JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Targeted Hypoglossal Nerve Stimulation for Patients With Obstructive Sleep Apnea
A Randomized Clinical Trial

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IMPORTANCE Evidence is lacking from randomized clinical trials of hypoglossal nerve stimulation in obstructive sleep apnea (OSA).

OBJECTIVE To evaluate the safety and effectiveness of targeted hypoglossal nerve stimulation (THN) of the proximal hypoglossal nerve in patients with OSA.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial (THN3) was conducted at 20 centers and included 138 patients with moderate to severe OSA with an apnea-hypopnea index (AHI) of 20 to 65 events per hour and body mass index (calculated as weight in kilograms divided by height in meters squared) of 35 or less. The trial was conducted from May 2015 through June 2018. Data were analyzed from January 2022 through January 2023.

INTERVENTION Implant with THN system; randomized 2:1 to activation at month 1 (treatment) or month 4 (control). All received 11 months of THN with follow-up at months 12 and 15, respectively.

MAIN OUTCOMES AND MEASURES Primary effectiveness end points comprised AHI and oxygen desaturation index (ODI) responder rates (RRs). Treatment responses at months 4 and 12/15 were defined as a 50% or greater reduction in AHI to 20 or less per hour and an ODI decrease of 25% or greater. Coprimary end points comprised (1) month 4 AHI and ODI RR in the treatment greater than the control group and (2) month 12/15 AHI and ODI RR in the entire cohort exceeding 50%. Secondary end points included sleep apnea severity (AHI and ODI) and patient-reported outcomes (Epworth Sleepiness Scale, Functional Outcomes of Sleep Questionnaire, and EQ-5D visual analog scale).

RESULTS Among 138 participants, the mean (SD) age was 56 (9) years, and 19 (13.8%) were women. Month 4 THN RRs were substantially greater in those in the treatment vs control group (AHI, 52.3% vs 19.6%; ODI, 62.5% vs 41.3%, respectively) with treatment-control standardized mean differences of 0.725 (95% CI, 0.360-1.163) and 0.434 (95% CI, 0.070-0.843) for AHI and ODI RRs, respectively. Months 12/15 RRs were 42.5% and 60.4% for AHI and ODI, respectively. Improvements in AHI, ODI, Epworth Sleepiness Scale, Functional Outcomes of Sleep Questionnaire, and EQ-5D visual analog scale scores were all clinically meaningful (medium to large effect size). Two serious adverse events and 100 nonserious related adverse events were observed from the implant procedure or study protocol.

CONCLUSIONS AND RELEVANCE This randomized clinical trial found that THN demonstrated improvements in sleep apnea, sleepiness, and quality of life in patients with OSAs over an extended AHI and body mass index range without prior knowledge of pharyngeal collapse pattern. Clinically meaningful improvements in AHI and patient-reported responses compared favorably with those of distal hypoglossal nerve stimulation trials, although clinically meaningful differences were not definitive for ODI.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02263859

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Supplemental content

JAMA Otolaryngol Head Neck Surg. 2023;149(6):512-520. doi:10.1001/jamaoto.2023.0161
Published online April 6, 2023. Corrected on March 21, 2024.

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Obstructive sleep apnea (OSA) is characterized by recurrent apneas and hypopneas during sleep, leading to nocturnal hypercapnia, repeated oxyhemoglobin desaturations, and arousals.[1,2] It is highly prevalent, affecting 4% to 24% of men and 2% to 9% of women, as well as more than 50% of individuals with obesity.[3] Obstructive sleep apnea is a major cause of morbidity and mortality.[4-8] It contributes to the development and progression of neurocognitive, metabolic, cardiovascular, and oncologic diseases,[7,9-16] as well as losses in workplace productivity, public safety, and related health care expenditures.[17-19] Nasal continuous positive airway pressure (CPAP) remains the mainstay of therapy for moderate to severe OSA. It relieves upper airway obstruction during sleep but does not reverse underlying defects in pharyngeal collapsibility. Poor adherence to CPAP severely limits its use,[20-22] and to our knowledge, few effective alternatives to CPAP exist.

Surgical alternatives for treating OSA offer variable degrees of success.[23] Surgical approaches can correct underlying skeletal, soft tissue, and neuromuscular mechanisms of upper airway obstruction during sleep. Among these, hypoglossal nerve stimulation can maintain lingual motor tone and restore upper airway patency by preventing the tongue from prolapsing into the pharynx during sleep.[24] This concept originated in a single-arm uncontrolled trial in which investigators demonstrated durable improvements in a limited spectrum of patients with OSA with mild to moderate obesity who had moderate to severe OSA without complete concentric collapse of the pharynx during drug-induced sleep endoscopy.[25] As described previously,[26-28] these investigators stimulated the distal hypoglossal nerve, targeting muscles that move the tongue anteriorly and protrude it from the mouth. Nevertheless, devices that stimulate the distal hypoglossal nerve still leave many patients with apnea inadequately untreated, despite stringent selection criteria.[25-27]

Targeted hypoglossal nerve (THN) stimulation offers an alternative approach for activating lingual muscles. In previous single-center and multicenter open-label studies,[29,30] investigators demonstrated substantial improvements in sleep apnea when specific portions of the proximal hypoglossal nerve were stimulated selectively with a multicontact electrode. Treatment with THN was generally well tolerated with relatively few adverse effects, although to our knowledge responses have not yet been systematically evaluated across a broad spectrum of patients with OSA.

