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Association of Hypoglossal Nerve Stimulation With Improvements in Long-term, Patient-Reported Outcomes and Comparison With Positive Airway Pressure for Patients With Obstructive Sleep Apnea

Maeve Pascoe, BS; Lu Wang, MS; Joan Aylor, BA; Reena Mehra, MD, MS; Alan Kominsky, MD; Nancy Foldvary-Schaefer, DO, MS; Vaishal Shah, MD; Tina Waters, MD; Harneet K. Walia, MD

IMPORTANCE Hypoglossal nerve stimulation (HNS) and positive airway pressure (PAP) have been shown to improve patient-reported outcomes (PROs) in obstructive sleep apnea (OSA). However, to our knowledge, there are no data that compare change in PROs between HNS and PAP or that indicate whether HNS improves comorbid insomnia or depression in the long term.

OBJECTIVES To determine whether HNS is associated with improvements in patient-reported sleepiness, insomnia, and depression in the long term and to compare the respective associations of HNS and PAP with improved PROs.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used data from patients treated at the Cleveland Clinic for OSA. Participants received either HNS (referred sample) from November 1, 2015, to September 31, 2018, or PAP (previous cohort) from January 1, 2010, to December 31, 2014, for OSA. Patients were matched 3:1 for PAP:HNS based on age, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), sex, and apnea hypopnea index (AHI). Data were collected at baseline and at prespecified follow-up points. Data were analyzed from March 26, 2020, to September 9, 2021.

EXPOSURES Treatment with HNS vs PAP.

MAIN OUTCOMES AND MEASURES Data collected included AHI and Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Patient Health Questionnaire-9 (PHQ-9; depression) scores.

RESULTS Among 85 patients receiving HNS (mean [SD] age, 62.8 [9.5] years; 59 men [69.4%]; 77 White patients [90.6%]; mean [SD] BMI, 28.8 [3.1]), compared with 217 matched patients receiving PAP (mean [SD] age, 62.1 [9.9] years; 157 men [72.4%]; 173 White patients [81.2%]; mean [SD] BMI, 29.5 [3.1]) included in the analysis, significant improvements were seen in PHQ-9 scores for HNS vs PAP (least square means, −4.06 [95% CI, −5.34 to −2.79] vs −2.58 [95% CI, −3.35 to −1.82]; mean difference, −1.48 [95% CI, −2.78 to −0.19]) with comparable improvements in ESS, FOSQ, and ISI scores. Clinically meaningful differences were observed in 42 of 65 HNS group patients (64.6%) vs 118 PAP group patients (54.5%) for ESS scores, 29 of 49 HNS group patients (59.2%) vs 67 of 217 PAP group patients (30.9%) for FOSQ scores, 14 of 48 HNS group patients (29.2%) vs 53 of 217 PAP group patients (24.4%) for PHQ-9 scores, and 23 of 49 HNS group patients (46.9%) vs 79 of 217 PAP group patients (36.4%) for ISI scores. At the 1-year post-HNS assessment, meaningful improvements were seen in 17 of 28 patients (60.7%) for ESS scores, 11 of 20 patients (55.0%) for FOSQ scores, 7 of 23 patients (30.4%) for PHQ-9 scores, and 11 of 25 patients (44.0%) for ISI scores.

CONCLUSIONS AND RELEVANCE In this cohort study of patients with OSA, sustained improvements in PROs were observed 1 year after HNS and were comparable to those for PAP at 3 months. These findings suggest that HNS is a viable treatment for improving insomnia and depression in patients with OSA.

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Supplemental content

Author Affiliations: Sleep Disorders Center, Cleveland Clinic, Cleveland, Ohio (Pascoe, Aylor, Mehra, Foldvary-Schaefer, Shah, Waters); Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio (Wang); Department of Otolaryngology, Cleveland Clinic, Cleveland, Ohio (Kominsky); Miami Cardiac and Vascular Institute, Baptist Health South Florida, Miami (Walia).

Corresponding Author: Harneet K. Walia, MD, Miami Cardiac and Vascular Institute, Baptist Health South Florida, 7400 SW 87 Ave, Miami, FL 33173 (harneetw@baptisthealth.net).

Obstructive sleep apnea (OSA) is a highly prevalent sleep disorder,[1] with adverse consequences such as cardiovascular morbidities and metabolic disorders.[2] In addition, OSA commonly coexists with other sleep and psychiatric conditions, such as insomnia and depression. Recent reports have found that 27% to 85% of patients with OSA have comorbid insomnia and 17% to 69% of patients with insomnia have comorbid OSA,[3] whereas 22% of patients with OSA are diagnosed with comorbid depression and 18% of depressed patients have comorbid OSA.[4] These comorbidities may interact as well, because comorbid OSA and insomnia can increase the prevalence and severity of depression.[5] Similarly, it is well established that OSA is associated with impaired quality of life and excessive daytime sleepiness.[6]

