Title: Evaluating Hypoglossal Nerve Stimulation Outcomes in Obstructive Sleep Apnea: Impact of Predisposing Conditions in a Retrospective Cohort

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Abstract

Background: This retrospective study aimed to analyze treatment outcomes for patients receiving a hypoglossal nerve stimulation (HNS) device for obstructive sleep apnea (OSA).

Methods: Chart reviews were conducted for HNS patients who underwent a post-implantation polysomnography (PSG) (typically performed approximately 2 months after device activation) to assess therapeutic response and optimize stimulation settings. Patients were categorized into “green (GP)” (optimal response: AHI <15, ≥4 hours/night device use, and subjective benefit) and “yellow (YP)” (suboptimal response: failure to meet one or more of these criteria) response pathways.

Results: Out of 111 patients assessed, 27 patients met pathway categorization criteria. 12 of those were classified in green and 15 in yellow. Median age and BMI were 63.9 years and 28.7 kg/m², respectively, with a balanced sex assigned at birth distribution. HNS treatment reduced median AHI by 85.6% (from 34.7 to 5.0) for the green pathway (GP), and by 87.4% (from 39.6 to 5.0) for the yellow pathway (YP). Patients who had at least one sleep-related comorbidity were more likely to be in the yellow pathway ($p < .001$). Comorbidities such as depression and insomnia were significantly associated with suboptimal treatment response (yellow pathway) ($p = .003$ and $p = .02$, respectively).

Conclusions: Sleep-related comorbidities may influence patient outcomes and should be considered before HNS implantation to optimize resource use. Due to the small sample size and single-institution, retrospective design, these findings should be interpreted with caution and may not be generalizable.

Introduction

Obstructive sleep apnea (OSA) affects approximately 35.9% of older adults and is associated with obesity, age, cardiovascular disease, diabetes, and excessive daytime sleepiness [1]. Although continuous positive airway pressure (CPAP) devices are effective for OSA management, adherence rates remain low, with only 30-60% of patients consistently using them as prescribed [2]. CPAP intolerance is prevalent, affecting patients due to discomfort, claustrophobia, and lifestyle incompatibility [3]. This leaves a significant portion of patients untreated or inadequately managed, highlighting the need for alternative OSA therapies. Recent studies demonstrate that targeted hypoglossal nerve stimulation (HNS) has emerged as a promising therapy for CPAP intolerant patients. It significantly improves apnea severity, quality of life, and sleepiness in patients with moderate to severe OSA. The therapy benefits a diverse range of patients across varying body mass index (BMI) and Apnea-Hypopnea Index (AHI) levels, with clinically meaningful responses observed in randomized clinical trials [4].

OSA is a potentially life-threatening disorder characterized by episodes of upper-airway collapse that recur during sleep. It presents during sleep as loud snoring and breathing interruptions that can lead to the low partial pressure of oxygen, high partial pressure of carbon dioxide, and excessive daytime sleepiness [5]. The most common treatment for OSA is the use of CPAP devices. However, lack of adherence continues to be a significant issue for using such devices. Studies show that only 40-60% of patients adhere to using the CPAP device as prescribed by their physician [6]. In addition, many OSA patients do not seek medical attention for the disorder and therefore do not use any method to manage it [7]. The lack of patient knowledge regarding their sleep apnea and the available treatment options has led to OSA being overlooked by many clinicians [8]. Untreated OSA is associated with diminished quality of life and increased risk of cardiovascular, neurologic, and psychiatric complications [9] [10]. These risks underscore the need for effective, tolerable alternatives such as hypoglossal nerve stimulation for patients who cannot adhere to CPAP therapy.

Recently, HNS has emerged as an alternative treatment for patients.. HNS is a second line of therapy for treating sleep apnea, particularly in patients who cannot tolerate CPAP and meet other eligibility criteria [11]. After implantation of HNS, the device is activated at the clinic, and settings are fine-tuned during a specialized titration night. Annual sleep medicine follow-ups ensure sustained efficacy and necessary adjustments. Treatment outcomes are documented by categorizing patients in two response pathways that are established by the HNS device maker: “green” and “yellow.” Prior studies on HNS has demonstrated its benefits for patients with moderate to severe OSA, but there is limited knowledge regarding which comorbidities predict treatment outcomes [12]. Given the diverse nature of OSA manifestations and its associated comorbidities, understanding factors that may contribute to patient outcomes facilitates individualized approaches which can increase treatment efficacy. This study aimed to

investigate whether sleep-related comorbidities and other patient characteristics predict categorization into these pathways among OSA patients undergoing HNS.

