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Relationship of Nocturnal Insomnia Symptoms and Outcomes After Hypoglossal Nerve Stimulation

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Abstract

Objective. In patients undergoing hypoglossal nerve stimulation (HGNS), we examined the Insomnia Severity Index (ISI) to understand how baseline sleep onset insomnia (SOI), sleep maintenance insomnia (SMI), and early morning awakening (EMA) affected postsurgical outcomes.

Study Design. Observational.

Setting. Multicenter registry.

Methods. We included patients from the Adherence and Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea International Registry (ADHERE) with a baseline ISI from 2020 to 2023. Regression analysis examined the association of ISI question scores for SOI, SMI, and EMA and outcomes: Apnea-Hypopnea Index (AHI) reduction, device usage, changes in the Epworth Sleepiness Scale (ESS) and overall ISI score, final visit (FV) completion, and satisfaction.

Results. No relationship was noted between insomnia subtypes and AHI reduction or FV completion. In the subgroup of patients with baseline moderate/severe insomnia, patients with major impairment for SOI used their device 64 min/day longer than those with minimal impairment. Among all patients, those with baseline major impairment for SOI had a 2.3 points greater improvement in ISI from baseline to FV compared to patients with minimal impairment, while patients with baseline major impairment for SMI had a 2.0 and 3.5 points greater improvement in the ESS and ISI than those with minimal impairment. Patients with EMA and moderate/severe baseline insomnia had decreased odds of being satisfied after surgery.

Conclusion. In ADHERE, nocturnal symptoms of insomnia did not limit HGNS efficacy or therapy use. Conversely, those with worse insomnia subtype impairments at baseline had improved outcomes related to adherence, sleepiness, and insomnia at the FV.

Keywords

hypoglossal nerve stimulation, insomnia, obstructive sleep apnea, upper airway stimulation

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The importance of adequate, restful sleep is increasingly recognized as critical to an individual's overall health. Common disorders such as obstructive sleep apnea (OSA) and insomnia result in decreased sleep time and quality, leading to impairments in cognition and emotional health as well as increased risk for stroke, obesity, diabetes, and hypertension.[1-3] OSA affects 9% to 38% of the population and is associated with excessive daytime sleepiness (EDS).[4] Insomnia, which affects 35% of the general population in any given year and 10% to 15% chronically, significantly impacts quality of life.[5,6] Subtypes of insomnia are categorized as sleep onset insomnia (SOI), sleep maintenance insomnia (SMI), and early morning awakening (EMA).[7] Given insomnia's impact on daily functioning and overall sleep health, tools have been developed to estimate impairment caused by insomnia, including the Insomnia Severity Index (ISI); its first 3 "nocturnal" questions specifically measure difficulties related to SOI, SMI, and EMA.[8] (**Figure 1**).

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OSA and insomnia commonly co-occur in an entity coined comorbid insomnia and sleep apnea (COMISA), with studies demonstrating 38% to 55% of individuals with OSA also complained of insomnia symptomatology.[9-13] OSA and insomnia act synergistically in COMISA, worsening mental health (MH), physical, and sleep-related outcomes.[3,14] The insomnia subtype most commonly associated with OSA is SMI, which may be related to sleep fragmentation with repeated arousals in OSA.[5,13,15] While positive airway pressure (PAP) is typically first-line treatment for OSA, treatments such as pharyngeal surgery have also been mainstays of treatment for the past several decades. More recently, hypoglossal nerve stimulation (HGNS) has emerged as a dynamic surgical treatment for OSA, with multiple studies confirming its efficacy and adherence.[16-19]

HGNS may be a promising therapy for patients with COMISA who face additional challenges of mask-related anxiety and discomfort that can in turn worsen insomnia symptoms and the ability to tolerate PAP. Although recent studies of HGNS in patients with COMISA and PAP intolerance demonstrated similar device adherence between patients with and without COMISA, these study sample sizes were small and multiple tools to report insomnia were used, prompting the need for larger studies to confirm this finding.[20-23] As HGNS becomes more commonplace, it remains incumbent on the sleep surgeon to measure overall baseline insomnia and delineate each patient's insomnia subtype to counsel patients and set expectations.

To track outcomes after HGNS, the Adherence and Outcomes of Upper Airway Stimulation for OSA International Registry (ADHERE) has provided data on efficacy, adherence, and patient-reported outcomes (PROMs) since 2016. In light of the importance of comorbid insomnia, the ISI was added to registry data in 2020. In this study, we utilized ADHERE to investigate if scores for SOI, SMI, and EMA predicted device efficacy, adherence, final visit (FV) completion, changes from baseline to FV in insomnia and sleepiness scores, and satisfaction scores. We hypothesized: (1) Increasing severity of baseline nocturnal insomnia subtypes *was not*

Name: _____ **Date:** _____

1. Please rate the current (i.e., last 2 weeks) **SEVERITY** of your insomnia problem(s).

	None	Mild	Moderate	Severe	Very
Difficulty falling asleep:	0	1	2	3	4
Difficulty staying asleep:	0	1	2	3	4
Problem waking up too early:	0	1	2	3	4

2. How **SATISFIED**/dissatisfied are you with your current sleep pattern?

Very Satisfied				Very Dissatisfied
0	1	2	3	4

3. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.).