Although treatment of OSA is on the rise, compliance with positive airway pressure (PAP), the current criterion standard treatment, is still a significant issue. Adherence reports estimate that 40% to 70% of patients prescribed PAP use the therapy less than is recommended for substantial therapeutic benefit.[7] Hypoglossal nerve stimulation (HNS) is a novel, US Food and Drug Administration–approved treatment for patients with moderate to severe OSA meeting specific criteria. Hypoglossal nerve stimulation has previously been shown to improve various OSA metrics and patient-reported outcomes (PROs), including sleep propensity and functional outcomes related to sleep.[8,9] To our knowledge, the effect of HNS on comorbid insomnia and depression, which are often underrecognized in OSA, has not been reported or compared with that of PAP. The goal of this study was to address this knowledge gap by investigating how HNS affects PROs in the long term, particularly with regard to insomnia and depression indices, as well as comparing outcomes in patients with HNS with those of matched patients who used PAP. We hypothesized that HNS would improve measures with sustained response and that these improvements would be comparable to those seen in patients using PAP.

Key Points

Questions Are there differences between positive airway pressure (PAP) and hypoglossal nerve stimulation (HNS) for treatment of patients with obstructive sleep apnea (OSA) with regard to patient-reported outcomes (PROs), and is HNS associated with long-term improvement in PROs in these patients?

Findings In this cohort study of 85 patients receiving HNS, a consistent and sustained improvement of PROs after HNS was observed during a 12-month follow-up period with comparable/increased improvement compared with PAP at 3 months in 217 patients.

Meaning These findings suggest that treatment of OSA with HNS is associated with sustained improvements regarding insomnia, sleepiness, quality of life, and depressive symptoms and that these improvements are comparable to those associated with PAP therapy.

Methods

Patient Populations

Data were collected retrospectively from electronic medical records (Epic Systems Corporation) and from the Inspire Post-Approval Study,[10] the Adherence and Outcome of Upper Airway Stimulation (UAS) for OSA International Registry (ADHERE registry),[11] and the internal database from patients who underwent HNS implantation and treatment at the Cleveland Clinic, Cleveland, Ohio, from November 1, 2015, to September 31, 2018. Informed consent was obtained from patients in the Inspire Post-Approval Study in person and from patients in the ADHERE registry either in person or by mail; the internal database received an exemption for retrospective reviews from the Cleveland Clinic Institutional Review Board. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Patients met the following inclusion/exclusion criteria for HNS implantation: apnea hypopnea index (AHI) of 15 to 65, lack of improvement with continuous PAP, 22 years or older, consent for all HNS-related procedures, absence of concentric collapse of the soft palate, central/mixed apneas of less than 25% of the AHI, no current pregnancy or plans to become pregnant, no upcoming magnetic resonance imaging, and no other implanted devices that would interfere with HNS. Data were collected before surgery/activation (baseline) and at 1, 3, and 6 months and 1 and 2 years after HNS activation. Of note, the 1-month post-HNS visit was a titration visit; HNS was activated, but not optimally titrated, for the month between the activation visit and this visit. Adherent HNS use was defined as weekly use of at least 28 hours.[12]

Data for the matched controls were derived from an existing database of patients with OSA with PAP use. Data for these patients, who must have been 18 years or older and reported to be using PAP from January 1, 2010, and December 31, 2014, were also derived from the electronic medical records. These patients had no prior PAP use at baseline and self-reported PAP use at follow-up; the follow-up visit was required to be more than 30 days but less than 1 year from baseline. Adherent PAP use was defined using Centers for Medicare & Medicaid Services criteria (≥4 hours per night for ≥70% of nights).

Demographic and Outcome Data

Demographic information was collected at baseline and included age, sex, race, and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). Based on the use of Black, White, or other race designations in our PAP patient database, race was defined by the investigators as White or non-White. Polysomnographic data were collected at baseline and 1 month after HNS for the HNS group and at baseline for the PAP group, including AHI. Patient-reported outcome data were collected at every assessment for both groups and included the Epworth Sleepiness Scale (ESS), Functional Outcomes Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Patient Health Questionnaire 9 (PHQ-9). The ESS measures subjective daytime sleep propensity, with a score of at least 10 indicating excessive daytime sleep propensity.[13] The minimum clinically important difference for the ESS in patients with moderate to severe OSA is a

2-point change.[14] The FOSQ is designed to assess the effect of sleepiness on the ability to conduct daily activities, conceptually defined as functional status, a component of quality of life; a score of at least 18 is considered normal.[15,16] The minimum clinically important difference for the FOSQ is 2 points.[17] The ISI is a self-report questionnaire assessing the nature, severity, and impact of insomnia symptoms.[18] Overall, a 6-point reduction in ISI score is considered a clinically significant improvement, whereas a score of 22 to 28 indicates severe insomnia; 15 to 21, moderate insomnia; 8 to 14, subthreshold insomnia; and 0 to 7, absence of insomnia.[19] The PHQ-9 is a self-administered survey that assesses each of the 9 *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for depression, with a 5-point overall reduction indicating a clinically meaningful improvement. A score of 20 to 27 is indicative of severe depressive symptoms; 15 to 19, moderately severe depressive symptoms; 10 to 14, moderate depressive symptoms; 5 to 9, mild depressive symptoms; and 0 to 4, none/minimal depressive symptoms.[20,21]