While HNS has shown promise, the factors influencing patient response to this treatment remain unclear. Prior studies lack comprehensive analyses of co-morbidities and other patient characteristics that might predict positive outcomes [12]. Therefore, the purpose of this retrospective study was to investigate the predictive factors for patient placement in “green” and “yellow” response pathways post-HNS implantation. By clarifying these factors, this study aims to contribute to more individualized and effective OSA management strategies. We hypothesized that patients with sleep-related comorbidities (such as insomnia, depression, or anxiety) would be more likely to experience suboptimal outcomes following HNS implantation, as reflected by yellow pathway classification.

Materials and Methods

A retrospective chart review was conducted on all patients diagnosed with OSA and CPAP intolerance who presented for HNS consult between 2019 and 2023. Chart reviews were conducted for 111 patients who underwent HNS implantation at our institution. All patients received the Inspire® Upper Airway Stimulation system (Inspire Medical Systems, Inc., Golden Valley, MN).

Inclusion criteria for HNS implantation included patients diagnosed with moderate to severe OSA, defined by an AHI of 15 or more, who demonstrated intolerance to CPAP therapy or inadequate response to CPAP. Additional criteria required patients to have a BMI of 35 or less, no complete concentric collapse observed on drug-induced sleep endoscopy (DISE), and no significant comorbid conditions that could interfere with HNS outcomes. Exclusion criteria involved patients with significant neuromuscular disease, central sleep apnea, or those with anatomical abnormalities that contraindicated HNS.

Health behaviors, comorbid conditions, and treatment outcomes, including data from a titration polysomnography (PSG), were documented. Device activation typically occurred four weeks post-surgery, followed by a titration PSG approximately two months later to assess therapeutic response and adjust stimulation settings. Patients were classified in the ‘green’ pathway if AHI was below 15, the device was used more than 4 hours/day, and the patient reported improvement in symptoms (reduced daytime sleepiness and enhanced sleep quality). Patients were classified as “yellow” pathway if any of the criteria were not met. Those clinical pathways are part of the clinical framework established by the HNS device maker based on the criteria mentioned above. Symptom improvement was determined based on clinician-documented patient reports during follow-up visits. No standardized survey instrument (ESS) was used. Comorbid conditions, including depression, insomnia, and anxiety, were identified through clinician documentation in the electronic medical record, based on entries in problem lists or clinical notes prior to HNS implantation. No structured diagnostic instruments or ICD-10 codes were used.

All data extraction and chart review were conducted by a single investigator using a standardized data abstraction template to ensure consistency across variables. Medians and interquartile ranges (IQRs) were used to summarize continuous data. Differences between the two pathway groups were analyzed using Chi-square and Fisher's exact tests for categorical variables, and Wilcoxon Rank Sum tests for continuous variables. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Of the 111 patients who proceeded with the HNS implantation post-implantation treatment, outcomes were available for 27 patients. The remaining 84 patients were excluded from analysis due to not yet reaching the required follow-up for pathway classification (e.g., pending titration PSG or clinical reassessment) or being lost to follow-up. Statistical analyses were completed for 12 in the green pathway (GP) and 15 in the yellow pathway (YP). Demographic characteristics are in Table 1. Patient age at initial visit, sex assigned at birth, and median BMI at the initial visit were not significantly different between groups. The median AHI pre-implantation was 34.7 in the GP and 39.6 in the YP (p=.94). Post-implantation, the median AHI was reduced to 5.0 in both the GP and YP groups (p=.48).

Significant differences in pathway categorization were noted in certain comorbid conditions. YP categorization was significantly more common in patients with depression (84.6%) compared to those without depression (28.6%) (absolute difference: 56%, p = .003). YP was more prevalent in patients with insomnia (100.0%) versus those without insomnia (42.9%) (absolute difference: 57.1%, p = .02). While more patients with anxiety were in the YP (80.0%) than those without anxiety (41.2%), this difference was not statistically significant, p = .11. Restless leg syndrome, sleepwalking/eating/talking, and nightmares or night terrors did not significantly differ between the pathway groups. Overall, patients who had at least one comorbidity of all the above-mentioned conditions were more likely to be in the YP (87.5%) than patients who did not have a comorbidity (9.1%), p < .001.

