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SCIENTIFIC INVESTIGATIONS

Idiopathic Hypersomnia Severity Scale to better quantify symptoms severity and their consequences in idiopathic hypersomnia

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Study Objectives: To assess the responsiveness of the Idiopathic Hypersomnia Severity Scale (IHSS) to medications and estimate the minimum clinically important difference, to report clinically relevant score ranges, and to confirm its psychometric properties and whether items need to be weighted in drug-free and treated patients with idiopathic hypersomnia (IH).

Methods Two-hundred twenty-six (166 drug-free and 60 treated) patients with IH (cross-sectional sample) completed the 14-item IHSS to quantify the severity of the 3 major IH symptoms (excessive daytime sleepiness, prolonged nighttime sleep, and sleep inertia) and consequences; 77 untreated patients were evaluated again after treatment (longitudinal sample). Patients filled in the Epworth Sleepiness Scale, Beck Depression Inventory II, and European Quality of Life questionnaires.

Results: The IHSS confirmed adequate psychometric properties with a factor analysis indicating a 3-component solution. IHSS total score was lower in treated than untreated patients, with a mean difference of 4–5 points in the cross-sectional and longitudinal samples. Distribution-based methods were used to estimate that 4 points represented the minimum clinically important difference. Four severity levels were defined with between-group differences related to treatment. The probability of having severe sleepiness, depressive symptoms, and low quality of life increased with the severity level. Our results showed that IHSS item-weighting was not necessary.

Conclusions: The IHSS is a valid and reliable tool to quantify IH symptoms, with 4 severity score levels of clinical importance. The IHSS has adequate psychometric properties and can detect symptom changes after treatment. These findings should stimulate its use in clinical settings and in research studies.

Keywords: idiopathic hypersomnia, sleepiness, sleep inertia, scale

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The Idiopathic Hypersomnia Severity Scale is a valid and reliable tool to quantify symptoms of idiopathic hypersomnia and their consequences. This study aimed to assess the responsiveness of the Idiopathic Hypersomnia Severity Scale to medications and estimate the minimum clinically important difference between untreated and treated conditions, to report clinically relevant score levels, and to confirm the scale's psychometric properties in adult patients with idiopathic hypersomnia.

Study Impact: This scale has adequate psychometric properties and sensitivity to detect clinical changes in symptoms after treatment. We recommend its use in clinical settings for initial and follow-up evaluations, to monitor and optimize management of patients with idiopathic hypersomnia, and as a tool in future trials.

INTRODUCTION

Idiopathic hypersomnia (IH) is a rare central hypersomnolence disorder characterized by 3 major symptoms: excessive daytime sleepiness (EDS), prolonged nighttime sleep, and sleep inertia.[1,2] Based on the *International Classification of Sleep Disorders*, third edition (ICSD-3),[3] criteria, EDS is required for IH diagnosis and is the most common and often the most debilitating symptom. However, most patients with IH also report prolonged nighttime sleep, long unrefreshing naps, sleep inertia (ie, great difficulties in awakening from sleep in the morning and after naps), impaired daytime alertness, cognitive difficulties, and brain fog.[4–6] In patients with IH, health-related quality of life is reduced,[7–10] social and work functioning are impaired, productivity is reduced, and car accidents are more frequent.[11] No treatment is currently approved for IH; however, patients are often treated with off-label stimulants and wake-promoting agents approved for use in narcolepsy.[12,13]

Several tools have been developed to evaluate EDS severity in the general population, including the widely used Epworth Sleepiness Scale[14] (ESS), which is often chosen to assess EDS in narcolepsy, in obstructive sleep apnea, as well as in IH. In 2019, we developed the Idiopathic Hypersomnia Severity Scale (IHSS), a 14-item self-assessment questionnaire, to measure the severity, frequency, and functional impact of the 3 key IH symptoms. In 218 participants (including 100 patients with IH), IHSS showed good psychometric properties, particularly internal consistency and content validity, and some responsiveness to treatment in

patients with IH.[15] However, due to the potential global health consequences of IH, we still needed to: define clinically relevant IHSS score ranges that more precisely described the severity of IH symptoms and their impact on daily functioning; and compare the IHSS scores in IH patients with/without long sleep time, as well as with other clinical measures of EDS, with depressive symptoms, and with quality of life. We needed also to confirm that IHSS could detect clinical changes in symptoms following treatment and to estimate the minimum clinically important difference (MCID) in order to provide guidelines for what constitutes meaningful within-person change between the with and without treatment conditions. Also, we had assumed that all IHSS items would be equal: however, the number of IHSS items per symptom is different as well as the scoring per item. Therefore, we needed to determine whether the different IHSS items require weighting to better assess IH symptoms, as well as the effects of age, disease duration, and sex on the global score.