Statistical Analysis

Data are presented as the mean (SD) or median (IQR) for continuous variables and number (percentage) for categorical variables. Spearman correlation was used to evaluate the association between change in AHI and change in PROs at 1 month after HNS. To account for correlation of repeated measures in the same patient, a linear mixed-effects model assuming compound symmetry correlation structure was used to test the change from baseline to 1 month, 3 months, 6 months, 1 year, and 2 years after HNS (2-year end points were not reported due to low numbers). Restricted maximum likelihood was used in this linear mixed-effects model to estimate covariance parameters and allows for the assumption of covariance structure to represent the correlation of repeated measures within the same patient. In this study, the PRO-containing measures from multiple visits were the dependent variables; time was used as a fixed effect to be associated with the PROs so that the change of the outcomes could be estimated by least square means; the patient (or patient identification) was included as a random effect so that each patient had a unique intercept; and least square means were reported to evaluate the estimation of mean PRO-containing measures at each visit and the change from baseline.

The greedy nearest-neighbor approach was used to create a 1:3 match between the 2 groups by age (caliper 5), BMI (caliper 3), and exact match on sex and AHI category (15 to <30 and ≥30). Difference between groups was presented by effect size so that the absolute difference was standardized by variation (Hedges g[22] and Cliff δ[23] for continuous variables, and Cramer V[24] for categorical variables; magnitude of 0 to <0.10 indicated very small; 0.10 to <0.20, small; 0.20 to <0.50, medium; 0.50 to <0.80, large; and ≥0.80, very large). Linear mixed-effects models were used to assess the difference of change in ESS, FOSQ, PHQ-9, and ISI scores on matched groups of cases and controls with adjustment for baseline PRO, age, sex, BMI, and AHI category.

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc). Data were analyzed from March 26, 2020, to September 9, 2021.

Results

Sample Characteristics

Sample demographics, polysomnographic findings, and PRO characteristics at baseline are provided in **Table 1**. In 85 patients in the HNS group (mean [SD] age. 62.8 [9.5]; 26 women [30.6%] and 59 men [69.4%]; 77 White [90.6%] and 8 non-White [9.4%] patients; mean [SD] BMI, 28.8 [3.1]), most had severe OSA (69 [81.2%] had AHI of ≥30). The 217 matched patients in the PAP group shared similar mean (SD) age (62.1 [9.9] years) and sex (60 women [27.6%] and 157 men [72.4%]) but were different in terms of race (173 of 213 White [81.2%] and 40 non-White [18.8%] patients; Cramer V, 0.12 [95% CI, 0.02-0.21], indicating small difference).

At baseline, comparison of PROs between the HNS and PAP groups showed that the HNS group had greater ESS (Cliff δ, −0.26 [95% CI, −0.40 to −0.11]), lower FOSQ (Cliff δ, 0.22 [95% CI, 0.06-0.37]), and greater ISI (Cliff δ, −0.24 [95% CI, −0.39 to −0.07]; all medium-level differences) scores (Table 1), indicating greater sleepiness, lesser quality of life, and greater insomnia symptoms in the HNS group. Clinically, baseline PRO measures for the HNS group indicated excessive daytime sleep propensity, less than normal functional outcomes of sleep, moderate insomnia symptoms, and mild depressive symptoms. In the PAP group, baseline PRO measures indicated normal daytime sleep propensity, less than normal functional outcomes of sleep, subthreshold insomnia, and mild depressive symptoms.

HNS vs PAP Outcomes

Table 2 and **Figure 1** present least square means for PRO changes for each group; the 3-month follow-up visit for the HNS group was used as a comparator to the PAP group given that the median follow-up time for the PAP group was 3.83 (IQR, 2.33-6.27) months. After adjustment for covariates (baseline PRO, age, sex, BMI, and AHI category), the HNS group experienced a 1.48-point greater decrease in PHQ-9 than the PAP group (least square means, −4.06 [95% CI, −5.34 to −2.79] vs −2.58 [95% CI, −3.35 to −1.82]; mean difference, −1.48 [95% CI, −2.78 to −0.19]). Mean differences from baseline to follow-up were clinically important in both groups for ESS scores and did not represent clinically important differences for the FOSQ, ISI, and PHQ-9 scores. For the ESS score, 42 of 65 HNS group participants (64.6%) and 118 of 217 PAP group patients (54.5%) experienced a clinically important ESS score reduction of 2 or more points. A clinically meaningful FOSQ score increase of at least 2 points was observed in 29 of 49 HNS group patients (59.2%) compared with 67 of 217 PAP group patients (30.9%), and a PHQ-9 score reduction of at least 5 points was seen in 14 of 48 HNS group patients (29.2%) and 53 of 217 PAP group patients (24.4%). A clinically meaningful reduction in ISI score of at least 6 points was observed in 23 of 49 HNS group patients (46.9%) and 79 of 217 PAP group patients (36.4%). Additional subgroup analyses of patients with adherent therapy use (defined using adherence criteria described in the Methods section) did not show any clinically significant differences in PRO changes between the PAP and HNS groups

