

## ORIGINAL RESEARCH

# Insomnia affects patient-reported outcome in sleep apnea treated with hypoglossal nerve stimulation

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This study contains some data from the industry-sponsored ADHERE study (month 6 and month 12 follow-up) and a research project on the collection of ISI data. The sponsor for both of these projects was Inspire Medical Systems, Minneapolis, Minnesota, USA. The main objective of this manuscript (to assess associations between ISI and outcome measures) and the timing of the follow-up assessment on outcome data was independent research.

## Abstract

**Objective:** Comorbid insomnia may impact outcomes of patients with obstructive sleep apnea (OSA) receiving hypoglossal nerve stimulation with respiratory sensing (HNS) therapy. To examine whether the presence of insomnia measured using the Insomnia Severity Index (ISI) is associated with patient-reported outcomes and objective OSA measures in patients receiving HNS therapy.

**Methods:** In this retrospective chart review, patients with an HNS implant and ISI score at follow-up assessment were categorized as having moderate/severe insomnia or no/subthreshold insomnia. OSA-related data (Apnea Hypopnea Index, AHI; Oxygen Desaturation Index, ODI), Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), and overall patient satisfaction was compared between these patient categories. Correlations between ISI scores and each of these variables were examined.

**Results:** Of the 132 patients, 26% had moderate/severe insomnia at follow-up assessment. ESS and FOSQ scores were worse in the insomnia group at baseline, follow-up, and in the change from baseline, but AHI and ODI scores did not differ between patients with and without insomnia. Frequency of overall satisfaction at follow-up was lower in the insomnia group (58.8% vs. 92.8% with no insomnia,  $P < .001$ ). Patients with insomnia were more likely to have depression (56% vs. 27% without insomnia,  $P < .002$ ).

**Conclusions:** Insomnia is associated with worse patient-reported outcomes of daytime sleepiness and sleep-related quality of life in patients with OSA receiving HNS therapy. Depression is more prevalent in patients with comorbid insomnia. The ISI may help physicians to address comorbid insomnia and achieve high patient satisfaction and adherence to HNS therapy.

**Level of Evidence:** 4

Armin Steffena and Peter Baptista contributed equally to this study.

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## KEYWORDS

hypoglossal nerve stimulation, insomnia, long-term outcome, sleep apnea, upper airway stimulation

## 1 | INTRODUCTION

Poor sleep quality, including insomnia, is a widespread complaint among the general population that can be measured using the Insomnia Severity Index (ISI), an established clinical tool for rating insomnia severity.<sup>1,2</sup> The ISI is a brief self-report instrument that gives the patient's perception of their insomnia symptoms, the degree of distress caused by these symptoms, and the impact they have on daily functioning. Such patient-reported outcomes associated with insomnia are important factors when considering patient satisfaction with or adherence to therapy. Patients with obstructive sleep apnea (OSA) often have insomnia and the reported prevalence rate of both sleep disorders (comorbid insomnia and sleep apnea, COMISA) is 30%–50%.<sup>3</sup> Patients with COMISA are known to have reduced adherence to positive airway pressure (PAP) therapy or persistent non-restorative sleep despite sufficient OSA control.<sup>3,4</sup> Insomnia symptoms and ISI scores are decreased during PAP therapy for OSA.<sup>5,6,7</sup> Poor adherence to or lower usage of OSA therapy, therefore, may allow insomnia to persist and lead to impaired daytime functioning and poorer quality of life.

Hypoglossal nerve stimulation with respiratory sensing (HNS), also known as upper airway stimulation (UAS) therapy, has become established as an effective treatment option for OSA in patients who are intolerant of or fail to adhere to PAP therapy.<sup>8,9</sup> Studies of HNS therapy, including those with long-term follow-up,<sup>10,11</sup> have shown improvements in objective OSA parameters such as the Apnea Hypopnea Index (AHI) and the Oxygen Desaturation Index (ODI), as well as subjective parameters such as reduced sleepiness evaluated using the Epworth Sleepiness Scale (ESS).<sup>12</sup>