The aims of the present study in consecutive untreated and treated adult patients with IH were: (1) to assess the responsiveness of IHSS to medications and estimate the MCID, (2) to report IHSS clinically relevant score levels, (3) to confirm its psychometric properties, and (4) to test whether items require weighting to improve IHSS performance.

METHODS

Patients

Consecutive patients aged 16 years and older with IH (n = 226; n = 166 drug-free and n = 60 treated) followed at the Reference National Center for Narcolepsy–Rare Hypersomnias of Montpellier, France, completed the IHSS, from January 2016 to September 2020 (cross-sectional sample). The sample included 100 patients from the first study (57 untreated, 43 treated) and 126 new patients (109 untreated, 17 treated). Among the 166 untreated patients (118 women, 71.08%; mean age: 30.29 ± 11.17 years), 77 (59 women, 76.62%; mean age 28.89 ± 9.19 years) filled in again the IHSS in the French language after treatment (longitudinal sample) following a median delay of 0.86 years [interquartile range = 0.47–1.35]. Among the 166 untreated patients, 8 (4.8%) had been receiving treatment by antidepressants that was stopped at least 1 month before the study inclusion.

IH was diagnosed in drug-free condition according to the ICSD-3 criteria.[3] All patients were evaluated by a sleep expert physician who collected also their demographic and clinical data. No participant had history of cataplexy. Patients with sleep-deprivation (< 7 hours of sleep per night), with moderate-to-severe sleep-disordered breathing, or with significant medical or neurologic comorbidity were excluded. Diagnosis was documented by nocturnal polysomnography (PSG) and Multiple Sleep Latency Test for 223 patients (166 in untreated condition and 57 in treated condition) and 32-hour polysomnography bed-rest was also performed in 172 patients (127 in untreated and 45 in treated condition). Overall, 144 patients (64.60%) had a Multiple Sleep Latency Test with a mean latency ≤ 8 minutes. Among the 172 patients who performed the 32-hour recording, 167 (98.8%) had a total sleep time (TST) ≥ 11 hours on the first 24-hour recording, and 147 patients (87.0%) had a TST ≥ 19 hours on the 32-hour recording (ie, alternative diagnostic criterion for IH).[16] Cerebrospinal fluid hypocretin-1 levels were available for 55 patients: All had normal level > 200 pg/ml, except 1 patient with intermediate level (131 pg/ml).

This study was approved by a French ethics committee (Comité de Protection des Personnes, France: "Constitution of a cohort and of a clinical, neurophysiological and biological bank of rare hypersomnolence disorders"–PHRC 07-138). Consent to participate was provided by all patients.

Measures

Patients were instructed to evaluate the severity of their symptoms during the previous month using the IHSS. The IHSS includes 2 items (1 and 2) on nighttime sleep duration and quality, 3 items (3, 4, and 5) on sleep inertia and sleep drunkenness after nighttime sleep and 1 (8) after daytime nap, and 3 items (6, 7, and 9) on diurnal symptoms (nap occurrence, daytime sleepiness). Items 10–14 assess daytime functioning alterations due to hypersomnolence. Six items are scored on a 3-point Likert scale and 8 items on a 4-point Likert scale; the Likert scale is a point scale that is used to allow the individual to express how much they agree or disagree with a particular statement. The total IHSS score is the sum of all item scores (range: 0–50), and higher scores indicate more severe symptoms. The definite presence of each of the 3 main symptoms (EDS, long nighttime sleep, and sleep inertia) is defined by a score > 1 to at least 1 of the items related to that symptom. All treated patients had stable drug dosages for at least 1 month before IHSS completion. The original IHSS was developed in French and validated in a French-speaking population; forward and back translations were performed to develop a certified English translation. The MAPI Research Institute (Lyon, France) hosts and distributes the scale and provides a central clearinghouse for all current and future copyrighted translations that may be used after appropriate permissions or licensure.