Discussion

This study summarized the outcomes for 27 patients following HNS implantation who met pathway classification criteria, revealing key insights into treatment efficacy and comorbidity impacts. It identified key comorbid predictors and factors associated with treatment outcomes following HNS implantation that were consistent with prior studies [13]. Our findings reveal that comorbidities significantly influenced pathway categorization, with patients having at least one comorbidity, such as depression or insomnia, more likely to be in the yellow pathway. These conditions may influence HNS outcomes through several well-recognized pathways. Insomnia can reduce the restorative quality of sleep and interfere with perceived benefit, even when respiratory parameters improve. Depression may impair treatment

adherence or amplify symptom perception, limiting subjective improvement. Both conditions are also associated with disrupted circadian regulation and altered sleep-wake dynamics, which may blunt the perceived efficacy of HNS. One of the most striking outcomes is the marked reduction in the average AHI post-Inspire implantation, dropping from 34.7 to 5.0 for the green pathway and from 39.6 to 5.0 for the yellow pathway. Recognizing that an AHI below 5.0 represents effective OSA control, this result underscores the potential efficacy of Inspire HNS.

Clinical outcomes may be improved by understanding comorbid predictive factors that impact the effectiveness of HNS treatment. A recently published study examined the impact of comorbid insomnia on patient-reported outcomes and objective measures in OSA patients. Results reported that OSA patients with insomnia (COMISA) experienced reduced improvement and were less satisfied compared to those without insomnia [14]. A similar study observed a significant drop in patient-reported insomnia three months after HNS activation. Although these results were encouraging, a strong inverse correlation between pre-op subjective assessments and post-op respiratory metrics suggests that patients with more severe pre-op insomnia may have less favorable clinical outcomes [15]. These findings have important clinical implications. Awareness of yellow pathway predictors, particularly insomnia and depression, may help clinicians identify patients at risk for suboptimal outcomes prior to HNS implantation. This could guide more informed shared decision-making, prompt early behavioral health referral, and tailor follow-up intensity. Incorporating pathway categorization into post-implantation workflows may also help flag patients who are not responding optimally and benefit from earlier intervention or re-titration, improving long-term device efficacy and patient satisfaction. These findings may also inform the design of future prospective studies aimed at validating predictive models for HNS response. Stratifying patients based on pre-existing comorbidities, particularly psychiatric and sleep-related, could support development of clinical decision-making tools to guide candidate selection, counseling, and personalized follow-up strategies. Prospective studies incorporating standardized outcome metrics and multivariable models could enhance the precision of HNS treatment pathways.

Overall, patients in our study with comorbidities of insomnia, depression, or anxiety, were more likely to be in the suboptimal YP post-treatment. This insight provides an opportunity for more personalized HNS approaches, as patients with these comorbidities may benefit from tailored pre-and post-implantation interventions, such as mental health support, targeted behavioral therapies, or enhanced follow-up protocols, to mitigate the effects of these comorbidities on treatment adherence and effectiveness. Recognizing this predisposition allows for the tailoring of interventions, potentially enhancing treatment outcomes. For instance, implementing structured pre-treatment counseling sessions could help set realistic expectations and address concerns specific to patients at higher risk for yellow pathway outcomes. Integrating mental health or sleep specialists into the care team may also support optimal outcomes for these patients. A closer look at the treatment response pathways revealed that while the GP

patients showed significant clinical benefits, a substantial portion of patients were classified in the YP. This categorization highlights the importance of a personalized approach to OSA management. Tailoring treatment strategies could enhance efficacy and adherence, addressing the critical problem of under-management of OSA.