However, the effect of comorbid insomnia on HNS usage and other outcome parameters in patients with OSA is unclear. Recent evidence from the Adherence and Outcomes of UAS in OSA (ADHERE) registry in over 2000 patients with an implanted HNS system demonstrated that comorbid insomnia (2% of the registry) was associated with significantly less HNS usage over 12 months (–1.47 h/night, univariate analysis) compared to patients without comorbid insomnia.<sup>13</sup> On the other hand, in a retrospective case series of 53 veterans receiving HNS at a Veterans Affairs hospital in the USA,<sup>14</sup> HNS usage (adherence) did not differ between patients with COMISA (57% of all patients) and those with OSA alone (5.6 vs. 6.4 h/night,  $P = .17$ ). The data for AHI, lowest oxygen saturation, and ESS were comparable between veterans with and without insomnia, but 57% of the patients with COMISA reported an improvement in their insomnia.<sup>14</sup>

Better understanding of the impact of insomnia on the efficacy of and adherence to HNS therapy for OSA is therefore needed. Also, for patients with OSA with or without comorbid insomnia, currently there

are only few data on the impact of HNS therapy on patient-reported outcomes, such as sleep-related quality of life or overall patient satisfaction.<sup>15,16</sup>

The aim of this retrospective study was to determine whether the presence of clinical insomnia (based on the ISI score) at a follow-up assessment after commencing HNS therapy for moderate-to-severe OSA was associated with patient-reported outcomes (daytime sleepiness, sleep-related quality of life, and overall satisfaction), HNS usage, and objective OSA measures (AHI, ODI).

## 2 | MATERIALS AND METHODS

In April 2020, the ISI was added to the regular annual follow-up assessment of patients with HNS implants at our otorhinolaryngology department. Prior to that date, ISI scoring was not obtained before implantation. This follow-up assessment also includes recent patient history and medication, body mass index (BMI), ESS,<sup>12,17</sup> Functional Outcome of Sleep Questionnaire (FOSQ),<sup>18</sup> HNS usage from telemetry data download, and home sleep testing (HST) for AHI and ODI. All patients with HNS implants are encouraged to attend this annual checkup, which is usually covered by their medical insurance. Patients gave prior informed consent for retrospective data analyses. This was a retrospective chart review conducted from November 2020 until February 2021.

As the COVID-19 pandemic restrictions prevented some patients from attending their follow-up assessment at the hospital, health status questionnaires were sent to them for completion. Telemetry read-out of HNS device usage was not available for these patients.

Study participants were consecutive patients implanted with the HNS system (Inspire Medical Systems, Minneapolis, Minnesota) who had at least a 6-month follow-up period after implantation. The surgical procedure for device implantation has been previously described.<sup>19</sup> The main inclusion criteria for HNS implantation were an AHI between 15 and 65 events/h (i.e., moderate-to-severe OSA), a central or mixed apnea index less than 25% of the total apnea index, and absence of complete concentric collapse (CCC) at the soft palate during drug-induced sleep endoscopy (DISE). In accordance with the European CE Mark approval for the Inspire<sup>®</sup> UAS system, there were no BMI limits for HNS implantation.

The implanted HNS device provides an automatically derived usage per week. The patient uses a remote control to activate their nightly sleep therapy. This device includes a programmable start delay that can be adjusted to defer the activation time by 0–75 min; the usual start delay period is 20–30 min.

The ISI is a brief seven-item instrument for assessing the severity and impact of insomnia.<sup>1,20</sup> The questionnaire covers several aspects

of insomnia: the severity of difficulty with sleep onset/staying asleep, interference of sleep difficulties with daily functioning, and sleep satisfaction related to the previous 2 weeks. Each item is scored on five-point Likert scale from 0 = no problem to 4 = very severe problem, giving a total score ranging from 0 to 28. Based on the ISI total score, patients can be categorized as having no clinically significant insomnia (0–7), subthreshold insomnia (8–14), clinical insomnia of moderate severity (15–21), or severe clinical insomnia (22–28). The ISI questionnaire can be self-administered and is validated for German-speaking populations.<sup>1,2,20,21</sup>

The German version of the ESS was used to measure self-reported daytime sleepiness.<sup>12,17,22</sup> This scale consists of eight items scored on a four-point Likert scale that are summed to give a total score ranging from 0.0 to 24.0, with higher scores indicating greater daytime sleepiness. Scores  $\geq 11$  indicate excessive daytime sleepiness.<sup>22</sup>

The FOSQ was used to assess the impact of daytime sleepiness on self-reported functioning and sleep-related quality of life.<sup>18</sup> It consists of 30 items covering five subscales, producing a total score that ranges from 5.0 to 20.0 points, with higher scores indicating a better functional status/quality of life.<sup>18</sup> A FOSQ score  $< 17.9$  represents significant sleep-related functional impairment, and a change in score  $\geq 2.0$  points is considered a clinically meaningful change.<sup>23</sup>

The severity of OSA was assessed using the AHI and ODI. The AHI is reported as the median number of events per hour and the ODI indicates the number of times per hour of sleep that blood oxygen levels drop by  $\geq 4\%$  from baseline.