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

4. How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all Noticeable	Barely	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

5. How **WORRIED**/distressed are you about your current sleep problem?

Not at all	A Little	Somewhat	Much	Very Much
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add scores for all seven items (1a+1b+1c+ 2+3+4+5) = _____
Total score ranges from 0-28
0-7 = No clinically significant insomnia
8-14 = Subthreshold insomnia
15-21 = Clinical insomnia (moderate severity)
22-28 = Clinical insomnia (severe)

Figure 1. Insomnia Severity Index (Copyright, Charles M. Morin, 1993).[8]

associated with HGNS efficacy as measured by postoperative Apnea-Hypopnea Index (AHI) reduction and response at the FV; (2) increasing severity of baseline nocturnal insomnia subtypes *was* associated with decreased nightly adherence, decreased levels of FV completion, and decreased satisfaction; and (3) increasing severity of baseline nocturnal insomnia subtypes *was* associated with decreasing levels of improvement in the Epworth Sleepiness Score (ESS) and overall ISI score.

Methods

Study Design

ADHERE (NCT02907398) is an observational, multicenter, industry-sponsored registry of patients with HGNS (Inspire Medical Systems) since 2016, including data from baseline (preoperative), posttitration visit (within 12 months of implantation), and FV (within 12-24 months of implantation) entered retrospectively or prospectively. The ADHERE protocol was approved by the participating centers' Institutional Review Boards and all patients provided written informed consent.

Baseline Data and Outcome Measurements

Patients' data were included if they completed a baseline ISI and their postoperative 24-month window ended before the close of the study period (March 11, 2020 to May 26, 2023). Baseline data included demographic information, comorbid MH conditions (anxiety, depression, and PTSD), body mass index (BMI), AHI, ESS, and ISI. These data were compared between patients with overall baseline ISI < 15 (no/subthreshold insomnia) or ISI ≥ 15 (moderate/severe insomnia). FV data included device efficacy (AHI, response rate), adherence, ESS, ISI, and patient satisfaction. Sleep study data at FV were obtained from a full-night, nontitration study (in-lab PSG or home sleep test [HST]). AHI was classified as mild (≥5 but <15 events/h), moderate (≥15 but <30 events/h), and severe (≥30 events/h). Adherence data were recorded as hours of usage/day from device download. The response rate was defined as AHI < 15.

The ESS, an 8-question instrument that assesses sleepiness, was scored from 0 to 24 with ≥11 representing EDS. The ISI, a 7-question instrument that assesses sleep quality in relation to insomnia, was scored from 0 to 28 (0-7 classified as no insomnia, 8-14 subthreshold insomnia, 15-21 moderate insomnia, and 22-28 severe insomnia). Question 1 ("Difficulty falling asleep"), Question 2 ("Difficulty staying asleep"), and Question 3 ("Waking up too early") represented "nocturnal" question scores and impairment related to SOI, SMI, and EMA, respectively, although they did not directly denote a "diagnosis" of these insomnia subtypes. Scores for Questions 1 to 3 were classified as minor impairment (0-1) and major impairment (2-4) for purposes of discussion (**Figure 1**). Patient satisfaction was represented by "Overall, how satisfied are you with Inspire therapy?" with responses of "Strongly dissatisfied"/"Dissatisfied"/"Neither satisfied nor dissatisfied" classified as Not Satisfied, and "Satisfied"/"Strongly satisfied" classified as Satisfied.

Statistical Analysis

t Tests at a significance level of 5% were used to compare normally distributed numeric values between groups. For nonnormally distributed values, Wilcoxon rank sum tests were used. Chi-square tests with a significance level of 5% compared categorical variables between groups, unless otherwise noted. Numeric results were presented as mean ± standard deviation and categorical variables presented as total sample size and percentages. Additionally, multiple linear regression and logistic regression were performed to assess association between outcome measures and ISI Questions 1 to 3. All analyses were performed using R (R Core Team, 2022).

