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Hypoglossal Nerve Stimulation Usage by Therapy Nonresponders

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Abstract

Objective. The purpose of this study is to examine differences in therapy usage and outcomes of therapy between responder (R) and nonresponder (NR) groups in an international, multicenter prospective registry of patients undergoing hypoglossal nerve stimulation for obstructive sleep apnea (OSA).

Study Design. Database analysis (level III).

Setting. International, multicenter registry.

Methods. The studied registry prospectively collects data pre- and postimplantation, including sleep parameters, Epworth score, patient experience, and safety questions, over the course of 12 months. Patients are defined as a "responder" based on Sher criteria, which require a final apnea-hypopnea index (AHI) of $\leq$20 and a final AHI reduction of $>$50% at their 12-month follow-up.

Results. Overall, there were 497 (69%) R and 220 (31%) NR. Most patients in both groups experienced improvement in quality of life following implantation (96% of R; 77% of NR) with reductions in oxygen desaturation index and Epworth score. At final follow-up, the R group demonstrated significantly better adherence to recommended therapy ($>$4 hours/night) (P = .001), average hours of nightly use (P = .001), final Epworth scores (P = .001), and degree of subjective improvement ($P < .001$).

Conclusion. Patients classified as NR to upper airway stimulation continue to use therapy with improvement in percent time of sleep with O_2 $<$90%, reduction in daytime sleepiness, and improvement in quality of life. Therefore, ongoing usage of the device should be encouraged in NR patients who note improvement while integrating additional strategies to lower the long-term effects of OSA.

Keywords

obstructive sleep apnea, surgery, upper airway stimulation, hypoglossal nerve stimulation, Inspire implant, nonresponder

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Obstructive sleep apnea (OSA) is a disorder characterized by repetitive collapse of the upper airway during sleep. The severity of OSA is commonly defined using the apnea-hypopnea index (AHI), with scores greater than 15 being associated with increased cardiovascular risk, daytime sleepiness, decreased cognitive function, and early mortality.[1-3] While continuous positive airway pressure (CPAP) remains the gold standard, hypoglossal nerve stimulation (HNS) via an implantable device has become a promising treatment option for a select group of patients with CPAP intolerance.[4] The HNS system, which is the focus of this study, was approved by the US Food and Drug Administration (FDA) in 2014 on the basis of the Stimulation Therapy for Apnea Reduction (STAR) trial, which showed safety and efficacy with significant decreases in both AHI and ODI on average after 12 months of use.[5]

As more patients receive HNS therapy, there is an expected and growing subset of patients who are nonresponsive to therapy based on the Sher criteria (AHI reduction of $\geq$50% with an overall AHI $<$20), which are a routinely applied metric to assess the effectiveness of non–positive airway pressure (PAP) interventions.[6] Clinical experience, however, suggests that many of these nonresponders continue to use therapy and report positive outcomes despite their nonresponder status. It is unclear whether this represents a true improvement in certain patient outcomes beyond AHI or is due to placebo effect.

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Therefore, additional study is needed to determine the patterns of HNS therapy use and subjective experience in patients classified as nonresponders.

The objective of this study is to compare HNS responders (R) and nonresponders (NR) according to the Sher criteria to determine differences in patterns of use and well as non-AHI outcomes between the 2 groups.

Methods

The Adherence and Outcome for Upper Airway Stimulation (UAS) for OSA International (ADHERE) registry is a multicenter, international, prospective postmarketing study sponsored by Inspire Medical. It seeks to collect data on patient- and physician-reported outcomes following HNS implantation. The review board approving this study is the University of Tennessee Health Science Center institutional review board. The registry has been approved by ethics committees or institutional review boards at each implant center. The study is registered with www.clinicaltrials.gov (NCT02907398).

Hypoglossal Nerve Stimulation System

The HNS system includes an implantable pulse generator (IPG) and a respiration sensing lead placed in the intercostal space of the chest wall. Specific details on the implantation procedure have been published elsewhere.[5]

Data Collection

The registry includes adult patients who meet selection criteria for HNS device implantation. Selection criteria include patients who are intolerant to CPAP, have AHI between 15 and 65 events per hour, have a body mass index (BMI) of less than or equal to 35, and fail to demonstrate complete concentric collapse of the airway during drug-induced sleep endoscopy. The data collected include demographic patient data, medical history, past experience with treatments for OSA, Epworth Sleepiness Scale (ESS), implant information, objective therapy usage data, adverse events, patient experience with therapy, and physician perception of improvement. Data are collected at 4 major time points: preimplantation, implantation, posttitration of device, and final follow-up at 12 months postimplantation. OSA severity is determined by polysomnogram (PSG) or home sleep testing (HST) at preimplantation, posttitration, and final follow-up.