Patients also reported their overall satisfaction with the HNS therapy by answering the question “How satisfied are you with Inspire therapy”: extremely dissatisfied, somewhat dissatisfied, neither dissatisfied or satisfied, somewhat satisfied, or extremely satisfied.<sup>15</sup> Overall satisfaction is presented as the percentage of patients who reported being somewhat or extremely satisfied.

Using the ISI score obtained at the follow-up assessment, patients were categorized as having either no/subthreshold insomnia or moderate/severe insomnia. The presence or absence of depression at the follow-up assessment was determined from the medical records as depression is a common psychiatric comorbidity in patients with OSA<sup>13</sup> and may impact on adherence to OSA therapy, especially in patients with COMISA.<sup>24</sup>

Data were analyzed using version 25.0 of the Statistical Package for the Social Sciences software (SPSS, Chicago, Illinois) and R version 4.0. Descriptive statistics were calculated with continuous variables being reported as medians and categorical variables as frequencies. Descriptive comparisons between values for the groups with no/subthreshold insomnia versus moderate/severe insomnia and for the groups with shorter ( $\leq 24$  months) versus longer ( $\geq 36$  months) time since HNS implantation were made using the Mann-Whitney *U* test, chi-squared test or Fisher exact test as appropriate. Spearman's rank correlation coefficient (*rs*) was used to describe the association between the ISI as a continuous variable and each of the other variables measured. It can be interpreted as no association ( $rs = 0$ ) to a perfect monotonic relationship ( $rs = -1$  or  $+1$ ). All *P* values were

interpreted descriptively. Delta values were obtained as case-by-case values. Therefore, Delta values of the entire group do not just reflect the differences in baseline and follow-up values.

The local ethics committee (AZ 17-300A; Ethikkommission, Universität zu Lübeck, Germany) approved the study as a retrospective chart review.

### 3 | RESULTS

A total of 159 patients implanted with the HNS system were eligible for participation in the study, of whom 132 completed a follow-up assessment between April 2020 and February 2021. The reasons for exclusion from the analysis were that patients were lost to follow-up ( $n = 23$ ) or had died ( $n = 4$ ).

Of the 132 patients, 64 (48%) had their follow-up assessment between 6 and 24 months after HNS implantation, 20 (15%) after 36 months, 30 (23%) after 48 months, and 18 (14%) between 60 and 96 months of implantation.

Prior to implantation of the HNS device (baseline), the total cohort ( $n = 132$ ) had a median age of 56 years, median BMI of 29.0 kg/m<sup>2</sup>, and 81% were males (Table 1). Of these 132 patients, 34 (26%) had moderate/severe insomnia at their follow-up assessment and 45 (34%) had depression at their follow-up assessment; 19 patients (14%) had both insomnia and depression at follow-up. At baseline (preimplantation), patients with moderate/severe insomnia at their follow-up assessment were comparable in age, sex, and BMI, and had similar AHI and ODI scores to patients with no/subthreshold insomnia at the follow-up assessment (Table 1). The preimplantation scores for ESS and FOSQ differed between the moderate/severe insomnia and no/subthreshold insomnia groups, showing worse daytime sleepiness and sleep-related quality of life in the patients who had moderate/severe insomnia at follow-up (Table 1).

Data from the follow-up assessment (Table 1) show an improvement from preimplantation in the median ESS and FOSQ scores for the total cohort: the ESS decreased by 5.0 points from 14.0 at preimplantation to 8.0 points at follow-up, and the FOSQ increased by 3.3 points from 13.5 at preimplantation to 17.0 points at follow-up. Also, the median number of AHI and ODI events decreased by 14.7/h and 6.6/h, respectively, for the total cohort.