EDS severity was assessed with the ESS (n = 224, score ≤ 10/24: no EDS, 11–15: EDS, ≥ 16: severe EDS). The severity of depressive symptoms was evaluated with the Beck Depression Inventory II (BDI-II) scale[17] (n = 207, score ≤ 19: none or mild symptoms; ≥ 20/63: moderate-to-severe symptoms). The quality of life was evaluated in a subgroup (n = 196) using the European Quality of Life-5 Dimensions[18] that includes a descriptive system of 5 dimensions (EQ-5D utility score) and a visual analog scale (EQ-5D-VAS) categorized into tertiles. The lowest tertile (score < 60) indicating poorer health quality of life was compared to the other 2 tertiles.

Statistical analysis

Demographic characteristics and clinical data were described using means and standard deviations for continuous variables, and numbers and percentages for categorical variables. For demographic, clinical, and polysomnography characteristics and IHSS item scores, the independent Student's *t* test and analysis of variance were used to compare continuous variables, and the chi-square and Fisher exact tests to compare categorical variables between untreated and treated patients. The dependent *t* test was used to compare differences between continuous

variables at 2 different time points or in 2 different conditions, and the McNemar test or McNemar-Bowker test of symmetry for paired categorical data. Associations between continuous variables were assessed with the Pearson correlation coefficient. To analyze the IHSS factor structure, a principal components factor analysis was performed using a Varimax rotation. The number of factors was determined on the basis of the obtained factor loadings and eigen values. Sampling adequacy was assessed by calculating the Kaiser-Meyer-Olkin index. The internal consistency (reliability) of the item scores was estimated using the Cronbach coefficient α. To compare the different IHSS items with a higher ESS score (ESS ≥ 16), all the IHSS items were included in a single logistic regression model. From this model, the weighted-item total score was calculated for each item with the respective β coefficients. To make the score approach an integer and be more intuitive, all β coefficients were standardized in such a way that the lowest one had a value of 1. As the lowest β value was −0.1209, it was multiplied by 8 and was rounded to the closest integer. The weighted total score for each patient was obtained by summing the scores for the appropriate level of each item. The same methodology was used for depressive symptoms (BDI-II score ≥ 20) and poor health quality of life (EQ-5D-VAS score < 60). To evaluate the effectiveness of a treatment, the MCID was estimated using 2 distribution-based methods: Cohen's effect size (0.5 × standard deviation [SD] delta) and the empirical rule effect size (0.08 × 6 × SD delta), where delta represents the IHSS total score change between untreated and treated patients. Statistical significance was set at $P < .05$. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Among the 60 treated patients with IH (46 women, 76.67%; mean age 37.51 ± 13.74 years) of the cross-sectional sample, 54 were taking 1 stimulant or wake-promoting agent (n = 31 modafinil, n = 19 methylphenidate, and n = 4 pitolisant), 6 were taking 2 drugs (n = 2 methylphenidate and pitolisant, n = 2 methylphenidate and modafinil, and n = 2 modafinil and pitolisant), and 6 (10%) were also taking antidepressants together with a wake-promoting agent. Compared with the 166 untreated patients, treated patients were older, had shorter TST on the polysomnography bed rest recording, self-reported better quality of life, and fewer had severe EDS and depressive symptoms (**Table 1**). Among the 77 patients of the longitudinal sample, 68 were taking 1 stimulant or wake-promoting agent (n = 30 modafinil, n = 24 methylphenidate, n = 14 pitolisant), 3 were taking 2 drugs (n = 1 modafinil and pitolisant, n = 1 methylphenidate and pitolisant, and n = 1 methylphenidate and venlafaxine), 6 were taking only sodium oxybate, and 5 were also taking antidepressants together with a wake-promoting agent. Compared with the untreated condition, the treated condition was associated with lower ESS scores and less severe depressive symptoms (**Table 1**).

IHSS: construct validity

IHSS construct validity was evaluated in the whole sample (n = 226: 166 untreated, and 60 treated). The internal consistency of the entire scale was good as indicated by the Cronbach's α = 0.89. The correlation of each IHSS item with the total score was satisfactory (from 0.55 to 0.89, except for items 6, 7, and 14 that showed lower correlations: 0.25, 0.48, and 0.46, respectively) (**Table 2**).