The present study (THN3) was designed to evaluate the safety and effectiveness of proximal THN stimulation in PAP-intolerant patients with moderate to severe OSA. A rigorous randomized clinical trial with a concurrently implanted control group was designed to address this aim in an extended spectrum of patients with moderate obesity with undisclosed patterns of pharyngeal collapse.

Key Points

Question What are the safety and effectiveness of stimulating selected portions of the proximal hypoglossal nerve trunk in patients with moderate to severe obstructive sleep apnea (OSA)?

Findings This parallel-arm randomized clinical trial of 138 patients with moderate to severe OSA demonstrated that targeted hypoglossal nerve stimulation achieved clinically significant improvements in sleep apnea, sleepiness, and quality of life in a broad spectrum of patients with OSA with a wide range of apnea-hypopnea index and body mass index values and an undisclosed pattern of pharyngeal collapse.

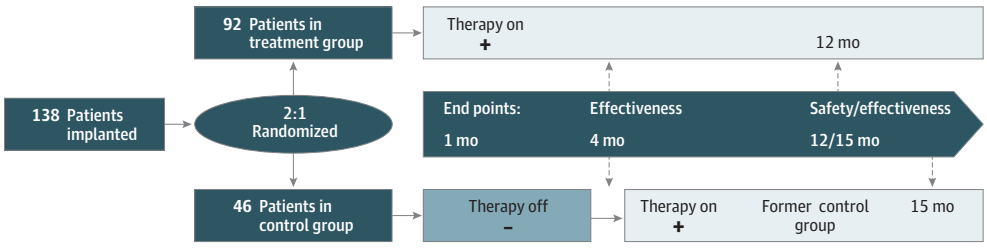
Meaning The results of this randomized clinical trial found that proximal targeted hypoglossal nerve responses proved safe and effective in treating sleep apnea and improving sleep architecture and quality of life while comparing favorably with those in distal hypoglossal nerve stimulation trials.

Methods

Study Design

The THN3 trial was an international, multicenter, randomized clinical trial designed by the investigators and sponsor (**Figure 1**). All patients were implanted with the THN therapy system (aura6000; ImThera Medical). Patients were randomly assigned 2:1 to receive THN therapy at 1 or 4 months after implant for the treatment and control groups, respectively. Long-term efficacy was measured at 11 months of therapy (12 and 15 months after implant, respectively, for treatment and control groups combined) vs preimplant baseline.

Figure 1. Study Design



All eligible patients who provided consent underwent implant. One month following implant, patients were randomized 2:1 to receive targeted hypoglossal nerve therapy beginning at month 1 (treatment) or month 4 (control). Short-term end points were measured between the treatment and control groups at month 4, and long-term end points were measured following 11 months of therapy, months 12 and 15, respectively, for the treatment and control groups pooled.

The protocol was approved by each site's institutional review board (Supplement 1 and Supplement 2; eTable 1 in Supplement 3). All participants provided written informed consent. The trial was overseen by a data safety monitoring board and clinical events committee to classify adverse events. Polysomnographic studies were scored according to 2007 American Academy of Sleep Medicine criteria,[31] with the recommended definition of hypopneas.

Participant Eligibility

Qualified participants were medically stable and had a baseline apnea-hypopnea index (AHI) of 20 to 65 events per hour on 2 screening polysomnographies (eFigure 2 in Supplement 3), a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 35 or less, age 18 years or older, and a history of positive airway pressure intolerance. A complete list of eligibility criteria appears in eTable 2 in Supplement 3. Participant flow through the protocol is illustrated in eFigure 1 in Supplement 3.

System, Implant, and Follow-up

The THN system comprised an implanted pulse generator, multicontact hypoglossal nerve electrode placed proximally, remote control/pulse generator charging system, and programmer (clinical manager) system (eFigure 3 in Supplement 3). The THN implant procedure was described[30] previously along with minor updates to system (eFigure 2 in Supplement 3).

Device activation occurred at months 1 and 4 for treatment and control participants, respectively. A stimulus titration protocol was implemented in stable sleep to determine optimal contacts (eFigure 4A in Supplement 3), for increasing tidal airflow and a therapeutic regimen for treating SDB (eFigure 4B in Supplement 3). Thereafter, participants used THN nightly. Titration polysomnographies for the treatment group were scheduled at months 1, 2, and 9 postactivation and as needed.

