics13111956.
3. Kirk V, Baughn J, D'Andrea L, et al. American Academy of Sleep Medicine position paper for the use of a home sleep apnea test for the diagnosis of OSA in children. *J Clin Sleep Med*. 2017;13:1199–203. DOI: 10.5664/jcsm.6772.
4. Zhang W, Si L. Obstructive sleep apnea syndrome (OSAS) and hypertension: Pathogenic mechanisms and possible therapeutic approaches. *Ups J Med Sci*. 2012;117:370–82. DOI: 10.3109/03009734.2012.707253.
5. Epstein LJ, Kristo D, Strollo PJ, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med*. 2009;5:263–76. DOI: 10.5664/jcsm.27497.
6. Ucros S, Granados C, Hill C, et al. Normal values for respiratory sleep polygraphy in children aged 4 to 9 years at 2,560 m above sea level. *J Sleep Res*. 2021;30:e13341. DOI: 10.1111/jsr.13341.
7. Bixler EO, Vgontzas AN, Lin H-M, et al. Sleep disordered breathing in children in a general population sample: Prevalence and risk factors. *Sleep*. 2009;32:731–6. DOI: 10.1093/sleep/32.6.731.
8. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2012;130:576–84. DOI: 10.1542/peds.2012-1671.
9. Baldassari CM, Mitchell RB, Schubert C, Rudnick EF. Paediatric obstructive sleep apnea and quality of life: A meta-analysis. *Off J Am Acad Otolaryngol-Head Neck Surg*. 2008;138:265–73. DOI: 10.1016/j.otohns.2007.11.003.
10. Guilleminault C, Korobkin R, Winkle R. A review of 50 children with obstructive sleep apnea syndrome. *Lung*. 1981;159:275–87. DOI: 10.1007/BF02713925.
11. Goldstein NA, Post JC, Rosenfeld RM, Campbell TF. Impact of tonsillectomy and adenoidectomy on child behavior. *Arch Otolaryngol Head Neck Surg*. 2000;126:494. DOI: 10.1001/archotol.126.4.494.
12. Katz ES, D'Ambrosio CM. Paediatric obstructive sleep apnea syndrome. *Clin Chest Med*. 2010;31:221–34. DOI: 10.1016/j.ccm.2010.02.002.
13. Nieminen P, Tolonen U, Löppönen H. Snoring and obstructive sleep apnea in children: A 6-month follow-up study. *Arch Otolaryngol Head Neck Surg*. 2000;126:481–6. DOI: 10.1001/archotol.126.4.481.
14. Landau YE, Bar-Yishay O, Greenberg-Dotan S, et al. Impaired behavioral and neurocognitive function in preschool children with obstructive sleep apnea. *Pediatr Pulmonol*. 2012;47:180–8. DOI: 10.1002/ppul.21534.
15. Parati G, Lombardi C, Narkiewicz K. Sleep apnea: Epidemiology, pathophysiology, and relation to cardiovascular risk. *Am J Physiol Regul Integr Comp Physiol*. 2007;293:R1671–83. DOI: 10.1152/ajpregu.00400.2007.
16. Weiss JW, Liu MDY, Huang J. Physiological basis for a causal relationship of obstructive sleep apnoea to hypertension. *Exp Physiol*. 2007;92:21–6. DOI: 10.1113/expphysiol.2006.035733.
17. Ai S, Li Z, Wang S, et al. Blood pressure and childhood obstructive sleep apnea: A systematic review and meta-analysis. *Sleep Med Rev*. 2022;65:101663. DOI: 10.1016/j.smrv.2022.101663.
18. Teplitzky TB, Zauher A, Isaiah A. Evaluation and diagnosis of paediatric obstructive sleep apnea—An update. *Front Sleep*. 2023;2. DOI: 10.3389/frsle.2023.1127784.
19. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;8:597–619. DOI: 10.5664/jcsm.2172.
20. Mitchell RB, Archer SM, Ishman SL, et al. Clinical practice guideline: Tonsillectomy in children (update). *Otolaryngol Head Neck Surg*. 2019;160:S1–42. DOI: 10.1177/0194599818801757.