Table 1. Demographic Characteristics and Baseline and Follow-up Patient-Reported Outcomes

Characteristic	Treatment group[a]						Effect size (95% CI)
	All (N = 302)		PAP (n = 217)		HNS (n = 85)		
	No. of patients	Data	No. of patients	Data	No. of patients	Data	
Age, mean (SD), y	302	62.3 (9.8)	217	62.1 (9.9)	85	62.8 (9.5)	−0.07 (−0.32 to 0.18)[b]
Sex, No. (%)							
Female	302	86 (28.5)	217	60 (27.6)	85	26 (30.6)	0.03 (0.00 to 0.16)[c]
Male		216 (71.5)		157 (72.4)		59 (69.4)	
Race, No. (%)							
White	298	250 (83.9)	213	173 (81.2)	85	77 (90.6)	0.12 (0.02 to 0.21)[c]
Non-White[d]		48 (16.1)		40 (18.8)		4 (9.4)	
BMI, mean (SD)	302	29.3 (3.2)	217	29.5 (3.1)	85	28.8 (3.1)	0.23 (−0.03 to 0.48)[b]
Baseline AHI, median (IQR)	302	43.4 (31.5 to 59.1)	217	46.1 (31.4 to 69.0)	85	41.1 (31.6 to 54.0)	0.15 (0.02 to 0.28)[e]
AHI category, No. (%)							
15 to <30	302	59 (19.5)	217	43 (19.8)	85	16 (18.8)	0.01 (0.00 to 0.13)[c]
≥30		243 (80.5)		174 (80.2)		69 (81.2)	
ESS score, median (IQR)							
Baseline	290	8.5 (5.0 to 13.0)	214	8.0 (4.0 to 12.0)	76	11.5 (7.0 to 16.0)	−0.26 (−0.40 to −0.11)[e]
3-mo follow-up	289	5.0 (3.0 to 8.0)	216	5.0 (3.0 to 8.0)	73	6.0 (3.0 to10.0)	−0.11 (−0.26 to −0.05)[e]
FOSQ score, median (IQR)							
Baseline	268	17.0 (14.0 to 19.0)	213	18.0 (15.0 to 19.0)	55	16.0 (14.0 to 18.0)	0.22 (0.06 to 0.37)[e]
3-mo follow-up	270	19.0 (17.0 to 20.0)	215	19.0 (17.0 to 20.0)	55	19.0 (17.0 to 19.0)	0.10 (−0.05 to 0.25)[e]
PHQ-9 score							
Baseline	268	6.0 (3.0 to 11.0)	211	6.0 (3.0 to 11.0)	57	7.0 (4.0 to 12.0)	−0.08 (−0.23 to 0.08)[e]
3-mo follow-up	284	3.0 (1.00 to 8.0)	215	3.0 (1.00 to 8.0)	69	3.0 (1.00 to 8.0)	−0.03 (−0.18 to 0.12)[e]
ISI score, median (IQR)							
Baseline	275	13.0 (8.0 to 18.0)	217	12.0 (8.0 to 17.0)	58	16.0 (10.0 to 20.0)	−0.24 (−0.39 to −0.07)[e]
3-mo follow-up	274	8.0 (4.0 to 14.0)	217	8.0 (4.0 to 14.0)	57	9.0 (5.0 to 13.0)	−0.09 (−0.24 to 0.06)[e]
Adherence in follow-up, No. (%)[f]	180	141 (78.3)	104	80 (76.9)	76	61 (80.3)	0.04 (0.00 to 0.18)[c]
Total use since last visit, median (IQR), h	NA	NA	NA	NA	74	269.5 (103.0 to 666.0)	NA
Use per week since last visit, median (IQR), h	NA	NA	NA	NA	76	40.5 (29.5 to 52.5)	NA

Abbreviations: AHI, apnea hypopnea index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; HNS, hypoglossal nerve stimulation; ISI, Insomnia Severity Index; NA, not applicable; PAP, positive airway pressure; PHQ-9, Patient Health Questionnaire 9.

[a] Percentages have been rounded and may not total 100.

[b] Calculated as Hedges *g*.

[c] Calculated as Cramer *V*.

[d] Includes Black and other categories.

[e] Calculated as Cliff δ.

[f] Calculated for the HNS group as weekly use of at least 28 hours and for the PAP group as at least 4 hours of device use on at least 70% of nights.

(eTable 1 in the Supplement and Figure 1). However, patients with adherent therapy use in both the PAP and HNS groups showed clinically important within-group changes in ESS scores (−3.37 and −3.19 points, respectively).