End Points and Statistical Analysis

Standardized mean differences were used to compare baseline characteristics between the treatment and control groups. The primary safety end point was defined as an estimate of the incidence of system-related, procedure-related, and device-related adverse events. Responder rates were used to evaluate efficacy end points, with responders defined by a 50% or greater reduction in AHI to 20 or fewer events per hour and a 25% or greater reduction in oxygen desaturation index (ODI) from baseline. There were 2 coprimary short-term and 2 coprimary long-term efficacy end points. The short-term coprimary end points comprised comparisons of (1) AHI responder rates and (2) ODI responder rates in the treatment compared with control group at month 4 with the 1-sided Fisher exact test. The long-term coprimary end points required a 50% or greater responder rate in the pooled treatment and control group in AHI and ODI at months 12/15 (by 1-sided binomial tests). Coprimary end points were tested for 1-sided $P < .02$ without multiple comparison corrections.

All end points were evaluated, with effect size estimates comprising standardized mean differences and a stochastic probability of superiority.[32] Effect sizes were reported as point estimates with 95% CIs. The trial sample size was prospectively established at 141 patients, driven by the long-term AHI end point, to achieve 85% power with 12.5% attrition at an assumed response rate of 62.5%.

Secondary efficacy end points comprised comparisons of the treatment vs control groups at month 4 of AHI, ODI, the Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), and EuroQol 5-D (EQ-5D) visual analog scale. Ancillary end points included (1) the EQ-5D Index and (2) patient satisfaction with their outcome. Additional exploratory analyses were also conducted to examine predictors of AHI responses, including baseline anthropometric, demographic, and sleep study variables.

Results

Participants

A total of 138 eligible participants from 1289 screened (10.7%) underwent implant at 20 study sites (eFigure 1 in Supplement 3). Participants were predominantly middle-aged to older White men with mild to moderate obesity and rather severe OSA (**Table 1**). Participants were generally normotensive with low rates of comorbidities. Characteristics were comparable in the treatment and control groups except for more women and a slightly higher average AHI and T90 (time spent during sleep with oxygen saturation less than 90%) in the treatment group (see the sensitivity analyses in eMethods and eResults in Supplement 3). The implant procedure took 77.5 minutes (range, 37 to 166 minutes). A total of 99 participants (72%) were discharged on the same day.

Safety Profile

In the year following implant, 2 severe related adverse events occurred (lead dislodgement and neck pain due to lead tension). Four severe unrelated adverse events also occurred in 4 patients (eTable 3 in Supplement 3). An additional 10 revisions, replacements, or explants occurred in 9 patients (6.5%). Overall, 100 patients (72.5%) experienced 164 procedure-related and study-related adverse events, including perioperative wound related (57 events), stimulation discomfort (46 events), and lack/loss of therapeutic effects (13 events). See eTable 3 in Supplement 3 for details.

Effectiveness

Responses in Treatment vs Control Group at Month 4

In the treatment compared with control group, strong and moderate effect sizes for AHI and ODI responder rates were observed, respectively (**Table 2**). There were improved secondary outcomes with THN, with clinically meaningful AHI and ODI reductions (**Figure 2**), and improved quality of life metrics, including ESS, FOSQ, and EQ-5D visual analog scale scores (**Table 3**). In treatment vs controls, the drop in AHI and ODI was greater (Figure 2). Snoring also decreased (eTable 7 in Supplement 3), EQ-5D index scores improved, but BMI, blood pressure, and pulse did not change during the course of the trial (eTable 8 in Supplement 3).

Table 1. Baseline Characteristics by Treatment Group[a]