Results

Baseline Data

This study included 475 patients with a baseline ISI who completed the 24-month postimplantation window for FV data entry within the study period. (**Figure 2**) They were primarily male (71.1%), white (92.1%), with mean baseline values: 62.1 years, body mass index 29.2 kg/m^2, AHI 33.1 events/h, and ESS 11.0. Patients with baseline ISI ≥ 15 (n = 315, 66.3%) were younger and had a significantly higher AHI, ESS, and ISI than ISI < 15 ($P < .05$). Scores for each of the nocturnal Questions 1 to 3 of the ISI revealed higher scores for those with baseline

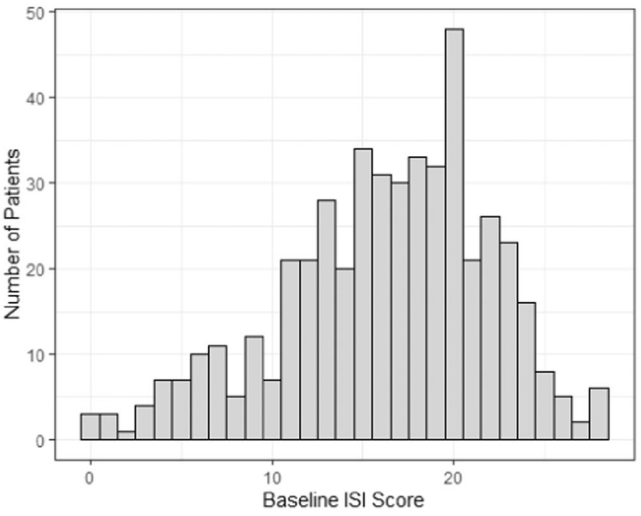

Figure 2. Distribution of baseline Insomnia Severity Index (ISI) scores in Adherence and Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea International Registry (ADHERE) patients enrolled between March 2020 and May 2023. All patients enrolled in ADHERE between March 11, 2020 and May 26, 2023 with a baseline ISI and a 24-month postimplant window for follow-up data entry within the study period are included in this figure, N = 475.

ISI ≥ 15 than ISI < 15 ($P < .001$). The overall prevalence of comorbid MH conditions at baseline was: anxiety (21.1%), depression (28.2%), and PTSD (4.2%). Anxiety and depression were more common with ISI ≥ 15 compared to ISI < 15 ($P < .05$) (**Table 1**).

Outcomes at FV

At least partial completion of FV data collection was accomplished in 231/475 patients (48.6%). In particular, baseline and FV data were available for the following outcomes: AHI and response rate (175/475, 36.8%), adherence (188/475, 39.6%), ESS (202/475, 42.5%), and overall ISI score (191/475, 40.2%) and is summarized by baseline categorized nocturnal ISI question scores in **Table 2**.

Device Efficacy

There was no association between categorical scores (major vs minimal impairment) for baseline ISI Questions 1 to 3 and device efficacy (AHI improvement and response rate) for all patients as well as the subgroup of patients with baseline ISI ≥ 15 (**Tables 3** and **4**).

Adherence

There was no association between categorical scores (major vs minimal impairment) for baseline ISI questions 1-3 and device adherence at FV when including all patients. However, for baseline ISI ≥ 15, those with major impairment for SOI used their device 64 minutes longer per night than those with minimal impairment (**Table 5**).

Sleepiness

The improvement in ESS score from baseline to FV for patients with baseline major impairment for SMI (n = 151) was 2 points higher compared to patients with minimal impairment (n = 51). This association did not persist when analyzing patients with baseline ISI ≥ 15 (**Table 6**).

Table 1. Baseline Demographic, Mental Health, and Sleep-Related Information in Patients Undergoing Hypoglossal Nerve Stimulation

Variable	All patients	ISI < 15	ISI ≥ 15	*P* value[a]
N	475	160 (33.7%)	315 (66.3%)	
Male	71.1% (335)	75% (120)	69.1% (215)	.221
Female	28.9% (136)	25% (40)	30.9% (96)	
Age	62.12 ± 10.6 (62), N = 475	64.2 ± 10.95 (65), N = 160	61.06 ± 10.28 (61), N = 315	.003
White	92.1% (432)	93.6% (147)	91.3% (285)	.494
Non-white	7.9% (37)	6.4% (10)	8.7% (27)	
Black	3.8% (18)	2.5% (4)	4.5% (14)	.437
Not black	96.2% (451)	97.5% (153)	95.5% (298)	
Other race	4.1% (19)	3.8% (6)	4.2% (13)	1
Hispanic or Latino	3.9% (18)	3.8% (6)	3.9% (12)	1
Not Hispanic or Latino	96.1% (447)	96.2% (151)	96.1% (296)	
Anxiety	21.1% (100)	15% (24)	24.1% (76)	.029
Depression	28.2% (134)	18.8% (30)	33% (104)	.002
PTSD	4.2% (20)	2.5% (4)	5.1% (16)	.28
Baseline BMI	29.18 ± 3.67 (29.68), N = 451	29.07 ± 3.78 (29.53), N = 157	29.24 ± 3.61 (29.76), N = 294	.654
Baseline ESS	10.97 ± 5.6 (11), N = 472	8.79 ± 4.95 (8), N = 157	12.06 ± 5.59 (13), N = 315	<.001
Baseline AHI[a]	33.08 ± 15.15 (30.1), N = 471	30.65 ± 13.89 (27.25), N = 158	34.3 ± 15.62 (31.4), N = 313	.014
Polysomnogram[b]	58.7% (272)	57.8% (89)	59.2% (183)	.846
Home sleep test[b]	41.3% (191)	42.2% (65)	40.8% (126)	
Baseline ISI	16.25 ± 5.72 (17), N = 475	9.76 ± 3.71 (11), N = 160	19.54 ± 3.18 (19), N = 315	<.001
Sleep onset insomnia[a]	1.35 ± 1.21 (1), N = 475	0.81 ± 0.93 (1), N = 160	1.62 ± 1.24 (2), N = 315	<.001
Sleep maintenance insomnia[a]	2.11 ± 1.23 (2), N = 475	1.04 ± 0.94 (1), N = 160	2.65 ± 0.98 (3), N = 315	<.001
Early morning awakening[a]	1.8 ± 1.3 (2), N = 475	0.88 ± 0.91 (1), N = 160	2.27 ± 1.22 (2), N = 315	<.001