21. Richardson MA. Sore throat, tonsillitis, and adenoiditis. *Med Clin North Am*. 1999;83:75–83. DOI: 10.1016/s0025-7125(05)70088-2.
22. Jung KY, Lim HH, Choi G, Choi JO. Age-related changes of IgA immunocytes and serum and salivary IgA after tonsillectomy. *Acta Otolaryngol Suppl*. 1996;523:115–9.
23. Sainz M, Gutierrez F, Moreno PM, et al. Changes in immunologic response in tonsillectomized children. I. Immunosuppression in recurrent tonsillitis. *Clin Otolaryngol Allied Sci*. 1992;17:376–9. DOI: 10.1111/j.1365-2273.1992.tb01677.x.
24. Verhulst SL, Van Gaal L, De Backer W, Desager K. The prevalence, anatomical correlates and treatment of sleep-disordered breathing in obese children and adolescents. *Sleep Med Rev*. 2008;12:339–46. DOI: 10.1016/j.smrv.2007.11.002.
25. Andersen IG, Holm J-C, Homøe P. Obstructive sleep apnea in obese children and adolescents, treatment methods and outcome of treatment – A systematic review. *Int J Pediatr Otorhinolaryngol*. 2016;87:190–7. DOI: 10.1016/j.ijporl.2016.06.017.
26. Marcus CL. Pathophysiology of childhood obstructive sleep apnea: Current concepts. *Respir Physiol*. 2000;119:143–54. DOI: 10.1016/s0034-5687(99)00109-7.
27. Wing YK, Hui SH, Pak WM, et al. A controlled study of sleep related disordered breathing in obese children. *Arch Dis Child*. 2003;88:1043–7. DOI: 10.1136/adc.88.12.1043.
28. Cielo CM, Marcus CL. Obstructive sleep apnoea in children with craniofacial syndromes. *Paediatr Respir Rev*. 2015;16:189–96. DOI: 10.1016/j.prrv.2014.11.003.
29. Katz SL. Assessment of sleep-disordered breathing in paediatric neuromuscular diseases. *Pediatrics*. 2009;123(Suppl.4):S222–5. DOI: 10.1542/peds.2008-2952E.
30. Seither K, Helm BM, Heubi C, et al. Sleep apnea in children with Down syndrome. *Pediatrics*. 2023;151:e2022058771. DOI: 10.1542/peds.2022-058771.
31. Dyken ME, Lin-Dyken DC, Poulton S, et al. Prospective polysomnographic analysis of obstructive sleep apnea in Down syndrome. *Arch Pediatr Adolesc Med*. 2003;157:655. DOI: 10.1001/archpedi.157.7.655.
32. Shott SR, Amin R, Chini B, et al. Obstructive sleep apnea: Should all children with Down syndrome be tested?. *Arch Otolaryngol Head Neck Surg*. 2006;132:432–6. DOI: 10.1001/archotol.132.4.432.
33. Hill CM, Evans HJ, Elphick H, et al. Prevalence and predictors of obstructive sleep apnoea in young children with Down syndrome. *Sleep Medicine*. 2016;27–28:99–106. DOI: 10.1016/j.sleep.2016.10.001.
34. Richtsmeier JT, Baxter LL, Reeves RH. Parallels of craniofacial maldevelopment in Down syndrome and Ts65Dn mice. *Dev Dyn*. 2000;217:137–45. DOI: 10.1002/(SICI)1097-0177(200002)217:2<137::AID-DVDY1>3.0.CO;2-N.
35. Breslin J, Spanò G, Bootzin R, et al. Obstructive sleep apnea syndrome and cognition in Down syndrome. *Develop Med Child Neuro*. 2014;56:657–64. DOI: 10.1111/dmcn.12376.
36. Donnelly LF, Shott SR, LaRose CR, et al. Causes of persistent obstructive sleep apnea despite previous tonsillectomy and adenoidectomy in children with Down syndrome as depicted on static and dynamic cine MRI. *AJR Am J Roentgenol*. 2004;183:175–81. DOI: 10.2214/ajr.183.1.1830175.
