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Editorial

A New Randomized Trial Broadens Neurostimulation Options for Obstructive Sleep Apnea: Insights from the OSPREY Trial

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Obstructive sleep apnea (OSA) remains one of the most prevalent and incompletely treated disorders encountered by otolaryngologists worldwide. Although positive airway pressure (PAP) therapy is the established first-line treatment, long-term intolerance and poor adherence limit its effectiveness for a substantial proportion of patients. Surgical interventions and oral appliance therapy provide alternative options, yet outcomes are variable and often highly dependent on patient selection and anatomical factors. Against this background, implantable neurostimulation has emerged over the past decade as a novel therapeutic strategy, and recent randomized evidence suggests that its clinical role is continuing to evolve.

In April 2026, *Annals of Internal Medicine* published the primary results of the OSPREY trial (treating Obstructive Sleep aPnea using taRgEted hYpoglossal nerve stimulation), a randomized controlled study evaluating proximal hypoglossal nerve stimulation (pHGNS) in adults with moderate-to-severe OSA who were unable to tolerate PAP therapy[1]. The study provides the most rigorous controlled evidence to date for this approach of hypoglossal nerve stimulation (HGNS) and offers important insights for otolaryngologists practicing across diverse healthcare systems.

Hypoglossal Nerve Stimulation in the Treatment Landscape of OSA

HGNS was introduced to address upper airway collapse during sleep by electrically activating tongue and related airway dilator muscles. The earliest widely adopted systems employ distal HGNS, targeting branches of the hypoglossal nerve with implantable electrodes to preferentially activate the genioglossus and produce anterior tongue displacement. The unilateral distal HGNS system developed by Inspire received regulatory approval in the United States in 2014[2], and more recently, a bilateral distal HGNS system developed by Nyxoah has also achieved regulatory approval in selected regions[3].

While clinical studies and registries have demonstrated meaningful reductions in OSA severity with distal HGNS in selected populations, these systems share several defining features that influence their use in practice. Patients are commonly selected using drug-induced sleep endoscopy (DISE) to exclude unfavorable patterns such as complete concentric collapse (CCC) of the pharynx, and eligibility criteria often include body mass index thresholds. These requirements, while helping to optimize outcomes, limit the proportion of patients who may be considered candidates for therapy and have motivated exploration of alternative stimulation paradigms.

Proximal Hypoglossal Nerve Stimulation: A Distinct Physiological Approach

This represents a fundamentally different strategy within the HGNS category. Instead of selectively stimulating distal nerve branches, the pHGNS system evaluated in the OSPREY trial (aura6000, LivaNova) targets the main trunk of the hypoglossal nerve using a multi-contact electrode array, enabling simultaneous activation of multiple motor branches.

From a physiological perspective, distal HGNS is designed primarily to produce tongue protrusion through selective activation of the medial branch innervating the genioglossus muscle. Proximal stimulation, by contrast,

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activates both protrusor and retractor muscle groups of the tongue. Rather than producing a single direction of tongue movement, this broader activation pattern produces a net stabilizing effect on the upper airway through several complementary mechanisms. In most individuals, genioglossus activation provides a dominant anterior or neutral mechanical force, while concurrent activation of retractor muscles increases overall tongue stiffness. These effects reduce tongue compliance and limit posterior displacement during inspiration. In addition, activation of muscles such as the hyoglossus may influence the position and stability of the hyoid complex and lateral pharyngeal walls, contributing to more global airway stabilization.

The OSPREY Trial: Study Design and Population

The OSPREY trial was conducted across 23 centers in the United States and enrolled adults aged 22 years or older with moderate-to-severe OSA, defined by an apnea–hypopnea index (AHI) of 15–65 events per hour. All participants were unable to tolerate PAP therapy[4]. The study population exhibited a mean baseline AHI of approximately 36 events per hour and included patients with body mass index values up to 35 kg/m[2], reflecting a cohort with more severe disease and greater obesity than those typically enrolled in earlier distal HGNS trials, such as STAR[5].