Format for numerical values Mean ± SD (median).

P values were derived using a Student's *t* test for numeric variables and a χ^2 test for categorical variables unless otherwise specified.

ISI < 15: No/subthreshold Insomnia, ISI ≥ 15: moderate/severe insomnia.

All patients enrolled into ADHERE between March 11, 2020 and May 26, 2023 with a baseline ISI and a 24-month postimplant window for follow-up data entry within the study period are included in this table.

Abbreviations: AHI, Apnea-Hypopnea Index; BMI, body mass index; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; PTSD, posttraumatic stress disorder.

[a]*P* value derived using Wilcoxon test.

[b]Patients whose sleep test type was marked as "Unknown" are excluded from these numbers.

Table 2. Summary of Outcome Measures by Baseline Categorized Nocturnal ISI

			Sleep onset insomnia		Sleep maintenance insomnia		Early morning awakening	
Outcome	Measurement	All patients	Minimal impairment	Major impairment	Minimal impairment	Major impairment	Minimal impairment	Major impairment
AHI	Decrease in AHI from baseline to final visit	16.25 ± 19.08 (15.4), N = 175	16.46 ± 17.34 (16.65), N = 104	15.96 ± 21.5 (14.2), N = 71	19.09 ± 16.34 (18.5), N = 51	15.09 ± 20.04 (14.7), N = 124	16.82 ± 17.68 (18.4), N = 73	15.85 ± 20.09 (14.3), N = 102
Surgical response rate	Responder	51.4% (91)	51.4% (54)	51.4% (37)	51.9% (27)	51.2% (64)	50% (37)	52.4% (54)
	Nonresponder	48.6% (86)	48.6% (51)	48.6% (35)	48.1% (25)	48.8% (61)	50% (37)	47.6% (49)
Usage	Usage at final visit	6.15 ± 2.23 (6.43), N = 188	6.01 ± 2.18 (6.29), N = 111	6.35 ± 2.29 (6.86), N = 77	6.02 ± 2.1 (6.29), N = 51	6.2 ± 2.28 (6.43), N = 137	6.21 ± 2.09 (6.71), N = 79	6.11 ± 2.33 (6.43), N = 109
ESS	Decrease in ESS from baseline to final visit	4.3 ± 5.1 (3), N = 202	4.37 ± 4.62 (3), N = 115	4.21 ± 5.7 (3), N = 87	2.94 ± 5.51 (2), N = 51	4.75 ± 4.89 (4), N = 151	3.83 ± 5.56 (3), N = 80	4.61 ± 4.77 (3), N = 122
ISI	Decrease in ISI from baseline to final visit	7.61 ± 7.25 (8), N = 191	6.1 ± 7.05 (7), N = 109	9.62 ± 7.06 (10), N = 82	4.04 ± 7.63 (5), N = 49	8.84 ± 6.71 (9), N = 142	6.03 ± 7.66 (7), N = 79	8.73 ± 6.76 (8), N = 112
Overall satisfaction	Satisfied	80.2% (134)	78.1% (75)	83.1% (59)	77.5% (31)	81.1% (103)	84.6% (55)	77.5% (79)
	Dissatisfied	19.8% (33)	21.9% (21)	16.9% (12)	22.5% (9)	18.9% (24)	15.4% (10)	22.5% (23)
Final visit completion	Completed final	48.6% (231)	49.3% (134)	47.8% (97)	45.4% (64)	50% (167)	48.5% (94)	48.8% (137)
	Missed final	51.4% (244)	50.7% (138)	52.2% (106)	54.6% (77)	50% (167)	51.5% (100)	51.2% (144)

Minimal impairment: Individual ISI question score of 0 to 1; major impairment: individual ISI question score of 2 to 4.
Surgical response defined as final AHI < 15.
All patients enrolled into ADHERE between March 11, 2020 and May 26, 2023 with a baseline ISI and a 24-month postimplant window for follow-up data entry within the study period are included in this table.
Abbreviations: AHI, Apnea-Hypopnea Index; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index.

