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SCIENTIFIC INVESTIGATIONS

Early objective adherence to hypoglossal nerve stimulation therapy

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Study Objectives: To assess early adherence to therapy with hypoglossal nerve stimulation therapy.

Methods: This is a prospective study of consecutive patients with moderate to severe obstructive sleep apnea who underwent implantation of hypoglossal nerve stimulation therapy within a single academic practice and attended a follow-up appointment after greater than 30 days of therapy use. Objective adherence data were extracted from an objective monitoring database and compared to patient characteristics.

Results: The study population was 79 participants who were 29.1% female with a mean age of 58.7 ± 12.8 years old, body mass index of 28.9 ± 3.4 kg/m^2, and baseline apnea-hypopnea index of 33.8 ± 17.6 events/h. In the first 7 days after device activation, average use was 7.8 h/night, with 91.9% of nights with greater than 4 hours of therapy use and an average of 0.2 pauses in therapy per night. These figures remained stable after 30 days of use: 7.7 h/night, 91.0% of nights longer than 4 hours, and 0.3 pauses per night. Objective evidence of difficulty with acclimatization was associated with age less than 60 years (odds ratio 2.8, 95% confidence interval 1.1–7.1, P = .03) and a history of prior upper airway surgery (3.9, 1.2–11.9, P = .015). Insomnia was present in 31 patients and was not associated with objective evidence of difficulty tolerating therapy.

Conclusions: Early adherence to hypoglossal nerve stimulation is excellent (92.4% >4 hours on >70% of nights), suggesting that the acclimatization period is straightforward in most. Younger age and a history of prior upper airway surgery appear to be associated with an increased risk of difficulty with acclimatization.

Keywords: obstructive sleep apnea, hypoglossal nerve stimulation, adherence to therapy

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Device-based treatments for obstructive sleep apnea, such as positive airway pressure, oral appliance, positional and hypoglossal nerve stimulation therapy, are use dependent. Effectiveness is therefore dependent upon efficacy and adherence to therapy, but there are no prior reports of objective adherence to hypoglossal nerve stimulation therapy using the novel monitoring database.

Study Impact: Although variable efficacy has been reported with hypoglossal nerve stimulation, patients using this therapy demonstrate excellent adherence to therapy in the first month of usage. This suggests that the initiation of therapy is well-tolerated in the majority of patients.

INTRODUCTION

The first-line treatment of moderate to severe obstructive sleep apnea (OSA) is positive airway pressure therapy (PAP). Although this therapy consistently provides the greatest efficacy in treating OSA, the effectiveness of PAP is limited by patient adherence to therapy.[1] Adherence to PAP therapy is defined as using therapy for longer than 4 hours on >70% of nights and studies of short-term and long-term PAP use indicate a wide range of adherence rates that certainly never achieve 100%.[2–8] The quality of life and health benefits derived from PAP are likely dose dependent, more often limited by therapy use rather than by efficacy.

Considerable efforts have been made to identify predictors of PAP use as well as employ strategies to improve use such as education, autotitrating modes, expiratory pressure relief, heated humidification, hypnotics, telemedicine follow-up, and nasal surgery.[9–25] Regardless of the methodology, many studies show that a substantial proportion of patients discontinue PAP therapy and many ultimately pursue second-line therapies for OSA.[4,26] In general, second-line therapies tend to have lower efficacy rates but improved adherence, oftentimes resulting in improved effectiveness. For example, expansion pharyngoplasty may be 70–80% effective in reducing OSA but adherence is 100% as it represents a permanent modification of the upper airway structure.[27] Oral appliance therapy tends to have wide ranging efficacy rates but adherence rates that are often reported to be superior to PAP.[28–30]