Data Analysis

Outcome measures of AHI, ESS, oxygen desaturation index (ODI), percentage of sleep time with O_2 <90% (T90%), therapy usage, and patient experience via the Clinical Global Impression (CGI) scale were compared between the R and NR groups at baseline and final follow-up. The CGI improvement scale asks patients to choose which response best represents their experience from 1 (very much improved, nearly all better, good level of functioning) to 7 (very much worse, severe exacerbation of symptoms, and loss of functioning).[6] Patients are defined as R or NR based on the Sher criteria, which state that a patient has responded to therapy if they have a postoperative AHI <20 and a total decrease in AHI of ≥50% by 12 months postimplantation.[7] Patients were included in this analysis if they had completed final follow-up and had AHI recorded at baseline and final follow-up. For each respective outcome analysis, patients were included if they did not have missing values at all needed visits for the variable(s) being analyzed. The number of patients (n) included in each data set will be reported alongside the results in the associated tables. Results are presented as median and/or mean. Raw data were provided by the registry research team and independently verified using the SAS 9.4 platform (SAS Institute). Statistical tests included the F test for CGI data, χ^2 test for qualitative values, and Student t test for all others.

Results

Baseline Data

The study registry enrolled 2168 patients between October 2016 and September 2020. Of these, 2090 patients were implanted with the device, 966 completed a final follow-up visit, and 717 patients reported data on responder status (Sher criteria). Overall, 69% (n = 497) of these patients are defined as R. At baseline, there is a significant difference (P = .004) between the groups in terms of BMI with the NR being significantly heavier on average. The baseline data for both groups can be found in **Table 1**.

Nonresponder Group Analysis

The NR group showed significant improvement in AHI and ESS. Additional parameters, such as ODI and CGI quality-of-life scores, did not demonstrate significant improvement. The outcomes data for all time points for the NR group can be found in **Table 2**.

Between-Group Analysis at Posttitration

On average, the R group demonstrates better adherence to therapy after treatment initiation. The R group was found to be significantly more compliant to the recommended 4 or more hours per night, although this difference was small. The R group also demonstrated significantly better treatment satisfaction based on the CGI quality-of-life scores. The posttitration data for both groups can be found in **Table 3**.

Between-Group Analysis at Final Follow-up

The R group was found to be significantly more compliant to the recommended 4 or more hours of per night per patient report and on average used the device more than the NR group at the final 12-month follow-up. Both groups demonstrated a decline in device usage from the posttitration end point to final follow-up, with a larger decline seen for the NR group (16%) than the R group (8%). The R group demonstrated significantly better results than the NR group with regard to daytime sleepiness (ESS; P = .001), ODI (P < .001), and CGI quality-of-life scores (P < .001). There were no significant changes in BMI for either group between baseline, posttitration, and final follow-up. The final follow-up data for both groups can be found in **Table 4**.

Table 1. Baseline Characteristics of the R and NR Groups.[a]

Characteristic	Responder (n = 497)	Nonresponder (n = 220)	*P* value
Age, y	60.05 ± 10.7	58.74 ± 11.7	.158
% Male	78.59	80.91	.540
AHI (median)	32.2 ± 9.1	33.0 ± 10.0	.940
ESS	11.76 ± 5.5	11.83 ± 5.5	.882
ODI	24.09 ± 12.6	32.10 ± 48.6	.453
T90%	14.29 ± 25.8	11.20 ± 19.7	.495
BMI,[b] kg/m^2	28.91 ± 3.8	29.84 ± 4.0	.004

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; T90%, percentage of sleep time with O_2 <90%.
[a]Values are reported as mean ± SD or number (%) unless otherwise indicated. AHI is reported as median ± median absolute deviation.
[b]Indicates statistically significant difference between groups.