Table 3. Multiple Linear Regressions for Decrease in Apnea-Hypopnea Index (AHI) From Baseline to Final Visit by Baseline Categorized Nocturnal Insomnia Severity Index (ISI) Question Scores

	Estimate	Standard error	*t* Value	*P* value	N
All patients with a baseline ISI and completed baseline and final AHI					
Intercept	18.762	2.812	6.672	3.4e−10	175
Sleep onset insomnia: Major Impairment	0.733	3.122	0.235	8.1e−01	
Sleep maintenance insomnia: Major Impairment	−4.762	3.759	−1.267	2.1e−01	
Early morning awakening: Major Impairment	0.975	3.346	0.291	7.7e−01	
Patients with an ISI ≥ 15 at baseline and completed baseline and final AHI					
Intercept	22.420	5.744	3.903	1.6e−04	119
Sleep onset insomnia: Major impairment	3.047	3.892	0.783	4.4e−01	
Sleep maintenance insomnia: Major impairment	−10.223	6.571	−1.556	1.2e−01	
Early morning awakening: Major impairment	1.696	4.805	0.353	7.2e−01	

ISI ≥ 15 = moderate/severe insomnia.
Major impairment = individual ISI question score 2 to 4.

Table 4. Multiple Logistic Regressions for Surgical Response (AHI < 15) by Baseline Categorized Nocturnal ISI Question Scores

	Estimate	Standard error	OR (95% CI)	*z* Value	*P* value	N
All patients with a baseline ISI and AHI at the final visit						
Intercept	0.047	0.291	1.048 (0.59, 1.86)	0.160	8.7e−01	177
Sleep onset insomnia: Major impairment	0.000	0.325	1 (0.53, 1.9)	0.000	1.0e+00	
Sleep maintenance insomnia: Major impairment	−0.104	0.392	0.901 (0.41, 1.94)	−0.266	7.9e−01	
Early morning awakening: Major impairment	0.144	0.350	1.155 (0.58, 2.3)	0.412	6.8e−01	
Patients with an ISI ≥ 15 at the baseline and AHI at the final visit						
Intercept	0.217	0.563	1.242 (0.41, 3.93)	0.385	7.0e−01	120
Sleep onset insomnia: Major impairment	0.256	0.378	1.292 (0.62, 2.73)	0.677	5.0e−01	
Sleep maintenance insomnia: Major impairment	−0.413	0.645	0.662 (0.18, 2.33)	−0.640	5.2e−01	
Early morning awakening: Major impairment	0.060	0.468	1.062 (0.42, 2.69)	0.128	9.0e−01	

ISI ≥ 15 = moderate/severe insomnia.
Major impairment = individual ISI question score 2 to 4.
Abbreviations: AHI, Apnea-Hypopnea Index; CI, confidence interval; ISI, Insomnia Severity Index; OR, odds ratio.

Table 5. Multiple Linear Regressions for Final Usage by Baseline Categorized Nocturnal Insomnia Severity Index (ISI) Question Scores

	Estimate	Standard error	*t* Value	*P* value	N
All patients with a baseline isi and documented final nightly usage					
Intercept	6.016	0.322	18.685	2.3e−44	188
Sleep onset insomnia: Major impairment	0.333	0.352	0.946	3.5e−01	
Sleep maintenance insomnia: Major impairment	0.212	0.447	0.475	6.4e−01	
Early morning awakening: Major impairment	−0.268	0.387	−0.691	4.9e−01	
Patients with an ISI ≥ 15 at baseline and documented final nightly usage					
Intercept	4.817	0.604	7.979	7.8e−13	130
Sleep onset insomnia: Major impairment	1.058	0.406	2.607	1.0e−02	
Sleep maintenance insomnia: Major impairment	1.009	0.739	1.366	1.7e−01	
Early morning awakening: Major impairment	−0.350	0.505	−0.694	4.9e−01	

ISI ≥ 15 = moderate/severe insomnia.
Major impairment = individual ISI question score 2 to 4.

Insomnia

The improvement in overall ISI score from baseline to FV for patients with major impairment for SOI (n = 82) was 2.3 points higher as compared to patients with minimal impairment (n = 109). In addition, the improvement in overall ISI score from baseline to FV for patients with major impairment for SMI (n = 142) was 3.5 points higher compared to those with minimal impairment (n = 49).