37. Nation J, Brigger M. The efficacy of adenotonsillectomy for obstructive sleep apnea in children with Down syndrome: A systematic review.. *Otolaryngol Head Neck Surg*. 2017;157:401–8. DOI: 10.1177/0194599817703921.
38. Maris M, Verhulst S, Wojciechowski M, et al. Outcome of adenotonsillectomy in children with Down syndrome and obstructive sleep apnoea. *Arch Dis Child*. 2017;102:331–6. DOI: 10.1136/archdischild-2015-310351.
39. Ye J, Liu H, Zhang G, et al. Outcome of adenotonsillectomy for obstructive sleep apnea syndrome in children. *Ann Otol Rhinol Laryngol*. 2010;119:506–13. DOI: 10.1177/000348941011900802.
40. Connolly HV, Tomaselli LT, McKenna Benoit MK. Adenotonsillectomy for paediatric obstructive sleep apnea: How to predict those at risk for postoperative complications. *J Clin Sleep Med*. 2020;16:3–4. DOI: 10.5664/jcsm.8150.
41. Brietzke SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of paediatric obstructive sleep apnea/hypopnea syndrome: A meta-analysis. *Otolaryngol Head Neck Surg*. 2006;134:979–84. DOI: 10.1016/j.otohns.2006.02.033.
42. Marcus CL, Moore RH, Rosen CL, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med*. 2013;368:2366–76. DOI: 10.1056/NEJMoa1215881.
43. Mitchell RB, Kelly J. Child behavior after adenotonsillectomy for obstructive sleep apnea syndrome. *Laryngoscope*. 2005;115:2051–5. DOI: 10.1097/01.MLG.0000181516.65577.94.
44. Raposo D, Menezes M, Rito J, et al. Predictors of OSA following adenotonsillectomy in children with trisomy 21. *Clin Otolaryngol*. 2021;46:256–62. DOI: 10.1111/coa.13657.
45. Cottrell J, Zahr SK, Propst EJ, et al. Morbidity and mortality from adenotonsillectomy in children with trisomy 21. *Int J Pediatr Otorhinolaryngol*. 2020;138:110377. DOI: 10.1016/j.ijporl.2020.110377.
46. Goldstein NA, Armfield DR, Kingsley LA, et al. Postoperative complications after tonsillectomy and adenoidectomy in children with Down syndrome. *Arch Otolaryngol Head Neck Surg*. 1998;124:171. DOI: 10.1001/archotol.124.2.171.
47. Garde AJB, Gibson NA, Samuels MP, Evans HJ. Recent advances in paediatric sleep disordered breathing. *Breathe*. 2022;18:220151. DOI: 10.1183/20734735.0151-2022.
48. Ishman SL, Maturo S, Schwartz S, et al. Expert consensus statement: Management of paediatric persistent obstructive sleep apnea after adenotonsillectomy. *Otolaryngol Head Neck Surg*. 2023;168:115–30. DOI: 10.1002/ohn.159.
49. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet*. 2014;383:736–47. DOI: 10.1016/S0140-6736(13)60734-5.
50. McDaid C, Durée KH, Griffin SC, et al. A systematic review of continuous positive airway pressure for obstructive sleep apnoea–hypopnoea syndrome. *Sleep Med Rev*. 2009;13:427–36. DOI: 10.1016/j.smrv.2009.02.004.
51. Giles TL, Lasserson TJ, Smith BJ, et al. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev*. 2006;CD001106:CD001106. DOI: 10.1002/14651858.CD001106.pub2.
52. Kribbs NB, Pack AI, Kline LR, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis*. 1993;147:887–95. DOI: 10.1164/ajrccm/147.4.887.
53. Weaver TE, Kribbs NB, Pack AI, et al. Night-to-night variability in CPAP use over the first three months of treatment. *Sleep*. 1997;20:278–83. DOI: 10.1093/sleep/20.4.278.
54. Sawunyavisuth B, Ngamjarus C, Sawanyawisuth K. Any effective intervention to improve CPAP adherence in children with obstructive sleep apnea: A systematic review. *Glob Pediatr Health*. 2021;8:2333794X211019884. DOI: 10.1177/2333794X211019884.
55. Medical Coverage Database. Continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea (OSA) (CAG-00093N) - decision memo. 2021. Available at: www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=19&fromdb=true (Date last accessed: 28 February 2024).