The Kaiser-Meyer-Olkin index was 0.89, confirming the sampling adequacy. The factor analysis and the scree plot indicated a 3-factor solution with eigen values > 1 that explained 58% of the total variance (**Table 2**). Component I was composed of 7 items on daytime functioning (items 5, 9, 10, 11, 12, 13, 14), component II included 5 items on long sleep duration and sleep inertia (items 1, 2, 3, 4, 8), and component III included 2 items on napping (items 6 and 7). Of note, for the 13.3% of patients who did not drive, item 14 was scored 0 (no problem). The item loading values, which represent how strongly each item is associated with the underlying component, ranged from 0.43 to 0.85 (**Table 2**). Communalities, which refer to the percentage of variance for each item, ranged from 0.32 to 0.76.

Concerning the construct convergent validity, IHSS total score correlated in untreated and treated patients with the ESS ($r = .49$, $P < .0001$; $r = .62$, $P < .0001$ respectively), BDI-II ($r = .44$, $P < .0001$; $r = .60$, $P < .0001$), and EQ-5D-VAS scores ($r = –.44$, $P < .0001$; $r = –.53$, $P < .0001$). The IHSS components I and II scores also correlated with the ESS, BDI-II, and EQ-5D-VAS scores in untreated and treated patients, whereas the component III score correlated with the BDI-II and EQ-5D-VAS scores only in the untreated population (data not shown).

Number of symptoms and IHSS scores in treated and untreated patients

In the cross-sectional sample, the number of symptoms (ie, EDS, long nighttime sleep, and sleep inertia) defined by their presence on at least 1 of the IHSS items related to that symptom was lower in treated than untreated patients (**Table 3**). Among the 166 untreated patients, 80.7% had all 3 symptoms, 12.7% 2 symptoms (mostly EDS with long nighttime sleep or sleep inertia), and 6.6% only 1 symptom (EDS). Among the 60 treated patients, 63.3% had all 3 symptoms, 20.0% 2 symptoms (n = 6 long nighttime sleep and sleep inertia, n = 4 EDS and long nighttime sleep, and n = 2 EDS and sleep inertia), and 16.7% only 1 symptom (mostly EDS). Similar distributions were found in the longitudinal sample (n = 77 patients), but the differences between untreated and treated condition were not significant (**Table 3**). In both cross-sectional and longitudinal samples, the number of patients with EDS was lower in the treated groups, although no difference was found concerning prolonged nighttime sleep and sleep inertia. In both samples, between-group differences (treated vs untreated) were found for 7 items in the cross-sectional sample and for 6 items for the longitudinal sample. Five of these items were the same in both groups (**Table 3**).

IHSS total score was higher in untreated patients than in treated patients with a mean difference of 4.88 points (SD = 9.18, $P < .01$) in the cross-sectional sample and of 4.38 points (SD = 7.41, $P < .0001$) in the longitudinal sample. The estimated MCID of the IHSS score between untreated and treated

Table 1—Demographic, clinical, and polysomnographic characteristics of untreated and treated adult patients with idiopathic hypersomnia.