Table 6. Multiple Linear Regressions for Decrease in Epworth Sleepiness Scale (ESS) From Baseline to Final Visit by Baseline Categorized Nocturnal Insomnia Severity Index (ISI) Question Scores

	Estimate	Standard error	*t* Value	*P* value	N
All patients with a baseline ISI and documented baseline and final ESS					
Intercept	3.026	0.742	4.078	6.6e−05	202
Sleep onset insomnia: Major Impairment	−0.755	0.761	−0.992	3.2e−01	
Sleep maintenance insomnia: Major Impairment	2.020	0.947	2.133	3.4e−02	
Early morning awakening: Major Impairment	0.143	0.812	0.177	8.6e−01	
Patients with an ISI ≥ 15 at baseline and documented baseline and final ESS					
Intercept	5.836	1.347	4.332	2.8e−05	141
Sleep onset insomnia: Major impairment	−0.731	0.880	−0.831	4.1e−01	
Sleep maintenance insomnia: Major impairment	0.403	1.523	0.265	7.9e−01	
Early morning awakening: Major impairment	−0.838	1.043	−0.804	4.2e−01	

ISI ≥ 15 = moderate/severe insomnia.
Major impairment = individual ISI question score 2 to 4.

Table 7. Multiple Linear Regressions for Decrease in Insomnia Severity Index (ISI) From Baseline to Final Visit by Baseline Categorized Nocturnal ISI Question Scores

	Estimate	Standard error	*t* Value	*P* value	N
All patients with a documented baseline and final ISI					
Intercept	3.502	1.026	3.414	7.9e−04	191
Sleep onset insomnia: Major Impairment	2.301	1.073	2.145	3.3e−02	
Sleep maintenance insomnia: Major Impairment	3.459	1.323	2.615	9.7e−03	
Early morning awakening: Major Impairment	0.937	1.124	0.833	4.1e−01	
Patients with an ISI ≥ 15 at baseline and documented final ISI					
Intercept	9.267	1.731	5.354	3.8e−07	133
Sleep onset insomnia: Major Impairment	2.210	1.166	1.895	6.0e−02	
Sleep maintenance insomnia: Major Impairment	0.444	1.961	0.226	8.2e−01	
Early morning awakening: Major Impairment	−1.660	1.349	−1.230	2.2e−01	

ISI ≥ 15 = moderate/severe insomnia.
Major impairment = individual ISI question score 2 to 4.

These associations did not persist for patients with baseline ISI ≥ 15 (**Table 7**).

FV Completion and Patient Satisfaction

There was no association between categorical scores (major vs minimal impairment) for baseline ISI questions 1-3 and FV completion as well as overall satisfaction for all patients. However, for baseline ISI ≥ 15, those with major impairment scores for EMA (n = 87) were associated with a 76% decrease in odds of having a satisfied rating than those with minimal impairment scores (n = 33) (**Tables 8** and **9**).

Discussion

In this study, we utilized data from the ADHERE registry to better understand the relationship between baseline impairment from insomnia subtypes of SOI, SMI, and EMA, and outcomes with HGNS at the FV within 12-24 months after implantation. We proved our first hypothesis by demonstrating that worse baseline nocturnal insomnia symptoms *were not* linked with decreased device efficacy in terms of AHI reduction, which was expected given that HGNS efficacy has been shown to be consistently high over many studies and with longer duration of follow-up.[16-19] However, our findings refuted our other hypotheses and instead demonstrated that worse baseline scores for nocturnal insomnia subtypes *were not* associated with worsened adherence and FV completion; they also *were not* associated with decreased levels of improvements of PROMs such as sleepiness and insomnia at the FV.

Our findings with regard to nocturnal insomnia symptoms and HGNS adherence were unexpected and ran counter to studies in the PAP literature showing that insomnia decreased PAP adherence.[15,24-26] In our study, the opposite was true for the smaller subgroup of patients with ISI ≥ 15 (moderate/severe insomnia) at baseline whose score for SOI was classified as major impairment—at the FV, these patients used their device over an hour longer than patients with minimal impairment. Possible factors include:

Table 8. Multiple Logistic Regressions for Final Visit Compliance by Baseline Categorized Nocturnal ISI Question Scores

	Estimate	Standard error	OR (95% CI)	z Value	P value	N
All patients with a documented baseline ISI and final visit expected						
Intercept	−0.143	0.181	0.867 (0.61, 1.23)	−0.793	4.3e−01	475
Sleep onset insomnia: Major Impairment	−0.131	0.198	0.877 (0.59, 1.29)	−0.662	5.1e−01	
Sleep maintenance insomnia: Major Impairment	0.268	0.235	1.307 (0.83, 2.08)	1.141	2.5e−01	
Early morning awakening: Major Impairment	−0.075	0.208	0.928 (0.62, 1.39)	−0.360	7.2e−01	
Patients with an ISI ≥ 15 at baseline and final visit expected						
Intercept	0.049	0.373	1.05 (0.5, 2.2)	0.132	9.0e−01	315
Sleep onset insomnia: Major Impairment	−0.065	0.230	0.937 (0.6, 1.47)	−0.285	7.8e−01	
Sleep maintenance insomnia: Major Impairment	0.048	0.398	1.049 (0.48, 2.3)	0.120	9.0e−01	
Early morning awakening: Major Impairment	−0.084	0.273	0.92 (0.54, 1.57)	−0.307	7.6e−01	

The final visit was expected for a patient if the date of implant was greater than 2 years prior to the close of the study period (5/26/23).
ISI ≥ 15 = moderate/severe insomnia.
Major impairment = individual ISI question score 2 to 4.
Abbreviations: CI, confidence interval; ISI, Insomnia Severity Index; OR, odds ratio.