Table 1 shows that the subgroups of patients with moderate/severe insomnia at follow-up were more likely to have depression than those with no/subthreshold insomnia at follow-up (56% vs. 27%,  $P < .002$ ). The AHI and ODI scores at follow-up and the change from baseline in these objective OSA parameters were comparable between the moderate/severe insomnia and no/subthreshold insomnia groups. At follow-up, patients with moderate/severe insomnia reported less improvement from baseline in daytime sleepiness (ESS) and sleep-related quality of life (FOSQ) than patients with no/subthreshold insomnia. Table 1 also shows a trend toward higher HNS therapy usage in the group with no/subthreshold insomnia and a higher proportion of these patients reported overall satisfaction with HNS therapy.

**TABLE 1** Patient characteristics at baseline (preimplantation) and at the follow-up assessment for the total cohort and by insomnia categories at follow-up assessment

	Total cohort (n = 132)	ISI category at follow-up assessment		P-value
		No or subthreshold insomnia <sup>a</sup> (n = 98)	Moderate or severe insomnia <sup>b</sup> (n = 34)	
Baseline				
Age, years	56.0	57.0	53.5	.507
Male/female, n (%)	107 (81.1)/25 (18.9)	81 (82.7)/17 (17.3)	26 (76.5)/8 (23.5)	.423
BMI, kg/m <sup>2</sup>	29.0	29.1	28.7	.709
ESS <sup>c</sup>	14.0	13.0	15.5	<b>.002</b>
FOSQ <sup>d</sup>	13.5	14.9	12.0	<b>.010</b>
AHI, events/h	27.0	26.5	28.2	.935
ODI, events/h	15.0	15.5	15.5	.739
Follow-up				
BMI, kg/m <sup>2</sup>	28.7	28.8	28.3	.488
Depression, n (%)	45 (34.1)	26 (26.5)	19 (55.9)	<b>.002</b>
Medication for depression/anxiety, n (%)	24 (18.2)	16 (16.3)	8 (23.5)	.362
ESS <sup>c</sup>	8.0	7.0	11.5	<b>&lt;.001</b>
ΔESS <sup>e</sup>	5.0	6.0	3.5	<b>.002</b>
FOSQ <sup>d</sup>	17.0	18.6	13.5	<b>&lt;.001</b>
ΔFOSQ <sup>e</sup>	3.3	4.5	1.5	<b>&lt;.001</b>
ISI <sup>f</sup>	8.5	6.0	18.5	<b>&lt;.001</b>
AHI, events/h	13.7	13.0	15.3	.404
ΔAHI <sup>e</sup>	14.7	15.1	15.5	.635
ODI, events/h	7.1	8.4	10.6	.876
ΔODI <sup>e</sup>	6.6	6.6	9.5	.272
HNS usage, h/night	5.9	6.1	5.2	.058
Start delay, min	30.0	30.0	30.0	.299
Overall satisfaction, n (%)	111 (84.1)	91 (92.9)	20 (58.8)	<b>&lt;.001</b>

Note: Data presented as medians unless indicated otherwise. Delta values have been calculated case by case. Therefore, median delta values are not reflected as the difference between median baseline and median follow-up values. P values for comparisons between groups in bold text are below .05. Abbreviations: AHI, Apnea Hypopnea Index; BMI, body mass index; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; HNS, hypoglossal nerve stimulation with respiratory sensing; ISI, Insomnia Severity Index; ODI, Oxygen Desaturation Index.

<sup>a</sup>ISI score 0–7 = no insomnia and 8–14 = subthreshold insomnia.

<sup>b</sup>ISI score 15–21 = moderate insomnia and 22–28 = severe insomnia.

<sup>c</sup>ESS scores range from 0.0 to 24.0; higher scores indicate more daytime sleepiness.

<sup>d</sup>FOSQ scores range from 5.0 to 20.0; higher scores indicate better sleep-related quality of life.

<sup>e</sup>Change from baseline.

<sup>f</sup>ISI score ranges from 0 to 28; higher score indicates more severe insomnia.

Correlation analysis for the total cohort (n = 132) showed an association between continuous ISI values for insomnia and patient-reported outcomes, such that higher ISI values (greater insomnia severity) were associated with higher ESS scores (greater daytime sleepiness;  $r_s = .29$ ;  $P < .001$ ) and lower FOSQ scores (poorer sleep-related quality of life;  $r_s = -.25$ ;  $P < .01$ ). There was no correlation between ISI values and the number of AHI or ODI events/h at the follow-up assessment, but a higher ISI score was associated with lower HNS usage ( $r_s = -.22$ ;  $P = .013$ ).