56. Weiss MR, Allen ML, Landeo-Gutierrez JS, et al. Defining the patterns of PAP adherence in paediatric obstructive sleep apnea: A clustering analysis using real-world data. *J Clin Sleep Med*. 2021;17:1005–13. DOI: 10.5664/jcsm.9100.
57. King MS, Xanthopoulos MS, Marcus CL. Improving positive airway pressure adherence in children. *Sleep Med Clin*. 2014;9:219–34. DOI: 10.1016/j.jsmc.2014.02.003.
58. Perriol M-P, Jullian-Desayes I, Joyeux-Faure M, et al. Long-term adherence to ambulatory initiated continuous positive airway pressure in non-syndromic OSA children. *Sleep Breath*. 2019;23:575–8. DOI: 10.1007/s11325-018-01775-2.
59. Tanner S, Collaro A, Chawla J. The management of residual OSA post-adenotonsillectomy in children with Down syndrome: The experience of a large tertiary sleep service. *Sleep Med*. 2023;109:158–63. DOI: 10.1016/j.sleep.2023.06.009.
60. MacDonagh L, Farrell L, O'Reilly R, et al. Efficacy and adherence of noninvasive ventilation treatment in children with Down syndrome. *Pediatr Pulmonol*. 2021;56:1704–15. DOI: 10.1002/ppul.25308.
61. Trucco F, Chatwin M, Semple T, et al. Sleep disordered breathing and ventilatory support in children with Down syndrome. *Pediatr Pulmonol*. 2018;53:1414–21. DOI: 10.1002/ppul.24122.
62. Villa MP, Malagola C, Pagani J, et al. Rapid maxillary expansion in children with obstructive sleep apnea syndrome: 12-month follow-up. *Sleep Med*. 2007;8:128–34. DOI: 10.1016/j.sleep.2006.06.009.
63. Amaddeo A, Khirani S, Griffon L, et al. Non-invasive ventilation and CPAP failure in children and indications for invasive ventilation. *Front Pediatr*. 2020;8:544921. DOI: 10.3389/fped.2020.544921.
64. Whitla L, Lennon P. Non-surgical management of obstructive sleep apnoea: A review. *Paediatr Int Child Health*. 2017;37:1–5. DOI: 10.1080/20469047.2016.1162391.
65. Yanyan M, Min Y, Xuemei G. Mandibular advancement appliances for the treatment of obstructive sleep apnea in children: A systematic review and meta-analysis. *Sleep Med*. 2019;60:145–51. DOI: 10.1016/j.sleep.2018.12.022.
66. Yu M, Ma Y, Xu Y, et al. Orthodontic appliances for the treatment of paediatric obstructive sleep apnea: A systematic review and network meta-analysis. *Sleep Med Rev*. 2023;72:101855. DOI: 10.1016/j.smrv.2023.101855.
67. Zaghi S, Holty J-EC, Certal V, et al. Maxillomandibular advancement for treatment of obstructive sleep apnea: A meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2016;142:58–66. DOI: 10.1001/jamaoto.2015.2678.
68. Hammoudeh J, Bindingnavele VK, Davis B. Neonatal and infant mandibular distraction as an alternative to tracheostomy in severe obstructive sleep apnea. *Cleft Palate Craniofac J*. 2012;49:32–8. DOI: 10.1597/10-069.
69. Tahiri Y, Viezel-Mathieu A, Aldekhayel S, et al. The effectiveness of mandibular distraction in improving airway obstruction in the paediatric population. *Plast Reconstr Surg*. 2014;133:352e–9e. DOI: 10.1097/01.prs.0000438049.29258.a8.
70. Ulualp S. Outcomes of tongue base reduction and lingual tonsillectomy for residual paediatric obstructive sleep apnea after adenotonsillectomy. *Int Arch Otorhinolaryngol*. 2019;23:e415–21. DOI: 10.1055/s-0039-1685156.
71. Camacho M, Noller MW, Zaghi S, et al. Tongue surgeries for paediatric obstructive sleep apnea: A systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. 2017;274:2981–90. DOI: 10.1007/s00405-017-4545-4.