Hypoglossal nerve stimulation (HGNS) is similar to PAP and oral appliance therapy in that effectiveness is dependent upon usage. It is therefore imperative to follow patients using HGNS not just until postimplant testing but indefinitely to monitor usage, just as is done for PAP users. In line with clinical guidelines on objective PAP reporting, Inspire Medical Systems introduced an objective monitoring database in 2019.[31] This allows for precise monitoring of settings and therapy use on a nightly basis. The objective of this study was to report on the early objective adherence in first-time HGNS users, termed the acclimatization period, and examine any predictors of lower adherence to therapy. Similar to first time PAP users, it is hypothesized that this is potentially a difficult transitional period for patients and early interventions may be critical to establish long-term use.[32]

METHODS

This study prospectively enrolled all patients undergoing implantation of the Inspire hypoglossal nerve stimulation therapy (Inspire Medical Systems, Golden Valley, MN) at a single, academic subspecialty hospital. The first 79 consecutive patients who attended an in person follow-up with their sleep remote are included in this analysis. These cases are all within the first 101 adult HGNS implants performed at Massachusetts Eye and Ear Infirmary between October 2019 and February 2021. Those not included among these 101 cases followed up in person but without their remote (n = 3), had no data stored from the first 30 days of use due to data memory loss (n = 4), moved out of state before in person follow-up (n = 1), had a good symptomatic response and opted to follow-up via telemedicine only (n = 5), or have an upcoming follow-up appointment (n = 9).

At the time of activation, the stimulation amplitude was incrementally increased until the sensation and functional thresholds are identified, defined as the lowest amplitude of stimulation that a patient perceives and is felt to extend the tongue beyond the lower incisors, respectively. The patient remote was then programmed to the functional threshold plus ten settings above this level. All patients were started on the +-+ electrode configuration. Patients who expressed discomfort as the respiratory waveform was being tested at the functional threshold amplitude are given 1 setting below the functional threshold but were still instructed to begin night 1 at the functional threshold. The start delay, run time, and pause were customized to the patient's sleep schedule. Patients were instructed to increase by 1 setting every 3 or 4 nights as long as the current amplitude was well tolerated, with the goal of identifying the setting that adequately reduces signs/symptoms of OSA (snoring, sleep continuity, daytime energy level, etc.). Patients were explicitly instructed that reaching the top setting is not necessary but rather to stop the self-titration at an efficacious or intolerable setting during the acclimatization period.

Patient characteristics including age, sex, body mass index, comorbid insomnia, sleep study, drug-induced sleep endoscopy, and history data were extracted from the medical record. The sleep history is reported on a standardized comprehensive intake form that includes baseline estimated total sleep time, estimated sleep latency, and a self-assessment of depth of sleep (light or deep). Low arousal threshold endotype was estimated using the Edwards method, which assigns 1 point each to an apnea-hypopnea index < 30 events/h, O_2 nadir >82.5%, and >58.3% of OSA events being hypopneas.[33] Scores of 2 or 3 are >80% predictive of having low arousal threshold.

Objective adherence and settings data were extracted from the Inspire Cloud (Inspire Medical Systems, Golden Valley, MN). Data from the sleep remote are downloaded during an in-person follow-up appointment and subsequently uploaded to the Inspire Cloud database. This database allows for examination of duration of use, start and stop time, use of the pause feature, and device settings on a nightly basis.

Objective evidence of difficulty in tolerating HGNS therapy during the first 30 days was defined in several different ways because the vast majority of patients did not have overt evidence of difficulty with acclimatization. Prescription of new hypnotic therapy within the first 30 days, use of therapy greater than 4 hours for less than 70% of nights at any time point (7, 14 or 30 days), average use of the pause feature more than once per night at any time point, and use of therapy for shorter than the estimated baseline total sleep time (as determined from the sleep intake form) were all considered to be objective signs of difficulty with acclimatization.

Statistical analysis was performed using SPSS version 24 (SPSS Inc., Chicago, IL). Descriptive statistics are reported as means, standard deviation, and range. Comparisons were made between patient characteristics and objective evidence of difficulty tolerating HGNS using the Pearson chi-square or Fisher's exact test when appropriate. Each of the aforementioned signs of difficulty tolerating therapy were tested independently and as an aggregate. Statistical significance was set at $P < .05$. The study was approved by the Partners Healthcare institutional review board. Patients additionally signed informed consent to enroll in Inspire Cloud database.