Table 2 summarizes the results for the subgroups with a shorter ( $\leq 24$  months) and longer ( $\geq 36$  months) time since implantation at the follow-up assessment. Compared with patients with  $\leq 24$  months since implantation, those with a longer time since implantation were younger (55 vs. 59 years,  $P = .011$ ), more likely to have depression (44.1% vs. 23.4%,  $P = .014$ ), and a higher rate of overall satisfaction (92.6% vs. 75.0%,  $P = .031$ ). At the follow-up assessment, patients with a shorter time since implantation had a higher ESS score, lower number of AHI events/h, and greater reduction in the number of AHI events/h from baseline despite comparable HNS therapy usage.

**TABLE 2** Demographic characteristics and outcome scores at baseline (preimplantation) and at the follow-up assessment by subgroup according to time since implantation

	Time since implantation		P-value
	≤24 months <sup>a</sup> (n = 64)	≥36 months <sup>b</sup> (n = 68)	
Baseline			
Age, years	59.0	55.0	<b>.011</b>
Male/female, n (%)	49 (76.6)/15 (23.4)	58 (85.3)/10 (14.7)	.201
BMI, kg/m <sup>2</sup>	29.0	29.0	.061
ESS	14.0	14.0	.893
FOSQ	13.6	13.4	.528
AHI, events/h	27.6	26.0	.908
ODI, events/h	15.5	15.5	.816
Follow-up assessment			
BMI, kg/m <sup>2</sup>	28.0	29.9	.153
Depression, n (%)	15 (23.4)	30 (44.1)	<b>.014</b>
Medication for depression/anxiety, n (%)	9 (14.1)	15 (22.1)	.251
ESS <sup>c</sup>	8.0	7.0	<b>.041</b>
ΔESS <sup>e</sup>	5.0	5.5	.080
FOSQ <sup>d</sup>	16.9	18.1	.098
ΔFOSQ <sup>e</sup>	3.1	4.4	.199
ISI <sup>f</sup>	10.0	7.0	.084
AHI, events/h	12.3	15.7	<b>.043</b>
ΔAHI <sup>e</sup>	16.5	12.7	<b>.049</b>
ODI, events/h	6.8	11.0	.086
ΔODI <sup>e</sup>	7.5	5.0	.108
HNS usage, h/night	6.1	5.8	.703
Start delay, min	30.0	30.0	.307
Overall satisfaction, n (%)	48 (75.0)	63 (92.6)	<b>.031</b>

Note: Data are presented as medians unless indicated otherwise. Delta values have been calculated case by case. Therefore, median delta values are not reflected as the difference between median baseline and median follow-up values. P values for comparison between subgroups are given bold if below .05. Abbreviations: AHI, Apnea Hypopnea Index; BMI, body mass index; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; HNS, hypoglossal nerve stimulation with respiratory sensing; ISI, Insomnia Severity Index; ODI, Oxygen Desaturation Index.

<sup>a</sup>Follow-up assessment at 6, 12, or 24 months postimplantation.

<sup>b</sup>Follow-up assessment at 36, 48, 60, 72, or 96 months postimplantation.

<sup>c</sup>ESS scores range from 0.0 to 24.0; higher scores indicate more daytime sleepiness.

<sup>d</sup>FOSQ scores range from 5.0 to 20.0; higher scores indicate better sleep-related quality of life.

<sup>e</sup>Change from baseline.

<sup>f</sup>ISI score ranges from 0 to 28; higher score indicates more severe insomnia.

## 4 | DISCUSSION

In this analysis of 132 patients receiving HNS therapy for OSA, we examined the effect of comorbid insomnia symptoms on patient-reported outcomes, objective OSA-related data, and HNS therapy usage. Our findings demonstrate that patients with moderate/severe insomnia at their follow-up assessment (at varying times after implantation of the HNS device) had worse scores and less improvement from baseline in patient-reported outcomes (ESS, FOSQ, overall satisfaction) than patients without insomnia at follow-up, despite having similar OSA characteristics (AHI, ODI). At follow-up, patients with no insomnia had numerically greater HNS usage and a higher proportion

were satisfied with their therapy compared to those with insomnia. Depression was more prevalent in patients with moderate/severe insomnia at follow-up (56%) than in those with no/subthreshold insomnia (27%). The correlations found between the ISI score and the ESS or FOSQ scores indicate that comorbid insomnia can reduce the improvements in daytime sleepiness and sleep-related quality of life reported by patients receiving HNS therapy. These findings support the use of ISI to identify insomnia in patients undergoing HNS therapy for OSA so that it can be addressed to improve patient outcomes and satisfaction, especially during long-term follow-up of these patients.