72. Ulualp SO. Modified expansion sphincter pharyngoplasty for treatment of children with obstructive sleep apnea. *JAMA Otolaryngol Head Neck Surg*. 2014;140:817. DOI: 10.1001/jamaoto.2014.1329.
73. Sulman CG. Paediatric sleep surgery. *Front Pediatr*. 2014;2:51. DOI: 10.3389/fped.2014.00051.
74. Rizzi CJ, Amin JD, Isaiah A, et al. Tracheostomy for severe paediatric obstructive sleep apnea: Indications and outcomes. *Otolaryngol Head Neck Surg*. 2017;157:309–13. DOI: 10.1177/0194599817702369.
75. Diercks GR, Wentland C, Keamy D, et al. Hypoglossal nerve stimulation in adolescents with Down syndrome and obstructive sleep apnea. *JAMA Otolaryngol Head Neck Surg*. 2018;144:37–42. DOI: 10.1001/jamaoto.2017.1871.
76. Sudarsan SS, Paramasivan VK, Arumugam SV, et al. Comparison of treatment modalities in syndromic children with obstructive sleep apnea – A randomized cohort study. *Int*

J Pediatr Otorhinolaryngol. 2014;78:1526–33. DOI: 10.1016/j.ijporl.2014.06.027.
77. Carvalho FR, Lentini-Oliveira DA, Prado LB, et al. Oral appliances and functional orthopaedic appliances for obstructive sleep apnoea in children. *Cochrane Database Syst Rev*. 2016;10:CD005520. DOI: 10.1002/14651858.CD005520.pub3.
78. Nazarali N, Altalibi M, Nazarali S, et al. Mandibular advancement appliances for the treatment of paediatric obstructive sleep apnea: A systematic review. *Eur J Orthod*. 2015;37:618–26. DOI: 10.1093/ejo/cju101.
79. Kang K-T, Koltai PJ, Lee C-H, et al. Lingual tonsillectomy for treatment of paediatric obstructive sleep apnea: A meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2017;143:561–8. DOI: 10.1001/jamaoto.2016.4274.
80. Fregosi RF, Fuller DD. Respiratory-related control of extrinsic tongue muscle activity. *Respir Physiol*. 1997;110:295–306. DOI: 10.1016/s0034-5687(97)00095-9.
81. John J, Bailey EF, Fregosi RF. Respiratory-related discharge of genioglossus muscle motor units. *Am J Respir Crit Care Med*. 2005;172:1331–7. DOI: 10.1164/rccm.200505-790OC.
82. Wilkinson V, Malhotra A, Nicholas CL, et al. Discharge patterns of human genioglossus motor units during sleep onset. *Sleep*. 2008;31:525–33. DOI: 10.1093/sleep/31.4.525.
83. Gruenberg E, Cooper J, Zamora T, et al. Beyond CPAP: Modifying upper airway output for the treatment of OSA. *Front Neurol*. 2023;14:1202271. DOI: 10.3389/fneur.2023.1202271.
84. Silverstein K, Costello BJ, Giannakpoulos H, Hendler B. Genioglossus muscle attachments: An anatomic analysis and the implications for genioglossus advancement. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2000;90:686–8. DOI: 10.1067/moe.2000.111187.
85. Cheng S, Butler JE, Gandevia SC, Bilston LE. Movement of the human upper airway during inspiration with and without inspiratory resistive loading. *J Appl Physiol (1985)*. 2011;110:69–75. DOI: 10.1152/japplphysiol.00413.2010.
86. Cori JM, O'Donoghue FJ, Jordan AS. Sleeping tongue: Current perspectives of genioglossus control in healthy individuals and patients with obstructive sleep apnea. *Nat Sci Sleep*. 2018;10:169–79. DOI: 10.2147/NSS.S143296.
87. Rueda J-R, Mugueta-Aguinaga I, Vilaró J, Rueda-Etxebarria M. Myofunctional therapy (oropharyngeal exercises) for obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2020;11:CD013449. DOI: 10.1002/14651858.CD013449.pub2.