Characteristics	All participants (n = 138)		Treatment (n = 92)		Control (n = 46)		Standardized mean difference (95% CI)
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Anthropometric and demographic							
Age, y	55.5 (9.09)	56.0 (50.0 to 61.0)	55.8 (8.3)	56.0 (50.5 to 61.0)	55.1 (10.51)	55.0 (49.0 to 60.0)	0.068 (−0.296 to 0.457)
BMI	29.84 (3.03)	30.04 (27.72 to 32.14)	29.94 (2.99)	30.21 (27.74 to 32.13)	29.62 (3.112)	29.69 (27.02 to 32.14)	0.104 (−0.254 to 0.466)
Neck size, cm[b]	41.88 (3.59)	42.00 (40.00 to 44.00)	41.66 (3.815)	42.00 (39.00 to 44.00)	42.32 (3.09)	43.00 (41.00 to 44.00)	−0.190 (−0.543 to 0.157)
Female sex, No./total No. (%)	19/138 (13.8)	NA	17/92 (18.5)	NA	2/46 (95.7)	NA	0.456 (0.129 to 0.769)
Male sex, No./total No. (%)	119/138 (86.2)	NA	75/92 (81.5)	NA	44/46 (95.7)	NA	−0.456 (−0.769 to −0.129)
Hispanic or Latino, No./total No. (%)	19/138 (13.8)	NA	10/92 (10.9)	NA	9/46 (19.6)	NA	−0.244 (−0.594 to 0.129)
Non-Hispanic or Latino, No./total No. (%)	119/138 (86.2)	NA	82/92 (89.1)	NA	37/46 (80.4)	NA	0.244 (−0.129 to 0.594)
Racial or ethnic minority group, No./total No. (%)	12/138 (8.7)	NA	8/92 (8.7)	NA	4/46 (8.7)	NA	0 (−0.340 to 0.374)
White, No./total No. (%)	126/138 (91.3)	NA	84/92 (91.3)	NA	42/46 (91.3)	NA	0 (−0.374 to 0.340)
Respiratory							
AHI, events/h	37.9 (9.8)	36.5 (31.0 to 44.9)	39.2 (10.1)	37.3 (32.1 to 47.0)	35.4 (8.8)	34.6 (29.1 to 41.6)	0.403 (0.059 to 0.772)
ODI, events/h	37.3 (9.91)	35.1 (31.2 to 44.6)	37.9 (10.11)	36.3 (31.7 to 45.4)	36.0 (9.5)	33.7 (29.2 to 43.6)	0.195 (−0.152 to 0.562)
T90, %	11.7 (9.76)	9.4 (4.4 to 15.6)	12.7 (10.44)	9.9 (5.6 to 16.5)	9.6 (7.93)	7.4 (3.6 to 14.1)	0.339 (0.004 to 0.679)
SpO_2 nadir, %	76.9 (6.4)	77.5 (73.0 to 81.5)	76.2 (6.67)	77.0 (72.5 to 81.5)	78.2 (5.80)	79.8 (74.5 to 82.5)	−0.311 (−0.669 to 0.035)
Cardiovascular							
Heart rate, bpm[c]	76.3 (11.2)	76.0 (68.0 to 82.0)	77.0 (11.17)	76.0 (70.0 to 82.0)	74.9 (11.29)	74.0 (66.0 to 83.0)	0.189 (−0.171 to 0.549)
Systolic BP, mm Hg	130.8 (12.1)	130.0 (123.0 to 140.0)	129.9 (12.73)	130.0 (121.5 to 140.0)	132.5 (10.66)	133.0 (127.0 to 139.0)	−0.227 (−0.579 to 0.113)
Diastolic BP, mm Hg	83.1 (9.1)	83.5 (78.0 to 89.0)	83.2 (9.60)	84.0 (78.0 to 89.5)	83.0 (8.02)	83.0 (80.0 to 89.0)	0.018 (−0.328 to 0.372)
Previous OSA surgery, No./total No. (%)							
Uvulopalatopharyngoplasty	23/138 (17)	NA	13/92 (14)	NA	10/46 (22)	NA	0.199 (−0.559 to 0.169)
Comorbidities, No./total No. (%)							
Diabetes	10/138 (7)	NA	5/92 (5)	NA	5/46 (11)	NA	0.200 (−0.530 to 0.177)
Asthma	7/138 (5)	NA	4/92 (4)	NA	3/46 (7)	NA	0.096 (−0.422 to 0.302)
Congestive heart failure	0	NA	0	NA	0	NA	0
Hypertension	66/138 (48)	NA	43/92 (46.7)	NA	23/46 (50)	NA	0.065 (−0.424 to 0.292)
Concomitant substance/ medication use, No./total No. (%)							
Current smoker	16/138 (12)	NA	9/92 (10)	NA	7/46 (15)	NA	−0.165 (−0.509 to 0.213)
Antidepressants	45/138 (33)	NA	31/92 (34)	NA	14/46 (30)	NA	0.070 (−0.281 to 0.440)
Sedatives/hypnotics	75/138 (54)	NA	54/92 (59)	NA	21/46 (46)	NA	0.263 (−0.091 to 0.642)

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; bpm, beats per minute; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; SpO_2, oxygen saturation by pulse oximetry; T90, time spent during sleep with oxygen saturation less than 90%.

[a] The critical values for a significance level of .05 were 0.248 for neck size, 0.247 for heart rate, and 0.245 for the remaining end points.

[b] Neck size sample was 135 participants (treatment, 90 [66.7%]; control, 45 [33.3%]).

[c] Heart rate sample was 137 participants (treatment, 92 [67.2%]; control, 45 [32.8%]).