COMISA has received increasing attention in recent years and more pragmatic approaches for managing these sleep disorders are

needed.<sup>25</sup> For OSA patients with insomnia, it can be difficult for physicians to decide which of the two sleep disorders is primarily responsible for poor sleep quality and what should be treated first. This situation is made even more difficult when OSA treatment with PAP therapy fails. As modern treatment approaches recommend “patient-centered considerations that integrate patient characteristics, treatment preferences...”,<sup>25</sup> sleep physicians should consider alternative treatments if PAP therapy is not well-accepted by patients with COMISA. As insomnia symptoms in OSA may contribute to poor OSA treatment satisfaction and adherence, measurement of insomnia severity using the ISI should provide useful information for the clinical management of patients with OSA.

Research on ISI measurement in patients with comorbid insomnia receiving alternative OSA treatments to PAP is limited. In March 2020, the ADHERE registry study for HNS with respiratory sensing was updated to include additional comorbidities, including insomnia, which likely explains the increased prevalence of insomnia from 1.2% in previous registry publications to 7.4% reported recently.<sup>13</sup> We expect the reported prevalence of insomnia to increase in the future as more ADHERE registry sites use insomnia assessment tools when participating in the registry. Almost all of our cohort of patients are in the ADHERE registry but as they did not have prospective ISI measurements at that time, we do not know whether insomnia was present at or before implantation of the HNS device. However, 26% of patients had moderate/severe insomnia based on the ISI score at their follow-up assessment postimplantation. In a recent retrospective study, 57% of a selected group of veterans with OSA undergoing HNS had comorbid insomnia.<sup>14</sup> However, they do not represent the type of patients typically receiving HNS implants. Nevertheless, these patients showed an improvement in objective OSA parameters and patient-reported outcomes, such as daytime sleepiness, despite having comorbid insomnia. Our findings may fill a gap by addressing the need for more information in a larger and more generalizable cohort of patients receiving HNS therapy over the longer term.

The efficacy and safety of HNS in the treatment of moderate-to-severe OSA was demonstrated in the long-term, prospective, international, Stimulation Therapy for Apnea Reduction (STAR) trial<sup>8</sup> and confirmed in a recent meta-analysis of 12 studies.<sup>26</sup> Several HNS studies of larger cohorts have demonstrated improvements in the patient-reported outcomes of ESS<sup>9,10,15,16</sup> and FOSQ.<sup>10,15,16,27</sup> However, these studies did not examine whether the presence of insomnia impacted these patient-reported outcomes.

Before HNS implantation, the median FOSQ score of our total cohort was 13.5 points, with an even lower FOSQ score (12.0) in the subgroup with comorbid insomnia at the follow-up assessment. Despite these low baseline values, patients reported improved sleep-related quality of life at follow-up and the median FOSQ value for those without insomnia (18.6) was above the cut-off normal value of 17.5 points. Patients with insomnia (higher ISI scores) reported less improvement in FOSQ scores at follow-up than those without insomnia (lower ISI scores).

The reduction in daytime sleepiness (ESS) seen in our total cohort of patients (median score decreased from 14.0 to 8.0 points) is

comparable with other publications.<sup>9,10,15,16,27</sup> Our study also shows that patients with moderate/severe insomnia at follow-up improved from a median ESS of 15.5 points before implantation to 11.5 points at follow-up, which is above the cut-off value of 10 points that is considered normal/non-sleepy.<sup>22</sup> In contrast, patients with no insomnia had a greater improvement from baseline and the ESS score was <10 at follow-up.

Overall patient satisfaction with HNS therapy in our total cohort (84%) was lower than the 96% reported in the German Post-market study at the 12-month final follow-up visit.<sup>15</sup> However, 93% of our patients without comorbid insomnia (lower ISI scores) were satisfied with their therapy compared to only 59% of those with insomnia (higher ISI scores). Taken together, we believe that patients with higher levels of insomnia have more daytime sleepiness and experience less improvement after HNS therapy, which may lead to a worse quality of life and lower treatment satisfaction scores.