All participants underwent implantation of the pHGNS system in an outpatient setting and were randomized in a 2:1 ratio to active treatment or control using a delayed-activation design. In the treatment group, stimulation was initiated one month after implantation, whereas in the control group the device remained inactive until month 7, after which patients crossed over to active therapy. Notably, DISE was not used for patient selection, and CCC was not an exclusion criterion.

Clinical Outcomes and Safety Profile

At the primary endpoint of seven months, the OSPREY trial met its predefined efficacy criteria. More than half of patients receiving active pHGNS achieved a clinically meaningful AHI response (i.e., a reduction of at least 50% from baseline and an AHI below 20 events per hour) compared with a small minority of patients in the control group. Significant improvements were also observed in oxygen desaturation index, measures of nocturnal hypoxemia, and respiratory arousal frequency.

Patient-reported outcomes mirrored these objective findings. Daytime sleepiness, assessed using the Epworth Sleepiness Scale, and functional measures of sleep-related quality of life improved significantly in the treatment group during the randomized phase but not among controls. Following crossover to active therapy after month 7, control patients demonstrated similar improvements by month 13, supporting reproducibility of treatment effect.

From a procedural standpoint, device implantation was well tolerated. All surgeries were performed on an outpatient basis, and no serious device- or procedure-related adverse events were reported through 13 months of follow-up. Most adverse events were mild or moderate, such as transient discomfort or stimulation-related sensations, and rates of device revision or explantation were low. On the basis of these data, the aura6000 system has received regulatory approval in the United States, supporting its transition from investigational therapy to clinical practice[6].

How OSPREY Advances the Evidence Base for Neurostimulation

The OSPREY trial builds directly on prior randomized evidence supporting pHGNS. In the earlier THN3 randomized controlled trial[7], pHGNS was also evaluated using an active treatment versus control design and demonstrated clinically meaningful improvements in OSA severity. Together, THN3 and OSPREY represent a departure from earlier single‐arm HGNS studies by incorporating randomized comparators, addressing inherent night‐to‐night variability in OSA severity and strengthening causal inference.

Compared with THN3, OSPREY incorporated additional design refinements, including a delayed‐activation control strategy and a longer randomized treatment period. The crossover component of OSPREY further demonstrated that observed improvements were attributable to active stimulation rather than implantation alone or nonspecific effects of follow‐up. These features provide more robust and generalizable randomized evidence supporting the role of pHGNS in PAP‐intolerant patients.

Future Directions in Airway Neuromodulation

While pHGNS represents an important advance, it is part of a broader exploration of neuromodulation strategies for sleep-disordered breathing. Investigational approaches have included stimulation of additional neural targets involved in airway control, such as the ansa cervicalis to recruit infrahyoid strap muscles[8], as well as phrenic nerve stimulation, which can influence respiratory timing, lung volume, and caudal traction on the upper airway. Conceptually, future therapies may involve multi-site or multi-nerve stimulation to optimize airway stability across diverse patterns of collapse[9]. Longer-term studies will be needed to clarify durability of effect, impact on cardiovascular outcomes, cost-effectiveness, and predic-

tors of individual response for all neuromodulatory therapies.

Conclusion

The publication of the OSPREY randomized controlled trial marks an important step in the maturation of neurostimulation as a treatment option for OSA. Proximal HGNS demonstrated clinically meaningful improvements in both objective sleep metrics and patient-reported outcomes, with an acceptable safety profile, in a patient population representative of everyday otolaryngology practice.

For sleep physicians and otolaryngologists worldwide, these findings highlight the expanding role of airway neuromodulation within a comprehensive, patient-centered approach to the management of sleep-disordered breathing.

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Author contributions

Yike Li: conceptualization, methodology, investigation, writing – original draft, writing – review & editing, supervision, and project administration.

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