RESULTS

The study population represents the first 79 consecutive patients to return to clinic with the sleep remote after >30 days of use after device activation. The included participants were 29.1% female, a mean of 58.7 ± 12.8 years old (range 19–78 years), and mean body mass index of 28.9 ± 3.5 kg/m^2 (range 18–35.3). Mean apnea-hypopnea index, O_2 nadir, time spent below SpO_2 of 88%, and oxygen desaturation index were 33.8 ± 17.6 events/h, 80.5 ± 6.0%, 35.2 ± 61.1 minutes, and 29.3 ± 19.2 events/h. Mean patient-reported total sleep time and sleep latency were 6.4 ± 1.5 hours and 27.5 ± 27.8 minutes, respectively. All had attempted PAP therapy, with the major reason(s) for discontinuation being mask claustrophobia/discomfort (n = 27), inadvertent mask removal (n = 12), pressure intolerance (n = 13), oral air escape (n = 1), inability to initiate sleep with PAP (n = 13), sleep fragmentation attributed to PAP (n = 25), no therapeutic benefit (n = 8), aerophagia (n = 3), and sinus issues (n = 3). Twenty-one percent had undergone prior upper airway surgery for OSA and 30.4% had attempted and been intolerant of or did not derive benefit from oral appliance therapy. Insomnia was comorbid to OSA in 39.2%, with 35.4% on hypnotic therapy before activation. The low arousal threshold score[33] was 0 for 15 patients, 1 for 27 patients, 2 for 16 patients, and 3 for 21 patients. Thirty-seven patients (46.9%) were therefore considered to have the low arousal threshold endotype (a score of 2 or 3). Twenty-one participants self-identified as deep sleepers.

Table 1 displays mean number of hours used per night, percentage of nights with use longer than 4 hours, and number of pauses in therapy per night at 7, 14, and 30 days after activation. The mean baseline estimated total sleep time (6.4 ± 1.5 h/night) was significantly less than the 7.7 ± 1.1 h/night of average therapy usage over the first 30 days ($P < .001$). Thirteen patients (16.5%) had less therapy use than baseline estimated total sleep time at any point. Five patients (6.3%) used the pause feature

Table 1—Overall therapy usage at 7, 14, and 30 days.

	First 7 Days			First 14 Days			First 30 Days		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Hours/night	7.8	1.0	4.8–10.1	7.7	0.1	4.8–9.6	7.7	1.1	4.0–9.7
Nights > 4 h	91.9%	16.6	29–100%	91.6%	15.2	21–100%	91.0%	15.2	17–100%
Pauses/night	0.2	0.3	0–1.3	0.2	0.3	0–1.7	0.3	0.4	0–2.4

SD = standard deviation.

greater than 1 time per night at any point. Twelve (15.2%) patients did not achieve at least 4 hours of use for 70% of nights at 1 or more time points. Participants meeting usage of >4 hours on >70% of nights were 91.1%, 89.9%, and 92.4% at 7, 14, and 30 days, respectively. New hypnotic therapy was prescribed to 10 patients (12.7%) during the first 30 days after activation (doxepin [n = 6], gabapentin [n = 2], eszopiclone [n = 1], zolpidem [n = 1]). In total, 31 patients demonstrated at least 1 of these objective signs of difficulty tolerating HGNS at any point. The mean number of days to reach setting numbers 2, 3, and 4 was 6.6 ± 7.5, 10.6 ± 9.2, and 15.4 ± 9.8 days, respectively.