88. van der Weijden FN, Lobbezoo F, Slot DE. The effect of playing a wind instrument or singing on risk of sleep apnea: A systematic review and meta-analysis. *J Clin Sleep Med*. 2020;16:1591–601. DOI: 10.5664/jcsm.8628.
89. White DP. Sleep-related breathing disorder. 2. Pathophysiology of obstructive sleep apnoea. *Thorax*. 1995;50:797–804. DOI: 10.1136/thx.50.7.797.
90. Oliven A, Odeh M, Schnall RP. Improved upper airway patency elicited by electrical stimulation of the hypoglossus nerves. *Respiration*. 1996;63:213–6. DOI: 10.1159/000196547.
91. Schwartz AR, Thut DC, Russ B, et al. Effect of electrical stimulation of the hypoglossal nerve on airflow mechanics in the isolated upper airway. *Am Rev Respir Dis*. 1993;147:1144–50. DOI: 10.1164/ajrccm/147.5.1144.
92. Eisele DW, Schwartz AR, Hari A, et al. The effects of selective nerve stimulation on upper airway airflow mechanics. *Arch Otolaryngol Head Neck Surg*. 1995;121:1361–4. DOI: 10.1001/archotol.1995.01890120021004.
93. Fuller D, Mateika JH, Fregosi RF. Co-activation of tongue protrudor and retractor muscles during chemoreceptor stimulation in the rat. *J Physiol*. 1998;507 (Pt 1):265–76. DOI: 10.1111/j.1469-7793.1998.265bu.x.
94. Oliven A, Odeh M, Geitini L, et al. Effect of coactivation of tongue protrusor and retractor muscles on pharyngeal lumen and airflow in sleep apnea patients. *J Appl Physiol*. 2007;103:1662–8. DOI: 10.1152/japplphysiol.00620.2007.
95. Miki H, Hida W, Chonan T, et al. Effects of submental electrical stimulation during sleep on upper airway patency in patients with obstructive sleep apnea. *Am Rev Respir Dis*. 1989;140:1285–9. DOI: 10.1164/ajrccm/140.5.1285.
96. Schwartz AR, Eisele DW, Hari A, et al. Electrical stimulation of the lingual musculature in obstructive sleep apnea. *J Appl Physiol*. 1996;81:643–52. DOI: 10.1152/jappl.1996.81.2.643.
97. 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*. 2003;95:2023–9. DOI: 10.1152/japplphysiol.00203.2003.
98. Eisele DW, Smith PL, Alam DS, Schwartz AR. Direct hypoglossal nerve stimulation in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg*. 1997;123:57–61. DOI: 10.1001/archotol.1997.01900010067009.
99. Fleury Curado T, Oliven A, Sennes LU, et al. Neurostimulation treatment of OSA. *Chest*. 2018;154:1435–47. DOI: 10.1016/j.chest.2018.08.1070.
100. Schwartz AR, Bennett ML, Smith PL, et al. Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg*. 2001;127:1216. DOI: 10.1001/archotol.127.10.1216.
101. Kezirian EJ, Goding GS, Malhotra A, et al. Hypoglossal nerve stimulation improves obstructive sleep apnea: 12-month outcomes. *J Sleep Res*. 2014;23:77–83. DOI: 10.1111/jsr.12079.
102. Woodson BT, Strohl KP, Soose RJ, et al. Upper airway stimulation for obstructive sleep apnea: 5-year outcomes. *Otolaryngol Head Neck Surg*. 2018;159:194–202. DOI: 10.1177/0194599818762383.
103. Schwartz AR, Jacobowitz O, Eisele DW, et al. Targeted hypoglossal nerve stimulation for patients with obstructive sleep apnea: A randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. 2023;149:512. DOI: 10.1001/jamaoto.2023.0161.
104. Eastwood PR, Barnes M, Walsh JH, et al. Treating obstructive sleep apnea with hypoglossal nerve stimulation. *Sleep*. 2011;34:1479–86. DOI: 10.5665/sleep.1380.
105. Friedman M, Jacobowitz O, Hwang MS, et al. Targeted hypoglossal nerve stimulation for the treatment of obstructive sleep apnea: six-month results. *Laryngoscope*. 2016;126:2618–23. DOI: 10.1002/lary.25909.