Responses in the Treatment and Control Groups at Months 12 and 15

The combined groups demonstrated AHI and ODI response rates of 42.5% and 60.4%, respectively (Table 2), meeting prespecified ODI but not AHI responder rates (Table 2). Differences in response rates between AHI and ODI may reflect differing prespecified responder thresholds and/or conversion of apneas to hypopneas during THN.

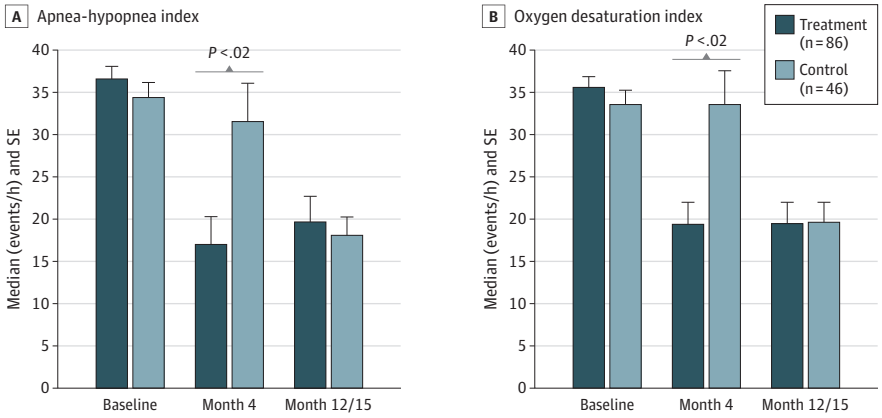
Clinically meaningful improvements in secondary outcomes were detected including AHI and ODI (Figure 2; eTable 4 and eFigure 5 in Supplement 3) and quality of life indices (ESS,

Table 2. Coprimary Effectiveness End Point Responses at Month 4 and Months 12 and 15

End point	No./total No. (%)		Treatment-control, RR (95% CI)	Standardized mean difference, Treatment-control (95% CI)
	Treatment	Control		
M4 AHI RR	46/88 (52.3)	9/46 (19.6)	32.7 (15.2 to 49.0)	0.725 (0.360 to 1.163)
M4 ODI RR	55/85 (62.5)	19/46 (41.3)	21.2 (3.3 to 38.1)	0.434 (0.070 to 0.843)
End point	Pooled 11-mo active therapy: treatment and control		Pooled therapy-performance goal of 50% (95% CI)	Standardized mean difference, pooled therapy-performance goal of 50% (95% CI)
M12/15 AHI RR	59/138 (42.5)		−7.5 (−16.0 to 1.4)	−0.151 (−0.330 to 0.015)
M12/15 ODI RR	83/138 (60.4)		10.4 (1.6 to 18.8)	0.214 (0.045 to 0.402)

Abbreviations: AHI, apnea-hypopnea index; M4, month 4; M12/15, month 12/15; ODI, oxygen desaturation index; RR, response rate.

Figure 2. Primary Effectiveness Outcomes at Baseline, at the Conclusion of the Trial (Month 4), and After 11 Months of Therapy (Months 12/15) for Patients With Complete Data at All Points



At baseline, apnea-hypopnea index (AHI) (A) differed but oxygen desaturation index (ODI) (B) did not differ between the treatment and control groups. At month 4, the treatment group exhibited significantly greater, clinically meaningful reductions in AHI and ODI than the control group (vs baseline), and AHI and ODI were meaningfully and significantly lower in the treatment vs control group. After 11 months of therapy, targeted hypoglossal nerve stimulation in the control group generated similar reductions in AHI and ODI as in the treatment group. These parameters were significantly lower than the baseline. Standard errors of the median and *P* values were computed with bootstrapping methods.

Table 3. Secondary Effectiveness End Points at M4

End point	Treatment	Control	Standardized mean difference, treatment-control (95% CI)
M4 ESS	−4.4 (4.2)	−1.1 (3.5)	−0.864 (−1.288 to −0.499)
M4 FOSQ	2.5 (3.0)	1.1 (3.2)	0.478 (0.102 to 0.927)
M4 EQ-5D VAS	5.3 (13.4)	0.6 (8.4)	0.423 (0.088 to 0.772)

Abbreviations: EQ-5D VAS, European Quality of Life 5-Dimension visual analog scale; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; M4, month 4.

FOSQ, EQ-5D visual analog scale, and EQ-5D; eFigure 5 in Supplement 3). Sleep architecture improved with reductions in transitional N1 sleep and commensurate increases in N2 sleep (eTable 6 in the Supplement 3). Reductions in snoring persisted (eTable 7 in Supplement 3), but heart rates and blood pressure did not change (eTable 8 in Supplement 3).