Variables	Cross-sectional Sample			Longitudinal Sample		
	Untreated Patients (n = 166), n (%)	Treated Patients (n = 60), n (%)	*P*	Untreated Patients (n = 77), n (%)	Treated Patients (n = 77), n (%)	*P*
Demographic and clinical characteristics						
Sex, women	118 (71.08)	46 (76.67)	.41	59 (76.62)	–	
Age,[a] y	166; 30.29 (± 11.17)	60; 37.51 (± 13.74)	< .0001	77; 28.89 (± 9.19)	77; 29.93 (± 9.28)	< .0001
Body mass index,[a] kg/m^2	166; 23.54 (± 4.27)	60; 24.14 (± 4.83)	.51	77; 23.32 (± 4.16)	77; 23.57 (± 4.73)	.61
Age at disease onset,[a] y	165; 17.72 (± 7.14)	60; 19.44 (± 10.36)	.74	77; 18.55 (± 7.26)	–	
Subjective rating scales						
ESS total score[a]	164; 15.26 (± 4.41)	60; 12.53 (± 5.04)	< .0001	74; 15.77 (± 3.75)	74; 12.85 (± 5.49)	< .0001
ESS total score, ≥ 16	143 (87.20)	37 (61.67)	< .0001	68 (91.89)	52 (70.27)	.0002
BDI-II total score[a]	155; 13.06 (± 9.02)	52; 9.08 (± 7.94)	< .0001	42; 14.83 (± 9.31)	42; 11.50 (± 8.81)	.01
BDI-II total score, ≥ 20	36 (23.23)	7 (13.46)	.13	14 (33.33)	7 (16.67)	.05
EQ-5D utility score[a]	145; 0.77 (± 0.20)	50; 0.80 (± 0.18)	.20	39; 0.73 (± 0.19)	39; 0.78 (± 0.19)	.05
EQ-5D-VAS[a]	142; 61.96 (± 19.47)	54; 68.26 (± 18.75)	.03	57; 59.58 (± 22.10)	57; 62.86 (± 18.24)	.14
Neurophysiological data						
TST,[a] min	163; 450.43 (± 39.03)	49; 449.27 (± 42.51)	.86	77; 457.43 (± 38.30)	77; 455.90 (± 39.54)	.63
Sleep efficiency,[a] %	163; 89.50 (± 5.75)	49; 90.65 (± 5.55)	.15	77; 89.76 (± 5.91)	77; 89.79 (± 5.89)	.99
24-h bed rest TST ≥ 11 h	124 (99.20)	43 (97.73)	.24	66 (98.51)	–	
32-h bed rest TST ≥ 19 h	114 (89.76)	33 (73.33)	< .0001	60 (89.55)	–	
MSLT sleep latency,[a,b] min	166; 7.71 (± 3.61)	57; 7.35 (± 4.01)	.37	77; 7.93 (± 3.70)	–	
MSLT sleep latency ≤ 8 min[a,b]	107 (64.46)	37 (64.91)	.95	46 (59.74)	–	

[a]Quantitative variables are described with numbers, mean (± SD). [b]Assessed in untreated condition. BDI-II = Beck Depression Inventory II, EQ-5D = European Quality of Life-5 Dimensions questionnaire, ESS = Epworth Sleepiness Scale, MSLT = Multiple Sleep Latency Test, TST = total sleep time, VAS = visual analog scale.

Table 2—Factor structure of the Idiopathic Hypersomnia Severity Scale in patients with idiopathic hypersomnia.

Questions	KMO Item by Item	In the Whole Sample (n = 226 patients)			
		Communalities	Factors		
			I	II	III
1	0.90	0.63	0.14	0.71	0.34
2	0.90	0.66	0.31	0.75	0.07
3	0.92	0.48	0.20	0.66	–0.003
4	0.92	0.58	0.39	0.65	0.07
5	0.86	0.32	0.43	0.37	–0.02
6	0.71	0.76	0.18	–0.10	0.85
7	0.86	0.68	0.09	0.37	0.73
8	0.90	0.52	0.24	0.68	–0.07
9	0.93	0.37	0.51	0.20	0.26
10	0.88	0.75	0.75	0.37	0.21
11	0.89	0.70	0.82	0.14	0.08
12	0.91	0.58	0.72	0.26	0.06
13	0.91	0.68	0.69	0.39	0.22
14	0.71	0.41	0.53	–0.34	0.08
Cronbach's α	0.89	–	–	–	–
KMO measure of sampling adequacy	0.89	–	–	–	–
Percentage of cumulative variance explained	–	0.58			

KMO = Kaiser-Meyer-Olkin index.

patients in the longitudinal sample was 3.71 with the Cohen's effect size, and 3.56 with the empirical rule effect size. According to the Youden's Index ([specificity + sensitivity] − 1), the IHSS cut-off value for discriminating between the 166 untreated and the 60 treated patients was 26 (area under the curve 62.8%, 95% confidence interval 54.2–71.2): 78.3% of untreated and 56.7% of treated patients had a score ≥ 26. Concerning the 3 IHSS dimensions, the components I and III scores were significantly lower in the treated groups of the cross-sectional and longitudinal samples, and the component II scores only in the treated group of the longitudinal sample (**Table 3**).