106. Mwenge GB, Rombaux P, Dury M, et al. Targeted hypoglossal neurostimulation for obstructive sleep apnoea: A 1-year pilot study. *Eur Respir J*. 2013;41:360–7. DOI: 10.1183/09031936.00042412.
107. Strollo PJ Jr, Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med*. 2014;370:139–49. DOI: 10.1056/NEJMoa1308659.
108. Woodson BT, Soose RJ, Gillespie MB, et al. Three-year outcomes of cranial nerve stimulation for obstructive sleep apnea: The STAR trial. *Otolaryngol Head Neck Surg*. 2016;154:181–8. DOI: 10.1177/0194599815616618.
109. Certal VF, Zaghi S, Riaz M, et al. Hypoglossal nerve stimulation in the treatment of obstructive sleep apnea: A systematic review and meta-analysis. *Laryngoscope*. 2015;125:1254–64. DOI: 10.1002/lary.25032.
110. Olson MD, Junna MR. Hypoglossal nerve stimulation therapy for the treatment of obstructive sleep apnea. *Neurotherapeutics*. 2021;18:91–9. DOI: 10.1007/s13311-021-01012-x.
111. U.S. Food and Drug Administration. Inspire® Upper Airway Stimulation – P130008/S039. 2020. Available at: www.fda.gov/medical-devices/recently-approved-devices/inspire-upper-airway-stimulation-p130008s090 (Date last accessed: 28 February 2024).
112. Nyxoah SA. A prospective, open-label multicentric extension study to assess the long-term safety of the Genio® system in study subjects who have been implanted with the Genio® Implantable Stimulator (IS) for the treatment of OSA in adult patients. 2023. Available at: https://clinicaltrials.gov/study/NCT05939141 (Date last accessed: 28 February 2024).
113. Eisele DW, Smith PL, Alam DS, Schwartz AR. Direct hypoglossal nerve stimulation in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg*. 1997;123:57–61. DOI: 10.1001/archotol.1997.01900010067009.
114. Vanderveken OM, Beyers J, Op de Beeck S, et al. Development of a clinical pathway and technical aspects of upper airway stimulation therapy for obstructive sleep apnea. *Front Neurosci*. 2017;11:523. DOI: 10.3389/fnins.2017.00523.
115. Heiser C, Thaler E, Boon M, et al. Updates of operative techniques for upper airway stimulation. *Laryngoscope*. 2016;126:S12–16. DOI: 10.1002/lary.26158.
116. Kent DT, Chio EG, Weiner JS, et al. A noninferiority analysis of 3- vs 2-incision techniques for hypoglossal nerve stimulator implantation. *Otolaryngol Head Neck Surg*. 2022;167:197–202. DOI: 10.1177/01945998211062150.
117. Maurer JT, Van de Heyning P, Lin H-S, et al. Operative technique of upper airway stimulation: An implantable treatment of obstructive sleep apnea. *Oper Tech Otolaryngol-Head Neck Surg*. 2012;23:227–33. DOI: 10.1016/j.otot.2012.07.002.
118. Kent DT, Weiner JS, Chio EG, Weidenbecher M. Hypoglossal nerve stimulator implantation via a 2-incision technique. *Oper Tech Otolaryngol-Head Neck Surg*. 2020;31:e35–42. DOI: 10.1016/j.otot.2020.06.002.
119. Saltagi MZ, Powell K, Saltagi AK, et al. Novel outcome analysis tool for hypoglossal nerve stimulator sensor lead function and comparison by incision type (2 versus 3). *Laryngoscope*. 2023;133:423–30. DOI: 10.1002/lary.30365.
120. Lin C, Olson MD, Huyett P, Chio EG. Implantation of the hypoglossal nerve stimulator via left-sided, 2-incision approach. *J Clin Sleep Med*. 2022;18:1219–22. DOI: 10.5664/jcsm.9856.
121. 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:E263–7. DOI: 10.1002/lary.28138.
122. Best J, Mutchnick S, Ida J, Billings KR. Trends in management of obstructive sleep apnea in paediatric patients with Down syndrome. *Int J Pediatr Otorhinolaryngol*. 2018;110:1–5. DOI: 10.1016/j.ijporl.2018.04.008.