Effect of Sleep Efficiency on Outcomes in Post Hoc Analyses

The effect of sleep continuity on responses to hypoglossal stimulation[33] prompted us to examine the influence of sleep efficiency at baseline on AHI response rates. Receiver operating characteristic demonstrated an 84.6% optimal cut point that distinguished AHI responders from nonresponders with a 0.62 area under the curve. Subgroups with baseline sleep efficiency greater and less than an 85% threshold demonstrated month 4 response rates in AHI of 59.5% vs 20.0% in the treatment vs control groups, respectively. In the subgroup with high sleep efficiency, pooled month 12/15 response rates for AHI and ODI exceeded prespecified thresholds at 50.9% and 64.9%, respectively. Secondary end points responded similarly in both subgroups (eTable 9 and eFigure 6 in Supplement 3).

Patient Satisfaction Measures

A total of 115 participants (83%) indicated that they were satisfied or very satisfied with their outcome; 121 (88%) expressed willingness to undergo the treatment again, and 123 (89%) stated that they would recommend treatment with THN

to others. A total of 113 (82%) used THN on 5 or more nights per week and found it easy to use.

Discussion

In this randomized clinical trial, THN stimulation proved effective in treating moderate to severe OSA. The treatment group achieved clinically significant reductions in apnea severity and patient-reported outcomes compared with the implanted control group, in which therapy was deferred. Thereafter, THN yielded durable decreases in apnea severity and OSA burden on quality of life, with a favorable safety profile after 11 months of active treatment in both groups. Improvements in sleep apnea were greater in the subgroup with relatively normal vs reduced sleep efficiency, suggesting that sleep-wake instability can diminish responses to hypoglossal nerve stimulation. In contrast to other trials that stimulated the distal hypoglossal nerve,[25,27] THN3 selectively targeted sectors of the proximal nerve.[34] This approach yielded comparable decreases in AHI over a wider range of BMI without regard to patterns of pharyngeal collapse. Finally, patients reported high satisfaction with THN and a strong willingness to repeat the procedure if they had it to do all over again. In all, the findings suggest that THN offers safe and effective treatment for a broad spectrum of patients with OSA.

In recent years, stimulating the distal hypoglossal nerve has become a recognized therapeutic option for PAP-intolerant patients with OSA.[26-28] Targeted hypoglossal nerve stimulation offers several unique features for stimulating the hypoglossal nerve. First, this system provides a multicontact electrode array for stimulating portions of the proximal nerve rather than stimulating the entire distal nerve. While distal stimulation primarily activates tongue protruders, the present multicontact array can stimulate lingual protruder, retractor, and intrinsic muscles to varying degrees. Second, the present system incorporates a rechargeable rather than a nonrechargeable battery or radio frequency inductance coil. Third, surgical implant was less time consuming due to ease in accessing the proximal nerve without the need for isolating branches that activate tongue protruders.[35] Ease of implant may also have hastened discharge of THN3 compared with the STAR trial[25] patients (same-day discharge was achieved in 72% vs 16%), in addition to surgeons' prior training and experience implanting these devices. Fourth, THN stimulation is asynchronous, eliminating the need for a respiratory sensing lead and further simplifying implant without compromising the therapeutic response. Taken together, these features streamline device implant and minimize surgical risk.

In a rigorous parallel-arm, randomized controlled design, THN3 yielded clinically significant improvements in sleep-disordered breathing, daytime sleepiness, and quality of life in treated compared with control participants at month 4. Improvements in the treatment group were offset by some improvement in these outcomes in the control group, suggesting that prior single-arm, open-label studies and registries[36,37] could have erroneously attributed clinical benefit to hypoglossal nerve stimulator therapy instead of factors related to study enrollment (eg, self-selection, nonspecific contact with medical practitioners or other study activities, or regression to the mean). Treatment with THN produced similar long-term reductions in AHI and ODI at months 12/15, although the long-term AHI response rate fell short of the 50% prespecified level (Table 2; eFigure 6 in Supplement 3). Several possibilities may account for the drop in the AHI response rate over the course of the trial. First, the variability in AHI was greater at months 12/15 than at baseline (Figure 2), possibly due to the use of a single sleep study at months 12/15 rather than 2 sleep studies at baseline. Variability in THN responses could also be explained by differences in sleep efficiency among participants[33] with greater decreases in AHI in those with high vs low sleep efficiency. Second, the baseline AHI was higher in the THN3 than the STAR trial,[25] possibly because the BMI limit for eligible participants was extended from 32 to 35. Third, a higher BMI accounted for higher mean (SD) baseline AHI in THN3 than STAR (THN3, 29.8 [3.0]; STAR, 28.4 [2.6]), thereby necessitating greater AHI drops from baseline for positive responses. Nevertheless, AHI fell substantially in the THN3 trial and dropped by similar amounts in the THN3 and STAR trials (THN3: events per hour, −14.4 [95% CI, −18.0 to −10.5]; STAR: events per hour, −17.3 [95% CI, −20.7 to −14.9]). Moreover, residual respiratory events while receiving therapy were predominantly hypopneas rather than obstructive apneas, accounting for a robust ODI response rate through months 12/15. Fourth, observed long-term reductions in AHI, albeit without complete OSA resolution, can be attributed to pathogenic defects in ventilatory control,[38] pharyngeal mechanics,[39-41] and neuromotor control[42,43] that still remain[44,45] after THN relieves airway obstruction. Nevertheless, THN achieved clinically meaningful responses in OSA and daytime dysfunction.[46,47] Responses account for high levels of satisfaction with THN, consistent with investigators of another large surgical RCT who stated that "many patients... will be satisfied with the improvement they achieve even with residual sleep apnea."[48]