Table 9. Multiple Logistic Regressions for Overall Satisfaction at the Final Visit by Baseline Categorized Nocturnal ISI Question Scores

	Estimate	Standard error	OR (95% CI)	z Value	P value	N
All patients with a baseline ISI and overall satisfaction rating at the final visit						
Intercept	1.398	0.419	4.047 (1.87, 9.82)	3.337	8.5e−04	167
Sleep onset insomnia: Major impairment	0.324	0.423	1.383 (0.61, 3.24)	0.766	4.4e−01	
Sleep maintenance insomnia: Major impairment	0.414	0.506	1.513 (0.55, 4.08)	0.817	4.1e−01	
Early awakening insomnia: Major impairment	−0.678	0.462	0.508 (0.2, 1.22)	−1.465	1.4e−01	
Patients with an ISI ≥ 15 at baseline and overall satisfaction rating at the final visit						
Intercept	1.675	0.770	5.336 (1.37, 30.75)	2.174	3.0e−02	120
Sleep onset insomnia: Major Impairment	0.354	0.476	1.425 (0.56, 3.67)	0.743	4.6e−01	
Sleep maintenance insomnia: Major Impairment	0.745	0.812	2.107 (0.38, 10.44)	0.918	3.6e−01	
Early morning awakening: Major Impairment	−1.420	0.722	0.242 (0.05, 0.86)	−1.967	4.9e−02	

Question for overall satisfaction rating: "Overall, how satisfied are you with Inspire therapy?"
Possible answers were: "Strongly Satisfied," "Satisfied," "Strongly dissatisfied," "Neither dissatisfied or satisfied," or "Dissatisfied" which were grouped as Satisfied: "Strongly Satisfied" or "Satisfied"; Dissatisfied: "Strongly dissatisfied," "Neither dissatisfied or satisfied," or "Dissatisfied."
ISI ≥ 15 = moderate/severe insomnia.
Major impairment = individual ISI question score 2 to 4.
Abbreviations: CI, confidence interval, ISI, Insomnia Severity Index; OR, odds ratio.

Comfort

While PAP users contend with mask and equipment discomfort that contributes to low reported adherence in the sleep literature,[27] HGNS users benefit from no external apparatus during the critical period of sleep onset. Patients with COMISA who were still attempting nightly usage with PAP before HGNS may have reported SOI when completing their baseline ISI. These same patients may have noted improvement with SOI after implantation due to a less obtrusive start of therapy with HGNS, contributing to increased usage.

Habituation

The phenomenon of habituation is defined as a psychological learning process whereby an individual experiences a progressively decreasing response to repetitive stimulation.[28] With HGNS, habituation occurs as patients gradually achieve comfort with tongue protrusion at increasing device voltages. It is possible that patients with baseline SOI who had substantial experience with HGNS at FV tolerated awake periods when HGNS switched on prior to sleep onset, contributing to elevated device usage.

MH

Sleep onset disturbances are included in diagnostic criteria for anxiety, depression, and PTSD.[29] In our study, patients with ISI ≥ 15 more commonly reported all 3 MH conditions than those with ISI < 15. When examining the subgroup of patients with ISI ≥ 15 and major impairment from SOI, it is possible that improved quality of sleep with HGNS over many months globally improved MH issues and their effect on SOI, ultimately contributing to increased device usage at the FV.

With regard to PROMs, worse insomnia subtype scores were surprisingly not associated with decreased

improvements in sleepiness and overall insomnia symptoms as measured by the ESS and ISI at FV. Instead, patients with baseline major impairment for SOI had a 2.3 points greater improvement in the ISI score from baseline to FV compared to patients with minor impairment, while patients with baseline major impairment for SMI had a 2.0 and 3.5 points greater improvement in the ESS and ISI score than those with minor impairment. Possible factors include.

Comfort

A high level of comfort with HGNS may have allowed for improved ability to stay asleep in patients with SMI, especially if certain patients were still attempting PAP usage at the time of baseline data collection. For example, the elimination of frequent awakenings due to mask slippage or entanglement with tubing with HGNS usage may have contributed to better sleep consolidation and increased sleep time, which subsequently improved subjective sleepiness and insomnia scores at the FV.

MH

Patients with comorbid MH issues may also experience SMI, whether due to racing thoughts and nighttime perseveration with anxiety, or claustrophobia and nightmares with PTSD.[3,11,30,31] The elimination of apneas and other respiratory events that contribute to arousals and frequent awakenings with HGNS may have assisted sensitive patients in our population, whose baseline scores for SMI were the highest for the 3 subtypes and consistent with previous studies demonstrating that SMI is the most common insomnia subtype in COMISA.[5,13,15] For example, patients whose anxiety might have prevented them from falling back asleep after an apnea-related arousal may have been helped by a decrease in respiratory events with HGNS usage. Similarly, improved sleep consolidation with HGNS in patients with PTSD may have decreased awareness of and awakenings from nightmares.[31] These mechanisms that positively affect sleep quality over time may have improved PROMs in our population at the FV.