123. 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;23:879–83. DOI: 10.1007/s11325-018-1752-1.
124. 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:E402–6. DOI: 10.1002/lary.27723.
125. Diercks GR, Wentland C, Keamy D, et al. Hypoglossal nerve stimulation in adolescents with Down syndrome and obstructive sleep apnea. *JAMA Otolaryngol Head Neck Surg*. 2018;144:37–42. DOI: 10.1001/jamaoto.2017.1871.
126. 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:E263–7. DOI: 10.1002/lary.28138.
127. Liu P, Kong W, Fang C, et al. Hypoglossal nerve stimulation in adolescents with Down syndrome and obstructive sleep apnea: A systematic review and meta-analysis. *Front Neurol*. 2022;13:1037926. DOI: 10.3389/fneur.2022.1037926.
128. ClinicalTrials.gov. Effects of hypoglossal nerve stimulation on cognition and language in Down syndrome and obstructive sleep apnea. ClinicalTrials.gov identifier: NCT04801771. 2024. Available at: https://clinicaltrials.gov/study/NCT04801771 (Date last accessed: 28 February 2024).
129. U.S. Food and Drug Administration. Inspire Upper Airway Stimulation – P130008/S090. 2023. Available at: www.fda.gov/medical-devices/recently-approved-devices/inspire-upper-airway-stimulation-p130008s090 (Date last accessed: 28 February 2024).
130. 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;17:2477–87. DOI: 10.5664/jcsm.9542.
131. Strohl MM, Yamauchi M, Peng Z, Strohl KP. Insights since FDA approval of hypoglossal nerve stimulation for the treatment of obstructive sleep apnea. *Curr Sleep Med Rep*. 2017;3:133–41. DOI: 10.1007/s40675-017-0088-x.
132. Withrow K, Evans S, Harwick J, et al. Upper airway stimulation response in older adults with moderate to severe obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2019;161:714–9. DOI: 10.1177/0194599819848709.
133. Vasconcellos AP, Huntley CT, Schell AE, et al. Dysfunctional hypoglossal nerve stimulator after electrical cardioversion: A case series. *Laryngoscope*. 2019;129:1949–53. DOI: 10.1002/lary.27488.
134. Lorenz FJ, Goyal N. Iatrogenic pneumothorax during hypoglossal nerve stimulator implantation: A large database analysis. *Otolaryngol Head Neck Surg*. 2023;168:876–80. DOI: 10.1177/01945998221122696.
135. Jayawardena ADL, Randolph GW, Hartnick CJ. Paediatric modifications to hypoglossal nerve stimulation for obstructive sleep apnea: How I do it. *Laryngoscope*. 2021;131:423–4. DOI: 10.1002/lary.28661.
136. 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;154:970–7. DOI: 10.1177/0194599816636835.
137. Chao TN, Thaler ER. Predictors of success in hypoglossal nerve stimulator implantation for obstructive sleep apnea. *World J Otorhinolaryngol Head Neck Surg*. 2021;7:40–4. DOI: 10.1016/j.wjorl.2020.02.007.
138. Xiao R, Trask DK, Kominsky AH. Preoperative predictors of response to hypoglossal nerve stimulation for obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2020;162:400–7. DOI: 10.1177/0194599820901499.
139. Lee CH, Seay EG, Walters BK, et al. Therapeutic positive airway pressure level predicts response to hypoglossal nerve stimulation for obstructive sleep apnea. *J Clin Sleep Med*. 2019;15:1165–72. DOI: 10.5664/jcsm.7814.
140. Seay EG, Keenan BT, Schwartz AR, Dedhia RC. Evaluation of therapeutic positive airway pressure as a hypoglossal nerve stimulation predictor in patients with obstructive sleep apnea. *JAMA Otolaryngol Head Neck Surg*. 2020;146:691–8. DOI: 10.1001/jamaoto.2020.1018.
141. Sarber KM, Chang KW, Ishman SL, et al. Hypoglossal nerve stimulator outcomes for patients outside the U.S. *Laryngoscope*. 2020;130:866–72. DOI: 10.1002/lary.28175.