Limitations of this study include the retrospective design, which may introduce certain biases. Selection bias is possible, as only patients who completed post-implantation follow-up and pathway classification were included in the analysis. This may disproportionately exclude patients with barriers to care, lower adherence, or worse outcomes, potentially skewing the representativeness of our sample. Moreover, certain potential confounding variables were not controlled for, including medication use, cognitive status, and socioeconomic factors such as insurance status or access to care, all of which could influence both treatment adherence and perceived clinical benefit.Additionally, the reliance on patient-reported outcomes, especially for subjective measures such as sleep quality and daytime sleepiness, introduces the potential for recall bias. Furthermore, the relatively small sample size of patients who underwent Inspire implantation and had available post-treatment data, combined with the single-institution setting, limits external validity. Furthermore, the relatively small sample size of patients who underwent Inspire implantation and had available post-treatment data, combined with the single-institution setting, limits external validity. Moreover, due to the limited sample size, we did not perform multivariable regression, and thus cannot rule out residual confounding by factors such as age, sex assigned at birth, BMI, and baseline AHI. Practice patterns, patient populations, and follow-up protocols may differ across institutions, which could affect generalizability, although ongoing data collection will expand this sample size in future analysis. Additionally, a large proportion of patients (84/111) could not be included in pathway analysis due to incomplete follow-up, which may reflect real-world barriers to care, such as access limitations, delayed titration PSG scheduling, or patient attrition. This restricts the generalizability of our findings and underscores the importance of implementation research in HNS therapy. Due to the retrospective design, continued follow-up data collection will expand the sample in the future.

In conclusion, this study sheds light on the potential benefits and challenges of utilizing HNS in managing OSA. It underscores the need for personalized and equitable approaches in treating this common yet often overlooked disorder. By proactively identifying patients who may fall into the yellow pathway, clinicians can modify treatment plans and potentially improve long-term outcomes for a broader patient population. Further research is warranted to validate these findings and to delve deeper into understanding how to optimize treatment pathways for all OSA patients with comorbid conditions.

241 **Table 1. Comparison of Yellow & Green Pathway Demographics and Treatment Results for**
242 **Patients Receiving a Hypoglossal Nerve Stimulation Device**

	Green Pathway (*n* = 12)	**Yellow Pathway** (*n* = 15)	*p*-value	
Median Age at Initial Visit (IQR)	64.6 (57.8, 73.6)	63.4 (55.6, 69.4)	.48	†
Sex Assigned at Birth n (%)			1.00	
Male	5 (45.5%)	6 (54.5%)		
Female	7 (43.8%)	9 (56.3%)		
Median BMI at Initial Visit (IQR)	28.5 (26.0, 31.0)	28.9 (27.0, 31.0)	0.54	†
Smoking Status n (%)			.08	††
Active or Former Smoker	4 (28.6%)	10 (71.4%)		
Never Smoker	8 (61.5%)	5 (38.5%)		
Comorbid Conditions n (%)				
Depression			.003	††
No	10 (71.4%)	4 (28.6%)		
Yes	2 (15.4%)	11 (84.6%)		
Insomnia			.02	
No	12 (57.1%)	9 (42.9%)		
Yes	0 (0.0%)	6 (100.0%)		
Anxiety			.11	
No	10 (58.8%)	7 (41.2%)		
Yes	2 (20.0%)	8 (80.0%)		
Restless Leg Syndrome			.49	
No	12 (48.0%)	13 (52.0%)		
Yes	0 (0.0%)	2 (100.0%)		
Narcolepsy			-	
No	12 (44.4%)	15 (55.6%)		
Sleepwalking/Eating/Talking			.49	
No	12 (48.0%)	13 (52.0%)		
Yes	0 (0.0%)	2 (100.0%)		
Nightmares or Night Terrors			1.00	
No	12 (46.2%)	14 (53.8%)		
Yes	0 (0.0%)	1 (100.0%)		
Bruxism			-	
No	12 (44.4%)	15 (55.6%)		

At least One Or More Comorbidity			< .001	
No	10 (90.9%)	1 (9.1%)		
Yes	2 (12.5%)	14 (87.5%)		
Median AHI (IQR)				
Pre-Implantation	34.7 (24.7, 52.1)	39.6 (23.0, 54.1)	.94	†
Post-Implantation	5.0 (3.6, 8.5)	5.0 (3.8, 10.4)	.48	†

243 P-values from Fisher's exact tests unless otherwise specified. †P-value from Wilcoxon rank-sum test. ††P-
244 value from Chi-Square test.
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