PROs 1 Month After Activation in HNS Group

Longitudinal data were available for 87 patients in the HNS group (mean [SD] age, 62.6 [9.5] years, 60 [69.0%] men; 79 White [90.8%] and 8 non-White [9.2%] patients; mean [SD] BMI, 28.8 [3.1]). Baseline to post-HNS PRO changes are shown in **Table 3** and **Figure 2**. After 1 month, all PROs improved significantly. The ESS scores decreased from 11.15 (95% CI, 10.10-12.20) to 7.88 (95% CI, 6.54-9.23) (difference, −3.27 [95% CI, −4.97 to −1.56]), and 34 of 48 patients (70.8%) experienced a clinically meaningful 2-point reduction in ESS score. The FOSQ scores increased from 15.70 (95% CI, 14.98-16.42) to 17.63 (95% CI, 16.78-18.49) (difference, 1.93 [95% CI, 0.82-3.05]), and 21 of 35 patients (60.0%) experienced a clinically meaningful 2-point increase. The ISI scores decreased from 15.16 (95% CI, 13.71-16.62) to 9.17 (95% CI, 7.38-10.96) (difference, −5.99 [95%

Table 2. Comparison of PRO Change From Baseline to 3-Month Follow-up[a]

Factor	PAP group			HNS group			Difference in change, LSM (95% CI)[c]	Difference in % surpassing MCID[d]
	No. of patients	LSM (95% CI)	>MCID, No. (%)[b]	No. of patients	LSM (95% CI)	>MCID, No. (%)[b]		
ESS	217	−2.88 (−3.56 to −2.20)	118 (54.4)	65	−2.83 (−3.83 to −1.82)	42 (64.6)	0.05 (−0.97 to 1.08)	10.2
FOSQ	217	1.38 (1.00 to 1.75)	67 (30.9)	49	1.84 (1.21 to 2.48)	29 (59.2)	0.47 (−0.19 to 1.13)	28.3
PHQ-9	217	−2.58 (−3.35 to −1.82)	53 (24.4)	48	−4.06 (−5.34 to −2.79)	14 (29.2)	−1.48 (−2.78 to −0.19)	4.8
ISI	217	−3.68 (−4.77 to −2.59)	79 (36.4)	49	−4.45 (−6.27 to −2.64)	23 (46.9)	−0.77 (−2.66 to 1.11)	10.5

Abbreviations: AHI, apnea hypopnea index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; HNS, hypoglossal nerve stimulation; ISI, Insomnia Severity Index; LSM, least square means; MCID, minimum clinically important difference; PAP, positive airway pressure therapy; PHQ-9, Patient Health Questionnaire 9; PRO, patient-reported outcome.

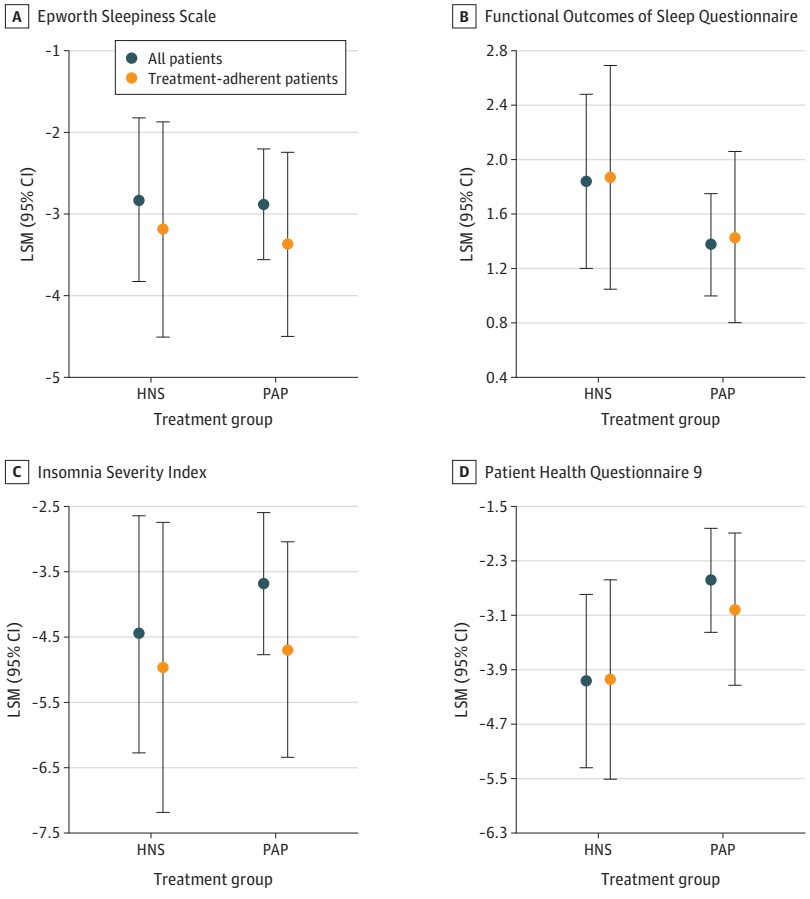
[a] Adjusted for baseline, age, sex, BMI, and AHI category (matching by BMI caliper 3).

[b] Defined as ESS reduction of at least 2 points, FOSQ increase of at least 2 points, PHQ-9 reduction of at least 5 points, and ISI reduction of at least 6 points (see Methods section).

[c] Calculated as HNS score minus PAP score.

[d] Calculated as percentage of HNS minus PAP score.