Patients' characteristics were compared to objective evidence of difficulty tolerating HGNS using several definitions (see Methods and **Table S1**, **Table S2**, **Table S3** and **Table S4** in the supplemental material). Use of pause greater than once per night on average was associated with deeper level of sleep (odds ratio 12.4, 95% confidence interval 1.3–119.3, $P = .02$). Initiation of new hypnotic therapy was associated with a history of prior upper airway surgery (4.7, 1.2–19, $P = .033$) and age greater than 60 years old (0.2, 0.4–1.0, $P = .048$). As seen in **Table 2**, history of prior surgery, younger age, and perceived deeper level of sleep were statistically associated with objective evidence of difficulty acclimating to HGNS (aggregate of all signs of difficulty tolerating HGNS). History of insomnia showed a trend toward less evidence of difficult tolerating HGNS. There was no association between type of PAP intolerance or anatomic level of obstruction on drug-induced sleep endoscopy and objective evidence of difficulty tolerating HGNS. Specifically, those with PAP-induced sleep onset or maintenance insomnia did not appear to have difficulty with HGNS.

DISCUSSION

This is the first study to report on objective adherence to HGNS therapy using the Inspire Cloud database. It is also the first focusing specifically on the initial period of HGNS use, termed the acclimatization period, which has been hypothesized to have the potential for poor tolerance of the new sensation of stimulation. To the contrary, it appears that the participants in this study accommodated to HGNS therapy remarkably quickly (mean usage of 7.8 h/night in the first 7 days), with very few demonstrating significant objective evidence of difficulty in tolerating stimulation at any point. The importance of this finding lies in the dependence of HGNS effectiveness on a combination of efficacy, which is known to be lower than PAP, and usage.

This analysis is not intended to be a direct comparison to PAP therapy, just as HGNS efficacy should not be directly compared to that of PAP. HGNS therapy is for patients

Table 2—Association between patient characteristics and any objective sign of struggle (new hypnotic, use shorter than estimated total sleep time, use < 4 hours on 70% of nights, average pause greater than once per night).

Characteristic	n	OR	95% CI	*P*
Female sex	23	1.3	0.5–3.4	.62
Age > 60 years	40	0.36	0.14–0.92	.03
BMI > 30 kg/m^2	30	1.1	0.4–2.8	.87
AHI > 30 events/h	37	0.9	0.4–2.2	.81
SL > 30 min	28	0.5	0.2–1.4	.21
Insomnia	31	0.38	0.1–1.0	.05
LAT	37	1.7	0.7–4.2	.25
Deep sleeper	21	4.3	1.5–12.7	.006
Prior surgery	17	3.9	1.2–11.9	.015
Prior OAT	24	0.70	0.3–1.9	.48

AHI = apnea-hypopnea index, BMI = body mass index, CI = confidence interval, LAT = low arousal threshold, OAT = oral appliance, OR = odds ratio, SL = sleep latency.

intolerant to PAP, and therefore lower efficacy rates are acceptable. This report demonstrates that at least in the initial period of usage, the product of efficacy and usage may favor HGNS in many, certainly those with very poor or no PAP usage. Walia and coauthors[34] compared otherwise similar patients using PAP or HGNS therapy at a single center and did find improved longer-term therapy usage in HGNS over PAP.

Prior to the introduction of Inspire Cloud in 2019, objective HGNS use was reported on the control tablet but was limited to number of hours used per week and therefore required frequent data downloads to assess specific periods of time. The largest studies commenting on HGNS therapy usage come from the ADHERE registry that show an average of 5.6–6.5 hours of therapy use per night (averaged over a week) at various longer-term time points.[34–36] The Inspire Cloud addresses many of its predecessor's limitations, allowing for the more precise analysis of usage and settings on individual days. In certain clinical situations, such as supporting commercial truck drivers licenses or evaluating persistent excessive daytime sleepiness despite treatment of OSA, the ability to review objective adherence data is critical. In routine clinical practice, adherence data monitoring carries the same value as it does for PAP—these therapies are use dependent.