Among untreated patients of the cross-sectional sample, the IHSS total score was higher in women than in men (32.1 ± 8.4 vs 28.1 ± 8.6, P = .006) and also the components II and III scores (P < .01). In the whole population, the IHSS total and component II scores were negatively correlated with age (r = –.20, P = .0027; r = –.34, P < .0001). IHSS total score was lower in patients with mean sleep latency > 8 minutes than in those with mean sleep latency below this cut-off (29.81 ± 8.25 vs 33.00 ± 9.02, P = .01), with similar results for the component I (P = .04) and component II scores (P = .05). No association was found between IHSS total score and TST longer or shorter than 11 hours during the first 24 hours, or longer or shorter than 19 hours during the 32-hour bed rest protocol. No correlation was found between IHSS total score, disease duration, and body mass index.

Crude and weighted IHSS total scores

Each item and the crude IHSS scores were compared with several outcomes related to sleepiness, depressive symptoms, and quality of life. Overall, 104 (46.43%) patients had severe EDS (ESS score ≥ 16), 43 (20.77%) moderate/severe depressive symptoms (BDI-II score ≥ 20), and 62 (31.63%) poor health status (EQ-5D-VAS < 60). In univariate analysis, the scores of most IHSS items were higher in patients with severe EDS (except for items 1, 2, 3, 7, and 8). The scores of items 1, 5, 9, 10, 11, 12, and 13 and of items 4, 5, 10, 11, 12, and 13 also were higher in patients with moderate/severe depressive symptoms and poor health status, respectively. Multivariate analysis showed that items 9, 10, and 14 were independently associated with severe EDS, items 1, 5, and 12 with depressive symptoms, and items 5 and 13 with poor health status (**Table 4**).

Between-group significant differences (eg, patients divided into groups as a function of the ESS score ≥ 16, BDI-II score ≥ 20, and EQ-5D-VAS score < 60) were found for the IHSS total score and total weighted score in unadjusted (**Table 5**) and adjusted models (P < .0001; adjusted for age and treatment group, or disease duration and treatment group) (data not shown).

Sleepiness, depressive symptoms, poor health status, and total IHSS score severity levels

Patients were divided into 4 equal ranks to report disease severity categories as a function of the IHSS total score: mild 0–12

Table 3—Number of IH symptoms, IHSS items, and total scores in the cross-sectional and longitudinal samples of patients with IH.

	Cross-sectional Sample			Longitudinal Sample		
Variables	Untreated Patients (n = 166), n (%)	Treated Patients (n = 60), n (%)	*P*	Untreated Patients (n = 77), n (%)	Treated Patients (n = 77), n (%)	*P*
Number of IH symptoms			.02			.12
0–1	11 (6.63)	10 (16.67)		6 (7.79)	8 (10.39)	
2	21 (12.65)	12 (20.00)		6 (7.79)	13 (16.88)	
3	134 (80.72)	38 (63.33)		65 (84.42)	56 (72.73)	
Number of IH symptoms[a]	2.72 (± 0.66)	2.43 (± 0.85)	< .01	2.73 (± 0.72)	2.57 (± 0.82)	.10
Diurnal symptoms (nap occurrence, sleepiness), yes	159 (95.78)	50 (83.33)	< .01	73 (94.81)	65 (84.42)	.01
Nighttime sleep duration and quality, yes	146 (87.95)	49 (81.67)	.23	67 (87.01)	67 (87.01)	.99
Sleep inertia and drunkenness, yes	146 (87.95)	47 (78.33)	.07	70 (90.91)	66 (85.71)	.25
Item #1: Ideal duration of nighttime sleep, ≥ 9 hours	127 (76.51)	37 (61.67)	.03	63 (81.82)	58 (75.32)	.17
Item #2: Feeling of not getting enough sleep in the morning, often/always	140 (84.34)	47 (78.33)	.29	64 (83.12)	60 (77.92)	.32
Item #3: Need of several alarm calls to wake up in the morning, often/always	94 (56.63)	26 (43.33)	.08	47 (61.04)	44 (57.14)	.47
Item #4: Time to feel fully functional after waking up in the morning, 1 hour	59 (35.54)	20 (33.33)	.76	31 (40.26)	25 (32.47)	.16
Item #5: Doing/saying irrational things or clumsiness upon awakening, often/always	41 (24.70)	16 (26.67)	.76	21 (27.27)	17 (22.08)	.29
Item #6: Naps during the day, often/very often	89 (53.61)	18 (30.00)	.002	44 (57.14)	31 (40.26)	.003
Item #7: Ideal length of your naps, ≥ 1 hour	107 (64.46)	26 (43.33)	.005	48 (62.34)	41 (53.25)	.11
Item #8: Feeling after a nap, sleepy/very sleepy	118 (71.08)	37 (61.67)	.18	59 (76.62)	55 (71.43)	.25
Item #9: Struggle to stay awake during monotonous tasks, often/very often	119 (71.69)	26 (43.33)	.0001	57 (74.03)	37 (48.05)	.0002
Item #10: Impact of hypersomnolence on general health, significant/very significant impact	130 (78.31)	35 (58.33)	.003	65 (84.42)	50 (64.94)	.002
Item #11: Impact of hypersomnolence on intellectual functioning, significant/very significant impact	109 (65.66)	28 (46.67)	.01	57 (74.03)	44 (57.14)	.003
Item #12: Impact of hypersomnolence on mood, significant/very significant impact	87 (52.41)	26 (43.33)	.23	46 (59.74)	42 (54.55)	.71
Item #13: Impact of hypersomnolence on daily tasks, significant/very significant impact	85 (51.20)	22 (36.67)	.05	45 (58.44)	33 (42.86)	.02
Item #14: Impact of hypersomnolence on driving performance, significant/very significant impact	64 (38.55)	8 (13.33)	.0006	40 (51.95)	20 (25.97)	< .0001
IHSS total score[a]	30.95 (± 8.64)	26.07 (± 10.54)	< .003	32.77 (± 8.17)	28.38 (± 9.31)	< .0001
IHSS total score, ≥ 26	130 (78.31)	34 (56.67)	.001	64 (83.12)	54 (70.13)	.03
IHSS component I (daytime functioning) score[a]	16.23 (± 5.20)	13.53 (± 6.64)	.006	17.53 (± 4.77)	14.73 (± 6.04)	< .0001
IHSS component II (long sleep duration/ sleep inertia) score[a]	10.27 (± 3.71)	9.20 (± 4.02)	.10	10.75 (± 3.66)	9.99 (± 3.30)	.04
IHSS component III (napping) score[a]	4.45 (± 2.00)	3.33 (± 1.75)	< .0001	4.48 (± 1.94)	3.66 (± 1.91)	.0002