Participants in THN3 also experienced a similar range of adverse events related to the implant and therapy delivery; however, unlike STAR patients, pneumothorax was averted because THN implant did not require intercostal sensing lead placement.[49] The STAR device activated tongue protruders,[35,50] which can abrade the tongue if protruded excessively. Instead, THN activated combinations of lingual muscle that were innervated by the proximal nerve, yielding marked differences in tongue movement. When coactivated, these tongue muscles could restore pharyngeal patency by stiffening rather than protruding the tongue.[51] Findings of THN were consistent with experimental evidence that multiple lingual muscles, including protruders and retractors, work together to maintain pharyngeal patency by stabilizing the tongue's shape and position in the oral cavity.[24,52,53]

Limitations

Several limitations should be considered when evaluating the THN3 trial results. First, 1 of the 4 prespecified primary efficacy end points was not met. Although the targeted AHI and ODI response rates were achieved at the 4-month point in the

randomized clinical trial, the AHI response rate was less than the prespecified end point in the single arm at months 12/15 (Table 2; eFigure 6 in Supplement 3). While using response rates as end points has become a de facto regulatory requirement for trials, such as THN3, dichotomous outcomes and percentage changes invariably decrease statistical power and hamper efforts for estimating the magnitude of therapeutic responses. Nonetheless, THN yielded long-term benefits, with meaningful reductions in AHI and ODI and improvements in daytime function. Second, the THN3 trial could not mask patients to hypoglossal nerve stimulation, which could have influenced responses to patient-reported outcomes, as in other hypoglossal stimulation and surgical trials. Nevertheless, consistent responses were observed in objective sleep apnea metrics (AHI and ODI), and the totality of evidence accounts for subsequent improvements in quality of life. Third, minor updates to system hardware and firmware were made at various times during the course of the trial to improve the reliability of the pulse generator, cuff, charging unit, and antenna. These changes did not appear to affect the safety, effectiveness, or validity of THN therapy because multiple sleep studies for each participant documented that system components continued to function throughout the trial. Similarly, multiple titration studies allowed ample opportunity to streamline and standardize procedures for selecting and titrating contacts that were ultimately included in the patient's therapeutic regimen, as described in eFigure 4 in Supplement 3. Fourth, we recognize that a prospective trial will be required to confirm whether baseline sleep efficiency predicts THN responses due to stimulation tolerability or differences in arousal threshold. Fifth, the trial results can only be generalized to the patient population with OSA that was included in the study (those with moderate to severe OSA and a BMI ≤35). We cannot extrapolate the findings to subgroups with and without complete concentric pharyngeal collapse, which was not assessed in this study. Finally, promising characteristics including sleep efficiency and that BMI and AHI might predict therapeutic responses, but these must be confirmed in prospective studies with a priori hypotheses and adequate sample size.

Conclusions

This randomized clinical trial demonstrated superiority of THN vs a concurrent control group that underwent implant. During the 4-month randomization period, THN therapy significantly improved measures of sleep-disordered breathing and patient-reported outcomes, including daytime somnolence and quality of life in treated vs control participants. Although AHI response rates appeared to decline during the period of longitudinal follow up, clinically important reductions in OSA burden were maintained, with comparable decreases in AHI and ODI after nearly a year of therapy in the entire group. Patient-reported outcomes further suggest that reductions in OSA severity, even without complete remission, can achieve clinically meaningful improvements in sleep quality and daytime function.[54] A post hoc analysis also suggested that sleep continuity may enhance THN responses. We speculate that patients with high sleep efficiency could tolerate even partial increases in pharyngeal patency without arousing them from sleep. Further studies are required to establish the precise indications for THN and predictors of therapeutic success.

ARTICLE INFORMATION

Accepted for Publication: February 3, 2023.

Published Online: April 6, 2023. doi:10.1001/jamaoto.2023.0161

Correction: This article was corrected on March 21, 2024, to fix errors in Table 2.