Beyond examining adherence to therapy tracking, Inspire Cloud has proven useful in a number of anecdotal scenarios. It can be extremely valuable in fine tuning the start delay, pause time, and run duration settings, because it reports use of therapy down to the minute. It can confirm that therapy was on during a particular night, for instance during a follow-up home sleep apnea test where respiratory inductance plethysmography belt technology can interfere with activation of the device from the remote. It has also identified a number of patients who unknowingly turned therapy off while asleep or received interference from other technologies in the bedroom. Lastly, 2 patients in the author's practice have presented for stroke rule out for slurred speech at outside hospitals and a subsequent Inspire Cloud download confirmed that therapy had not been shut off the morning of the events, which obviated the need for further postacute workup (and an opportunity for remote reteaching or reprogramming). One lesson learned is that stored usage data can be erased if the remote control is without batteries for >72 hours or is dropped. Other limitations to the current version of Inspire Cloud include the lack of an ability to remotely monitor adherence or make settings adjustments, and there is no estimated efficacy as exists in PAP therapy monitoring systems.

A secondary goal of this study was to identify characteristics that were associated with difficulty during the acclimatization period (**Table 2**) so as to influence the informed consent process and/or allow for prophylactic interventions, such as the introduction of hypnotics. Because so few patients had significant difficulty tolerating stimulation and the study size was relatively small, a very liberal definition was used. Even still, a number of variables appeared to be associated with decreased usage—younger age, history of upper airway surgery, and self-assessed deep sleeper.

The finding of improved adherence to therapy in older individuals was previously demonstrated by Withrow et al,[37] again using ADHERE registry data. In reviewing Inspire Cloud data, it is clear that older individuals tend to have more consistent sleep schedules and possibly a better appreciation for the need for therapy adherence. The association with prior upper airway surgery and decreased therapy usage may be a reflection that such patients are inherently harder to treat or less likely to comply with device-based therapies, having failed multiple interventions in the past. The paradoxical association between self-assessed deep sleeper and increased risk of difficulty with acclimatization is challenging to interpret. This appears to be driven by use of the pause feature that, while counterintuitive, did not affect actual therapy adherence. Depth of sleep is a non-validated question on the author's new patient intake forms and possibly reflects poor insight on the behalf of the patient. This question was added to the intake forms for the specific purpose of identifying light sleepers who may be at risk for difficulty tolerating HGNS, something that will have to be revisited moving forward. Furthermore, the subgroup of patients who used pause greater than once per night was only 5 patients. These findings regarding depth of sleep therefore may not accurately reflect the broader population of HGNS users.

Interestingly, comorbid insomnia and the presence of the low arousal threshold (LAT) were not statistically significantly associated with difficulty in tolerating HGNS therapy. Patients with insomnia actually trended toward better usage compared to those without insomnia (**Table 1**). Comorbid insomnia presents numerous challenges in treating OSA, and most implant centers approach those with insomnia with caution when considering HGNS implantation. The lack of difficulty with HGNS therapy is somewhat surprising but also reassuring that certain patients with insomnia can do very well with this therapy, at least in the first 30 days. Dhanda Patil et al[38] similarly found that comorbid insomnia did not influence HGNS therapy use (or efficacy) in a veteran population. This is of significant importance given the high coincidence of OSA and insomnia as well as high rates of PAP intolerance in this subpopulation.[39,40] This finding perhaps sheds additional light on the notion that many cases of insomnia, particularly sleep maintenance insomnia, may be driven by OSA. The present study also did not find an association between prior PAP-induced sleep onset or maintenance insomnia and difficulty with HGNS therapy, suggesting a different mechanism underlying HGNS intolerance. In those who did develop HGNS-induced insomnia or difficulty, low-dose doxepin or gabapentin proved to be very effective—in the 8 patients started on these medications after activation, the average nightly use at 30 days was 7.8 hours, with 100% adherence (>70% of nights for >4 hours).