Table 2. Nonresponder Group Analysis.[a]

Characteristic	Baseline	Posttitration	Final follow-up
AHI (median)[b]	33.0 ± 10.0	14.45 ± 9.45 (*P* < .001)	25.6 ± 8.55 (*P* < .001)
ESS[b]	11.83 ± 5.5	8.57 ± 5.0 (*P* < .001)	8.15 ± 4.9 (*P* < .001)
ODI	32.10 ± 48.6	17.01 ± 15.5 (*P* = .225)	25.72 ± 15.7 (*P* = .395)
T90%	11.20 ± 19.7	10.89 ± 20.9 (*P* = .684)	14.51 ± 20.5 (*P* = .748)
CGI-1 to 2, %	NA	46.5	56.9 (*P* = .076)
BMI, kg/m^2	29.84 ± 4.0	30.23 ± 4.9 (*P* = .384)	30.08 ± 4.1 (*P* = .553)

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CGI, Clinical Global Impression; ESS, Epworth Sleepiness Scale; NA, not applicable; ODI, oxygen desaturation index; T90%, percentage of sleep time with O_2 <90%.
[a]Values are reported as mean ± SD. *P* values shown represent comparison between time point and baseline; for CGI-1 to 2, it represents a comparison between the posttitration and final follow-up time points.
[b]Indicates statistically significant difference between groups.

Table 3. Comparison of Responder and Nonresponder Groups at Posttitration.[a]

Characteristic	Responder (n = 497)	Nonresponder (n = 220)	*P* value
Therapy adherence[b]	91% (n = 429)	88% (n = 188)	.004
Therapy usage per night,[b] h	6.59 ± 1.8 (n = 429)	6.28 ± 1.97 (n = 188)	.016
ESS	7.44 ± 4.4 (n = 404)	8.57 ± 5.0 (n = 176)	.127
T90%	6.93 ± 18.0 (n = 64)	10.89 ± 20.9 (n = 101)	.694
ODI	7.98 ± 8.1 (n = 246)	17.01 ± 15.5 (n = 110)	.343
CGI,[b,c] %	CGI-1 to 2: 88.4 (n = 351) CGI-3 to 5: 11.6 (n = 46) CGI-6 to 7: 0 (n = 0)	CGI-1 to 2: 46.5 (n = 60) CGI-3 to 5: 51.9 (n = 67) CGI-6 to 7: 1.6 (n = 2)	<.001
BMI,[b] kg/m^2	28.92 ± 3.9	30.22 ± 4.9	.001

Abbreviations: BMI, body mass index; CGI, Clinical Global Impression; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; T90%, percentage of sleep time with O_2 <90%.
[a]Values are reported as mean ± SD.
[b]Indicates statistically significant difference between groups.
[c]CGI-1 = very much improved, CGI-2 = much improved, CGI-3 = minimally improved, CGI-4 = no change, CGI-5 = minimally worse, CGI-6 = much worse, CGI-7 = very much worse.

Discussion

In this study, our aim was to determine if the NR group of patients had clinical improvement in parameters other than AHI that result in continued therapy usage despite the nonresponder status. Based on improvements in AHI, daytime sleepiness, oxygen desaturation index, and general symptoms per CGI scale score, it is found that the NR group does continue

Table 4. Comparison of Responder and Nonresponder Groups at Final Follow-up.[a]

Characteristic	Responder (n = 497)	Nonresponder (n = 220)	*P* value
Therapy adherence,[b] %	83% (n = 354)	72% (n = 130)	.005
Therapy usage per night,[b] h	5.89 ± 2.0 (n = 428)	5.24 ± 2.2 (n = 180)	.001
ESS[b]	6.78 ± 4.4 (n = 428)	8.15 ± 5.0 (n = 185)	.001
T90%	10.85 ± 20.9 (n = 229)	14.51 ± 20.5 (n = 125)	.896
ODI[b]	8.27 ± 7.4 (n = 285)	25.72 ± 15.7 (n = 123)	<.001
CGI,[b,c] %	CGI-1 to 2: 85.6 (n = 357)	CGI-1 to 2: 56.9 (n = 87)	<.001
	CGI-3 to 5: 13.4 (n = 56)	CGI-3 to 5: 41.8 (n = 64)	
	CGI-6 to 7: 1.0 (n = 4)	CGI-6 to 7: 1.3 (n = 2)	
BMI,[b] kg/m^2	28.76 ± 4.0	30.08 ± 4.1	<.001

Abbreviations: BMI, body mass index; CGI, Clinical Global Impression; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; T90%, percentage of sleep time with O_2 <90%.

[a]Values are reported as mean ± SD.

[b]Indicates statistically significant difference between groups.