[a]Quantitative variables are expressed as mean (± SD). IH = idiopathic hypersomnia, IHSS = Idiopathic Hypersomnia Severity Scale.

Table 4—Multivariate logistic regression model for excessive daytime sleepiness, high level of depression, and low health status according to the IHSS items and risk scores derived from the β coefficients.

	ESS Score ≥ 16 vs < 16				BDI-II Score ≥ 20 vs < 20				EQ-5D-VAS Score < 60 vs ≥ 60			
Variable	**β Coef.**	**OR [95% CI]**	***P***	**Score**	**β Coef.**	**OR [95% CI]**	***P***	**Score**	**β Coef.**	**OR [95% CI]**	***P***	**Score**
Item #1: Ideal duration of nighttime sleep			.11				.01				.22	
< 9 hours	0	1		0	0	1		0	0	1		0
≥ 9 hours	–0.8356	0.43 [0.16;1.20]		–7	–1.4700	0.23 [0.07;0.75]		–56	–0.6451	0.52 [0.19;1.47]		–295
Item #2: Feeling of not getting enough sleep in the morning			.18				.11				.31	
Never/sometimes	0	1		0	0	1		0	0	1		0
Often/always	0.9161	2.50 [0.66;9.54]		8	1.3361	3.80 [0.74;19.7]		51	0.7523	2.12 [0.50;9.00]		344
Item #3: Need of several alarm calls to wake up in the morning			.31				.60				.22	
Never/sometimes	0	1		0	0	1		0	0	1		0
Often/always	–0.3895	0.68 [0.32;1.44]		–3	–0.2282	0.80 [0.34;1.88]		–9	–0.4933	0.61 [0.28;1.35]		–225
Item #4: Time to feel fully functional after waking up in the morning			.30				.48				.23	
< 1 hour	0	1		0	0	1		0	0	1		0
≥ 1 hour	0.4029	1.50 [0.70;3.21]		3	–0.3208	0.73 [0.30;1.77]		–12	0.4804	1.62 [0.74;3.53]		219
Item #5: Doing/saying irrational things or clumsiness upon awakening			.16				.04				.005	
Never/sometimes	0	1		0	0	1		0	0	1		0
Often/always	0.6105	1.84 [0.79;4.28]		5	0.9068	2.48 [1.02;5.99]		35	1.1640	3.20 [1.43;7.16]		532
Item #6: Naps during the day			.12				.91				.87	
Never/rarely/sometimes	0	1		0	0	1		0	0	1		0
Often/very often	0.5609	1.75 [0.86;3.57]		5	0.0473	1.05 [0.45;2.45]		2	–0.0628	0.94 [0.44;2.02]		–29
Item #7: Ideal length of your naps			.76				.42				.78	
< 1 hour	0	1		0	0	1		0	0	1		0
≥ 1 hour	–0.1209	0.89 [0.40;1.95]		–1	0.4057	1.50 [0.57;3.98]		15	–0.1230	0.88 [0.38;2.07]		–56
Item #8: Feeling after a nap			.42				.56				.71	
Wide awake/awake	0	1		0	0	1		0	0	1		0
Sleepy/very sleepy	–0.3506	0.70 [0.30;1.64]		–3	–0.2898	0.75 [0.28;1.99]		–11	–0.1706	0.84 [0.34;2.09]		–78
Item #9: Struggle to stay awake during monotonous tasks			< .0001				0.69				0.99	
Never/rarely/sometimes	0	1		0	0	1		0	0	1		0
Often/very often	1.8258	6.21 [2.82;13.6]		15	0.1952	1.22 [0.47;3.14]		7	–0.00219	1.00 [0.44;2.24]		–1