Insomnia subtypes were not associated with overall satisfaction scores in all patients, but we did note that patients with ISI ≥ 15 and major impairment from EMA had a 76% decrease in the odds of being classified as Satisfied. This data point should be interpreted with caution given its small sample size, but it is a reminder to pay attention to EMA as an important subtype of insomnia common in older individuals.[32] This will be relevant for our patients (median age of 62 years at implantation) as they continue to age and EMA potentially becomes more impactful to their sleep. To better understand these patients' satisfaction with HGNS in future, it may be helpful to measure sleep-related QOL using tools such as the Functional Outcomes of Sleep Questionnaire.[21]

Lastly, there was no association between insomnia subtypes and FV completion, which refuted our hypothesis that patients with worse baseline impairment from nocturnal insomnia symptoms would be more prone to being lost to follow-up. This finding may reflect the improvements in adherence and PROMs described above. However, we must also consider that approximately half of patients whose 24-month postoperative window closed within the study period did not return for any portion of FV data collection; in particular only 40% had both baseline and FV ISI values. This drop-off could reflect favorable outcomes such that patients and/or providers did not feel the need to continue return appointments and obtain sleep studies after the posttitration PSG; however, it could also be a consequence of device nonusage in those with a suboptimal response. We also note that the study period encompassed the time of restrictions due to the COVID-19 pandemic which may have contributed to fewer in-person visits that were necessary for certain elements of ADHERE data collection.

Despite this relatively low rate of FV completion, data that was collected provided valuable information regarding longer-term outcomes after HGNS, particularly in almost 200 patients with baseline and FV ISI scores. Most importantly, our findings from ADHERE suggest that sleep impairment from baseline nocturnal symptoms of insomnia should not preclude consideration for HGNS. We should also interpret our results as representative of the efforts of ADHERE centers that contributed to the registry. These centers are typically high-volume, experienced with patient selection, and may be more likely to work within a multidisciplinary care team that includes MH providers. For example, cognitive behavioral therapy for insomnia or pharmacotherapy might be more accessible in a busy ADHERE site with its resources for care of complex patients with COMISA. Additionally, ADHERE centers might be poised to offer fine-tuning of HGNS with awake endoscopy and adjustment of start delay settings. All these interventions that might ameliorate discomfort and anxiety with one's ability to fall and stay asleep could have positively affected our results for adherence, PROMs, and satisfaction.

Limitations of this study included the drop-off in data collection for patients who did not return for FV follow-up as described above. Additionally, selection bias may have skewed our results toward more favorable outcomes if patients with greater satisfaction were more likely to return at the FV. Also notable is the heterogeneity of retrospective and prospective data within ADHERE. A majority of patients had retrospective data entry, such that they were enrolled in ADHERE after surgery while their centers may not have used the ISI as the standard of care at baseline, in effect limiting more complete collection of ISI information. Additionally, variability in sleep study information at baseline and FV was of concern, as data represented a mix of in-lab studies and HSTs. For example, sleep studies at FV were more

commonly HSTs than PSGs, which might create bias toward a lower AHI and a false impression of greater AHI reduction after surgery given that HSTs may underestimate AHI compared to in-lab PSG.[33] Also, our use of AHI < 15 as a measure of HGNS success aimed to include patients who benefited from the improved quality of life and decreased health risks of having no or mild OSA. However, it may have also included patients with only a small degree of AHI improvement from the moderate range to the mild range, although this would likely be a small effect given that our mean preoperative AHI = 33 was in the severe range. Finally, the ADHERE sample we examined was homogeneous, being predominantly male (71%) and white (92%), which limits generalizability of our results to more diverse populations. Future studies should focus on social determinants of health that may limit access to HGNS, particularly in non-white populations.

Conclusion

In the ADHERE registry, nocturnal symptoms of insomnia did not limit HGNS efficacy or therapy use. Conversely, those with worse insomnia impairments at baseline had improved outcomes with regard to adherence, sleepiness, and insomnia. Future research should focus on insomnia subtypes (SOI, SMI, EMA) and strive to understand how these conditions impact longitudinal care of COMISA patients using HGNS.

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Author Contributions

Reena Dhanda Patil, literature search, coordination of all research activities, writing of manuscript; **Maria V. Suurna**, data analysis, editing and revising of manuscript; **Armin Steffen**, editing and revising of manuscript; **Ryan Soose**, editing and revising of manuscript; **James Coxe**, data analysis, editing and revising of manuscript; **Teresa Chan**, editing and revising of manuscript; **Stacey L. Ishman**, data analysis, editing and revising of manuscript.

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