In the German post-market study of patients with OSA receiving HNS therapy, there was no correlation between objective OSA parameters (AHI response) and subjective patient-reported outcome variables (ESS, FOSQ) at 6 and 12 months of follow-up.<sup>15</sup> Similarly, we found no correlation between the level of insomnia (ISI score) and AHI or ODI values but there was a correlation between the ISI score and ESS or FOSQ scores. Nightly HNS usage was lower among patients with insomnia but the difference from patients without insomnia did not reach statistical relevance. The median start delay was also comparable across the subgroups (30 min).

We have been implanting HNS devices since 2012, but only recently included the ISI questionnaire in the patient's regular follow-up assessment. Therefore, the patients included in our analysis had different follow-up periods since implantation, which could have influenced the outcomes observed. When the total cohort was divided into two subgroups according to time since implantation, there were no differences in demographic characteristics except for the older age of patients with  $\leq 24$  months since implantation. Patients with  $\geq 36$  months since implantation had a similar change from baseline in ESS value and ODI events but less reduction in AHI events compared to those with a shorter time since implantation. For patients with  $\geq 36$  months since implantation, there was a higher prevalence of depression, a lower median ISI score (not statistically relevant), and higher overall patient satisfaction with HNS therapy at the follow-up assessment, than among patients with more recent implants. One explanation for this latter point may be that this group was more motivated to obtain funding for this therapy when newly available.

The study has several limitations. First, as the ISI questionnaire was not included in our regular annual follow-up assessment until 2020, we have no information on the presence or severity of insomnia prior to HNS implantation for most of the patients included in the study. The follow-up time covers a large period with various time points since implantation. This bias can be judged by our assessment (Table 2). Despite this, without an insomnia evaluation before implantation, a development of the demonstrated insomnia complaints under HNS cannot be excluded even though they are unlikely. Although we

used the total ISI score for defining the presence of moderate/severe insomnia in our cohort of patients with OSA, the ISI has not been validated in such a sample.<sup>28</sup> Both OSA and insomnia may contribute to those ISI items covering the daytime symptoms/impact of sleep problems. Wallace and Wohlgenuth<sup>28</sup> recently identified several distinct ISI subgroups in a large group of veterans with newly diagnosed OSA; 74% had both daytime and nocturnal symptoms, whereas 14% had daytime symptoms only, and 12% were asymptomatic with low scores across all ISI items. These authors cautioned against using the ISI cut-offs alone to define insomnia symptoms in patients with OSA.

Second, the presence of depression was based on medical records alone. We did not investigate whether depression, when present, was well treated at the time of HNS follow-up and are aware that a record of medication for depression/anxiety does not represent this aspect adequately. We also did not collect information from the medical records on whether patients were receiving treatment for insomnia.

Third, because of the COVID pandemic, some patients did not have their regular follow-up assessment at our hospital and only limited information was obtained from the questionnaires sent to them. Thus, complete data were not available for the total cohort of patients.

Finally, analysis of HNS usage data was limited due to restrictions on accessing the manufacturer's cloud-based patient remote read-out. Data on the frequency of use of the "pause" function in patients with sleep maintenance difficulties and the times when HNS therapy was activated may have been informative. We were unable to examine the correlation between comorbid insomnia and pause of HNS therapy usage. Further research is needed on identifying patients with sub-optimal changes in subjective outcomes despite improvements in objective OSA parameters (AHI and ODI) during HNS therapy.

## 5 | CONCLUSION

Insomnia is a frequent comorbid disorder in patients with OSA, who are candidates for second-line HNS therapy. The ISI questionnaire may be useful for identifying insomnia as a potential cause of poor patient quality of life and satisfaction with HNS therapy during follow-up despite improvements in objective OSA measures. A structured follow-up program that includes patient-reported outcome instruments will help to address relevant comorbidities among patients receiving HNS therapy.

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### CONFLICT OF INTEREST

Armin Steffen and Peter Baptista are study investigators and received honoraria and travel expenses for invited talks on behalf of Inspire

Medical Inc., outside the submitted work. The authors Eva-Maria Ebner, Stephanie Jeschke, Inke R. König, and Karl-Ludwig Bruchhage have no conflicts of interest to declare.

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