Figure 1. Changes in Patient-Related Outcomes From Baseline to 3-Month Follow-up in Hypoglossal Nerve Stimulation (HNS) and Positive Airway Pressure (PAP) Groups



Adherent weekly use is defined as at least 28 hours of HNS use in HNS group and at least 4 hours of PAP use on at least 70% of nights in PAP group. Data for all patients are shown in Table 2; for treatment-adherent patients, eTable 1 in the Supplement. LSM indicates least square means.

CI, −8.30 to −3.69]), which moved the median insomnia severity from moderate to subthreshold, and 15 of 34 patients (44.1%) experienced a clinically meaningful 6-point reduction. The PHQ-9 scores decreased from 8.11 (95% CI, 6.81-9.42) to 4.02 (95% CI, 2.45-5.60) (difference, −4.09 [95% CI, −6.14 to −2.04]), moving the median depression severity from mild to none/minimal, and 11 of 33 patients (33.3%) experienced a clinically meaningful 5-point reduction.

Table 3. Patient-Reported Outcomes at Baseline vs All Post-HNS Times

	Baseline (pre-HNS assessment)		Post-HNS assessment		Change from baseline to post-HNS assessment		
Factor	No. of patients	LSM (95% CI)	No. of patients	LSM (95% CI)	No. of patients	LSM (95% CI)	>MCID at post-HNS assessment, No. (%)[a]
1 mo							
ESS	85	11.15 (10.10 to 12.20)	52	7.88 (6.54 to 9.23)	48	−3.27 (−4.97 to −1.56)	34 (70.8)
FOSQ	57	15.70 (14.98 to 16.42)	41	17.63 (16.78 to 18.49)	35	1.93 (0.82 to 3.05)	21 (60.0)
ISI	62	15.16 (13.71 to 16.62)	41	9.17 (7.38 to 10.96)	34	−5.99 (−8.30 to −3.69)	15 (44.1)
PHQ-9	61	8.11 (6.81 to 9.42)	42	4.02 (2.45 to 5.60)	33	−4.09 (−6.14 to −2.04)	11 (33.3)
3 mo							
ESS	85	11.15 (10.10 to 12.20)	41	7.46 (5.95 to 8.98)	38	−3.69 (−5.53 to −1.85)	25 (65.8)
FOSQ	57	15.70 (14.98 to 16.42)	38	17.63 (16.75 to 18.52)	35	1.93 (0.79 to 3.07)	21 (60.0)
ISI	62	15.16 (13.71 to 16.62)	39	11.08 (9.24 to 12.91)	34	−4.08 (−6.43 to −1.74)	16 (47.1)
PHQ-9	61	8.11 (6.81 to 9.42)	44	5.07 (3.53 to 6.61)	36	−3.05 (−5.07 to −1.03)	11 (30.6)
6 mo							
ESS	85	11.15 (10.10 to 12.20)	40	6.28 (4.74 to 7.81)	36	−4.88 (−6.74 to −3.02)	23 (63.9)
FOSQ	57	15.70 (14.98 to 16.42)	26	17.65 (16.58 to 18.72)	24	1.95 (0.66 to 3.24)	12 (50.0)
ISI	62	15.16 (13.71 to 16.62)	28	10.18 (8.01 to 12.34)	24	−4.98 (−7.59 to −2.37)	9 (37.5)
PHQ-9	61	8.11 (6.81 to 9.42)	36	5.58 (3.88 to 7.29)	25	−2.53 (−4.68 to −0.38)	7 (28.0)
1 y							
ESS	85	11.15 (10.10 to 12.20)	34	8.21 (6.54 to 9.87)	28	−2.95 (−4.91 to −0.98)	17 (60.7)
FOSQ	57	15.70 (14.98 to 16.42)	21	17.29 (16.10 to 18.48)	20	1.58 (0.19 to 2.98)	11 (55.0)
ISI	62	15.16 (13.71 to 16.62)	26	10.46 (8.22 to 12.71)	25	−4.70 (−7.38 to −2.02)	11 (44.0)
PHQ-9	61	8.11 (6.81 to 9.42)	29	4.90 (3.00 to 6.79)	23	−3.22 (−5.52 to −0.91)	7 (30.4)

Abbreviations: ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; HNS, hypoglossal nerve stimulation; ISI, Insomnia Severity Index; LSM, least square means; MCID, minimum clinically important difference; PHQ-9, Patient Health Questionnaire 9.

[a] Defined as ESS reduction of at least 2 points, FOSQ increase of at least 2 points, PHQ-9 reduction of at least 5 points, and ISI reduction of at least 6 points (see Methods section).