[c]CGI-1 = very much improved, CGI-2 = much improved, CGI-3 = minimally improved, CGI-4 = no change, CGI-5 = minimally worse, CGI-6 = much worse, CGI-7 = very much worse.

to receive therapeutic benefit from therapy. As expected, however, the improvements in the NR group were less pronounced than in the R group. Both the R and NR groups demonstrated reduced device usage at final follow-up, indicating a general reduction in adherence over time, but the greater drop in adherence in the NR group may be explained by a lack of clinical improvement, as reflected in objective measures of response. The response rate of 69% closely reflects that found in the original STAR trial, which found a rate of 66%.[5] Regarding changes in T90% at different time points, it was found that the type of sleep test (PSG vs HST) employed varied among time points. PSG was used by 70.14% at baseline, 78.99% at posttitration, but only 40.5% at final follow-up. The increase in usage of HST data at final follow-up may have had an impact on the T90% values at this time point as it was found that T90% was significantly lower in patients who had a PSG vs those who had an HST, possibly indicating the larger percentage of sleep time in the supine position during PSG compared to HST. Of note, there are a significant number of patients who do not complete final follow-up, and this may have an impact on the results. On average, at 2 years following implantation, approximately 30% of all implanted patients fail to return for final follow-up examination.

A handful of studies have noted the benefits, both subjective and objective, provided even by partial (noncurative) OSA treatment.[8-11] In CPAP studies using a control group with reduced PAP pressures, the control group was found to have comparably improved sleep architecture and efficacy as the treatment group.[9] The respiratory disturbance index (RDI) was also reduced in the control group, although to a lesser extent than the treatment group. Notably, the treatment and control groups were found to have equally significant reduction in daytime mean arterial pressures.[11] Similar results have been reported in patients with an incomplete response to uvulopalatopharyngoplasty (UPPP), showing reduction in RDI, subjective improvement in quality of life, and daytime sleepiness.[9]

There is some evidence that patients receive benefit from treatment even when using it less than the recommended amount of time per night.[12] A CPAP study comparing outcomes between a >4 hours per night usage group vs a <4 hours per night usage group found there were similar improvements in subjective sleepiness.[12] This suggests that suboptimal amount of therapy usage still confers symptomatic benefit. This observation can likely be transferred to HNS therapy.

There are a number of potential strategies to salvage or optimize patients with incomplete response to HNS therapy. Of these, an initial approach includes an in-office advanced device titration with or without awake endoscopy.[13] This strategy allows for direct observation of stimulation with the opportunity for feedback from the patient and immediate titration of the device. If nonadherence is the cause of incomplete response, device titration to more comfortable settings may address the issue. In patients with trouble falling asleep, the device may be titrated to increase the delay to onset of therapy. Certain patients may benefit from a trial of low-dose hypnotic until they have acclimated to the device. The addition of an oral appliance (OA) is another noninvasive approach that has been used in patients with incomplete response to HNS who nevertheless have baseline AHI too high for OA therapy alone. The patient in this case study required additional titrations to achieve optimal comfort with the OA but afterward was found to have further improvement in sleep parameters.[14] Other salvage strategies include nasal surgery, removal of excess tonsillar tissue, or other airway reconstructive surgeries, including UPPP and maxillomandibular advancement.[15]

Implantation of an HNS device involves a large investment of health care resources with regard to physician time and cost of the device. Given the improved health benefits in NR, even

with reduced treatment time, ongoing use of the device should be encouraged and optimization of therapy prioritized. This will involve strategies to improve adherence with cognitive behavioral therapy, hypnotics, or lower noncurative stimulation settings, as well as attempts to optimize therapy with device titration, repeated sleep testing, chin strap, oral appliance, or additional surgery.

Although this study is conducted using the largest database of its kind, the data on patients considered therapy nonresponders are still being collected. While it was possible to perform statistical analysis on the data available, increasing the size of the cohort would increase statistical power and allow greater insight into subtle differences. Other limitations of this study include lack of information regarding what interventions were done prior to determination of NR status, on whether NR patients who continue to use the therapy have improved long-term health outcomes such as real reductions in hypertension, coronary artery disease, stroke, and motor vehicle accidents, as well as the loss to follow-up of nearly a third of all implanted patients.

Conclusions

HNS requires significant investment in time and expense by the patient, physician, and health care system. While most patients are adequately treated, nearly one-third are classified as nonresponders to therapy (by standard objective PSG criteria) at 1 year following implant. This study found that many therapy nonresponders continue to use therapy due to subjective benefit. Finding ways to improve an incomplete response to therapy is and will continue to be of high importance, as HNS becomes a more highly sought after solution to obstructive sleep apnea.

Author Contributions

Kimberly K. Coca, data collection, data analysis, manuscript writing; **Clemens Heiser**, data collection, manuscript review; **Colin Huntley**, data collection, manuscript review; **Maurits Boon**, data collection, manuscript review; **Nico de Vries**, data collection, manuscript review; **Madhu Mamidala**, research design, statistical analysis, manuscript review; **M. Boyd Gillespie**, data collection, data analysis, manuscript writing.

Disclosures

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