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Obtained funding: Lovett, Maurer.
Administrative, technical, or material support: Schwartz, Miller, Oliven, Hopp, Winslow, Huntley, Gillespie, Weeks, Lovett, Maurer.
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Conflict of Interest Disclosures: Dr Schwartz reported grants from ImThera during the conduct of the study as well as personal fees from LivaNova, AE Mann Foundation, Deerfield Catalyst, Invicta Medical, Nyxoah, and Respicardia/Zoll, Apnimed, Itamar/Zoll, Periodic Breathing, Respimetrix, and Sunrise as a scientific advisor outside the submitted work. Dr Jacobowitz reported personal fees and grants from LivaNova during the conduct of the study. Dr Gillespie reported grants from the University of Tennessee Health Science Center/LivaNova during the conduct of the study. Dr Lovett reported being employed by and a shareholder of LivaNova during the conduct of the study and outside the submitted work as well as a patent for LivaNova. Dr Malhotra reported personal fees from LivaNova, Jazz, Eli Lilly, and Zoll and research support from Resmed during the conduct of the

study. Dr Maurer reported grants and personal fees from LivaNova during the conduct of the study as well as personal fees from Inspire, Nyxoah, MedEl, and Neuwirth Medical Products outside the submitted work. No other disclosures were reported.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We acknowledge the following members of the trial clinic events committee and data monitoring safety board: Charles B. Tesar, MD, Sharp Memorial Hospital, John R. Houck Jr, MD, University of Oklahoma Health Science Center, Steven D. Kavy, MD, Sharp-Rees Stealy Medical Group, and Brita Lindstrom, RN, MPH, San Diego, California.

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Invited Commentary

Targeted Hypoglossal Nerve Stimulation—An Inspiring Alternative for Obstructive Sleep Apnea

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Reflecting the scientific advances of the past several decades, hypoglossal nerve stimulation has emerged as an important tool for the treatment of obstructive sleep apnea (OSA). Starting from the preliminary animal studies of the late 1980s, the evolution of our understanding of hypoglossal nerve stimulation culminated in the development of the Inspire II (Inspire Medical Systems, Inc; Maple Grove, Minnesota), the first, and currently only, US Food and Drug Administration (FDA)-approved implantable hypoglossal nerve stimulation system to treat OSA.[1] Through parallel development, targeted hypoglossal nerve stimulation (THN), which provides a different approach for activating the tongue muscles, has shown potential as an effective alternative implantable stimulation device for OSA through previous pilot and feasibility studies.[2,3] In this issue of *JAMA Otolaryngology–Head & Neck Surgery*, Schwartz et al[4] report on the safety and effectiveness of the aura6000 THN therapy system (ImThera Medical, San Diego, California) from the THN3 trial, a rigorous international multi-center, parallel-arm, randomized clinical trial. In this trial, Schwartz et al report significant improvements in physiologic measures of OSA and in important patient-reported outcome measures, including daytime sleepiness and quality of life, with THN. Combined with a favorable safety profile, these results may lead to FDA approval of the THN system, and thus a compelling potential new treatment option for patients with OSA.

The scientific rationale for use of the Inspire system relies on the concept that pharyngeal dilation, and upper airway stability, relies predominantly on activation of the genioglossus muscle. The Inspire system provides stimulation to the distal hypoglossal nerve branches to selectively stimulate the genioglossus muscle, the tongue protrusor, resulting in anterior tongue displacement. The Inspire system avoids stimulation of nerve branches to the styloglossus and hyoglossus muscles, the tongue retrusors, which may posteriorly displace the tongue and increase airway collapsibility.[5] The effect of the stimulation from the Inspire system results in net anterior displacement of the tongue to facilitate airway patency.[5]

In contrast, the scientific rationale for THN relies on the lingual hydrostat model, which posits that the tongue is a complex array of intertwined muscles that are relatively incompressible.[6] In this model, proximal stimulation of the hypoglossal nerve trunk results in complex coactivation of the protrusor, retrusor, and intrinsic muscles that has an overall "stiffening" effect of the tongue.[6] This provides less net anterior displacement of the tongue but may facilitate upper airway stability in a manner that is at least equivalent, if not superior, to selective protrusor stimulation.[5,6] In addition, THN also relies on the notion that the posterior and tongue base muscles have a greater proportion of fatigue-resistant muscle fibers than the anterior tongue muscles, and thus are more favorable for neurostimulation.[7] Because these muscles are more fatigue resistant, the THN device was designed with a 6-contact stimulation cuff to provide near continuous, yet cycled, asynchronous stimulation of the hypoglossal nerve via these 6 contact points to mitigate muscle fatigue. This represents an additional important difference compared with the Inspire system, which relies on timed neurostimulation that is synchronized with respiration using a respiratory sensing lead.[1]

From an operative standpoint, these features increase the ease of implantation of the THN device compared with the Inspire system. Accessing the proximal portion of the hypoglossal nerve is faster than accessing the distal portion of the nerve, which requires greater dissection on the nerve and delineation of protusor and retrusor branches. This reduces the