PRO Outcomes Past 1 Month

All improvements seen from baseline to the 1-month post-HNS follow-up were maintained at the 3-month post-HNS assessment. Of the patients evaluated at 3 months, 25 of 38 (65.8%) demonstrated a clinically meaningful change in ESS score; 21 of 35 patients (60.0%), in FOSQ score; 11 of 36 patients (30.6%), in PHQ-9 score; and 16 of 34 patients (47.1%), in ISI score. When compared with baseline, the amount of change at the 6-month post-HNS assessment was clinically meaningful for 23 of 36 patients (63.9%) for ESS score, 12 of 24 patients (50.0%) for FOSQ score, 7 of 25 patients (28.0%) for PHQ-9 score, and 9 of 24 patients (37.5%) for ISI. At the 1-year post-HNS assessment, clinically important differences were observed in 17 of 28 patients (60.7%) for ESS score, 11 of 20 patients (55.0%) for FOSQ score, 7 of 23 patients (30.4%) for PHQ-9 score, and 11 of 25 patients (44.0%) for ISI patients. Changes from baseline to the 2-year post-HNS assessment could not be reliably analyzed owing to low sample size at the 2-year assessment; most patients had not reached year 2 of HNS use.

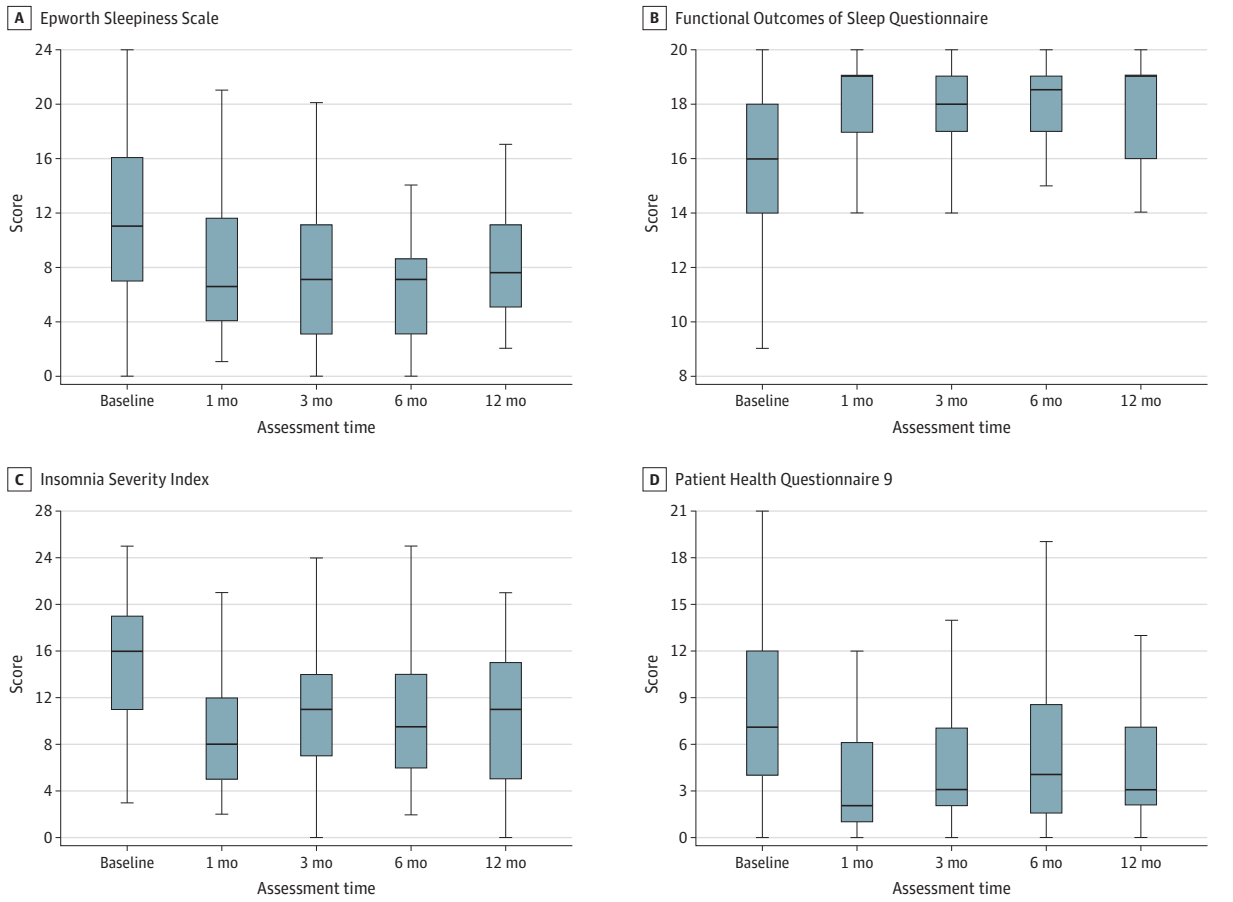
Correlation of OSA Severity With Polysomnographic Measures and PROs

Correlations between change in AHI and change in polysomnographic measures and PROs from baseline to the 1-month post-HNS assessment are shown in eTable 2 in the Supplement. There were no significant correlations between AHI change and any polysomnographic measure or PROs (range, −0.15 to 0.33). Because the greatest changes in outcomes were seen in the first month, and no correlations were observed between OSA severity and outcomes after 1 month, there appears to be no significant confounding association between OSA severity and changes in PROs after HNS.