LAT is a pathophysiologic trait contributing to OSA characterized by frequent arousals in response to airflow limitation.[41] Such individuals are thought of as light sleepers, and because it has previously been demonstrated that patients with LAT struggle with continuous PAP adherence, it has been hypothesized that the same would be true of all device-based therapies, including HGNS.[42] Two recent studies recently reported on LAT/arousability and HGNS efficacy from the STAR trial but none have previously looked at LAT and adherence to therapy.[43,44] HGNS use less than estimated total sleep time used and < 70% of night longer 4 hours showed clear trends toward worse adherence when LAT was present but neither met

statistical significance. This may reflect the small sample size or the use of an indirect measure of LAT.[33] Future studies should use more contemporary measures of LAT described by Sands et al[45] and Finnsson et al[46] and investigate longer term adherence. If it is found that both efficacy and adherence to therapy are poorer in patients with LAT, then HGNS is probably best avoided in these patients.

The data analysis also revealed that patients increase settings slightly slower than instructed, getting to the second, third, and fourth settings in an average of 6.6 ± 7.5, 10.6 ± 9.2, and 15.4 ± 9.8 days, respectively. The typical protocol advises patients to increase through each of the 10 settings every 3 or 4 days, which may be too fast in most given that the official protocol recommends 3 months of acclimatization prior to objective sleep testing rather than the previously recommended 1 month. Although those who were identified as having difficulty with acclimatization took longer to work through settings, it was not significantly different from those who did not struggle. Although every patient has a unique experience with HGNS, suggesting settings increases every 5–7 days may be a more conservative introduction to therapy. As seen in **Table 1**, the pause feature appears to be underutilized either because it is not necessary or patients are unaware of it. Encourage use of the pause function may enhance adherence rates.

The findings reported here may not be representative of the population of patients using HGNS at large. First, all aspects of the patient's care are directly performed by the author and any biases, such as patient selection, are present. Furthermore, in lieu of an early in person follow-up or check-in call, patients have the ability directly to contact the author at any sign of difficulty. The result of this is that struggling patients are more likely to return (and have their data included in this study) but are also more likely to have adjustments made early, perhaps explaining the slight improvement in adherence rate from day 14 to 30 days (89.9–92.4%). Finally, much of these data come from the coronavirus disease 2019 (COVID-19) pandemic, when work, social, and sleep schedules were likely different than prepandemic schedules. This also prevented several patients who were doing well from following up in person and were therefore excluded from this dataset.

The main limitation to this study is that while therapy was activated and being used on a nightly basis, these were not necessarily the efficacious device settings. In general, higher stimulation amplitudes are needed to adequately treat OSA with HGNS and these higher settings can be less comfortable. One can surmise, therefore, that adherence to therapy may decline as one approaches these higher settings due to discomfort. Indeed, the 6-month and 12-month usage data from the ADHERE registry indicates 5.5–6.5 hours of use per night.[35] Even in this dataset, usage at 7 days (7. 8 h/night) was significantly better than at 30 days (7.7 h/night, $P < .001$), although one may question whether this is clinically meaningful. Oftentimes, patients indicate that they are sleeping less because their sleep is of higher quality, which could be confirmed with quality of life measures. Future studies should examine long-term adherence to HGNS therapy using Inspire Cloud with attention to final therapeutic settings. Prospective data collection is ongoing for this cohort, but a multicenter collaboration using the Inspire Cloud data would be more informative and generalizable.

The purpose of this study was to examine the early acclimatization period that shows excellent overall adherence to therapy in the first 7, 14, and 30 days. It is reassuring that during this initial phase of HGNS use that the majority of patients seem to accommodate to the stimulation fairly seamlessly, and 92.4% meet the PAP definition of therapy adherence. However, there are certain populations, such as younger patients or those with a history of previous upper airway surgeries, that may warrant closer interval surveillance. Future studies should confirm long-term adherence to therapy given the dependence of therapy success on both efficacy and usage. Future improvements for Inspire Cloud include the ability to remotely monitor adherence as is the case for PAP.

ABBREVIATIONS

HGNS, hypoglossal nerve stimulation
LAT, low arousal threshold
OSA, obstructive sleep apnea
PAP, positive airway pressure

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DISCLOSURE STATEMENT

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