Discussion

To our knowledge, this single-center, clinic-based cohort study of HNS with a PAP comparator arm is the first to observe a consistent and sustained long-term improvement of polysomnographic measures and PROs after HNS during a 1-year follow-up period. From our sample of predominantly older, White men in the overweight BMI category, we observed the following: (1) all PRO changes from baseline to 1 month after HNS activation reflected clinical severity category change (ie, alleviating daytime sleep propensity, improving functional sleep outcomes to near-normal levels, and reducing insomnia and depression symptoms to subthreshold and none/minimal severity), and many patients experienced individual minimum clinically important differences in PROs; (2) the percentage of patients in the HNS group experiencing clinically important

Figure 2. Longitudinal Changes in Patient-Related Outcomes (PROs) With Hypoglossal Nerve Stimulation Use



Horizontal bars indicate median; boxes, IQR; and error bars, upper quartile +1.5 × IQR and lower quartile −1.5 × IQR.

PRO differences was greater for all PROs compared with patients in the PAP group; and (3) improvements were maintained in all PROs after 1 year among patients in the HNS group.

Because HNS is a relatively new therapy, most of the existing literature focuses on primary outcomes of therapy—namely, OSA severity and daytime symptoms related to OSA, such as daytime sleep propensity and functional outcomes of sleep. The original Stimulation Treatment for Apnea Reduction (STAR) trial[9] found that HNS therapy reduced OSA severity from severe to mild and improved ESS and FOSQ scores to normal levels during a period of 12 months, and recent studies and reviews[8,12,25-28] have corroborated these findings and shown maintenance of benefits past 1 year. Our findings are consistent with these data but extend these observations to insomnia and depression symptoms. We observed an association between HNS and clinically meaningful improvement in insomnia and depression symptoms during a 1-month period, even without optimal titration, with further reductions in symptoms to absent/minimal levels after 1 year. These findings suggest that patients can expect to see improvements in OSA, insomnia, and depressive symptoms within 1 month and sustained improvements, or even further improvements, over time.

To our knowledge, this study is the first to compare PROs between HNS and PAP therapies for OSA. The magnitude of difference in PROs from baseline to treatment was similar between groups and reconfirms the benefit of both therapies. Walia et al[29] previously demonstrated more improvement in ESS with HNS compared with PAP; however, the different sample size might account for these findings, as well as the use of a more heterogeneous group. In addition, we observed that more patients in the HNS group experienced a clinically meaningful difference in PROs compared with patients in the PAP group. Given the ease of use and high rates of adherence for HNS,[12,30] as well its success in individuals with treatment-resistant OSA,[31] HNS should be considered as an alternative to PAP for treatment of OSA.

Limitations

Although this study is strengthened by long-term, centralized data and clinically meaningful PROs, it is limited by potential bias and missing data. For some patients, the electrode configuration of the HNS device may need to be adjusted after the initial activation visit. Given that this factor was not controlled for when evaluating PROs, the additional visits and variable therapeutic effect of the device during the

longer titration period may have a differential effect on PROs. Furthermore, although PROs were assessed in association with OSA severity, they were not adjusted for prior diagnosis of comorbid conditions, concomitant medications, or treatment adherence, complicating the observed associations between treatment and outcome. Potential bias could also stem from the absence of PROs for some patients. Given that PROs were obtained through the postapproval study and electronic medical records, if a patient was not enrolled in the study and did not have PROs in the electronic medical records, the study team was not able to gather these data nor determine the reason for their absence. In addition, because we collected data at only 1 instance and all participants had not yet completed all of their study visits, including 2-year postactivation follow-up from only 9 patients at the time of analysis, our scope of interpretation is limited, and we were not able to analyze results at 2 years because of the small sample size. However, no differences in baseline characteristics were observed between participant groups at each follow-up time. Going forward, once data collection is more complete, we plan to stratify our analysis by treatment adherence and adjust for concomitant factors, such as titration visits and comorbid conditions. Finally, the mean duration from baseline to follow-up was variable for different procedures. Some of these differences may be due to scheduling delays, payor coverage delays, and other logistic factors. Although these periods may differ, our ability to evaluate outcomes longitudinally across many times shows us that many PROs are stable over time, and thus the comparison should not change substantially.

Conclusions

Given the high prevalence of comorbid insomnia and depression with OSA, the results of this cohort study provide important insight into the expanded indication and utility of HNS for improving insomnia and depression symptom outcomes in OSA. These data also reflect the long-term durability of these and other OSA severity and PRO benefits, as well as their comparability to benefits seen with PAP use. Future prospective trials are needed to confirm these findings.

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Concept and design: Mehra, Shah, Waters, Walia.
Acquisition, analysis, or interpretation of data: Pascoe, Wang, Aylor, Kominsky, Foldvary-Schaefer, Waters, Walia.
Drafting of the manuscript: Pascoe, Wang, Aylor, Mehra, Waters, Walia.
Critical revision of the manuscript for important intellectual content: Pascoe, Kominsky, Foldvary-Schaefer, Shah, Waters, Walia.
Statistical analysis: Wang.
Administrative, technical, or material support: Pascoe, Kominsky, Foldvary-Schaefer, Waters, Walia.
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