(continued on following page)

Table 4—Multivariate logistic regression model for excessive daytime sleepiness, high level of depression, and low health status according to the IHSS items and risk scores derived from the β coefficients. (*Continued*)

	ESS Score ≥ 16 vs < 16				BDI-II Score ≥ 20 vs < 20				EQ-5D-VAS Score < 60 vs ≥ 60			
Variable	**β Coef.**	**OR [95% CI]**	***P***	**Score**	**β Coef.**	**OR [95% CI]**	***P***	**Score**	**β Coef.**	**OR [95% CI]**	***P***	**Score**
Item #10: Impact of hypersomnolence on general health			.04				.97				.21	
No/minor/moderate impact	0	1		0	0	1		0	0	1		0
Significant/very significant impact	1.0379	2.82 [1.00;7.95]		9	–0.0262	0.97 [0.25;3.86]		–1	0.7311	2.08 [0.66;6.59]		334
Item #11: Impact of hypersomnolence on intellectual functioning			.39				.06				.88	
No/minor/moderate impact	0	1		0	0	1		0	0	1		0
Significant/very significant impact	0.3367	1.40 [0.65;3.04]		3	1.1070	3.03 [0.97;9.47]		42	–0.0659	0.94 [0.40;2.17]		–30
Item #12: Impact of hypersomnolence on mood			.13				.007				.94	
No/minor/moderate impact	0	1		0	0	1		0	0	1		0
Significant/very significant impact	–0.6045	0.55 [0.25;1.20]		–5	1.3620	3.90 [1.46;10.5]		52	0.0286	1.03 [0.46;2.28]		13
Item #13: Impact of hypersomnolence on daily tasks			.07				.18				.005	
No/minor/moderate impact	0	1		0	0	1		0	0	1		0
Significant/very significant impact	0.7180	2.05 [0.94;4.49]		6	0.6799	1.97 [0.73;5.35]		26	1.2355	3.44 [1.45;8.16]		564
Item #14: Impact of hypersomnolence on driving performance			.0005				.41				.59	
No/minor/moderate impact/not driving	0	1		0	0	1		0	0	1		0
Significant/very significant impact	1.3146	3.72 [1.78;7.79]		11	–0.3487	0.71 [0.31;1.62]		–13	0.2062	1.23 [0.58;2.58]		94

BDI-II = Beck Depression Inventory II, CI = confidence interval, Coef. = coefficient, EQ-5D = European Quality of Life-5 Dimensions questionnaire, ESS = Epworth Sleepiness Scale, IHSS = Idiopathic Hypersomnia Severity Scale, OR = odds ratio, VAS = visual analog scale.

Table 5—Comparisons of excessive daytime sleepiness, high level of depression, and low health status with IHSS total score and weighted IHSS total score.

Variable	ESS Score			BDI-II Score			EQ-5D-VAS Score		
	< 16 (n = 120), n (%)	≥ 16 (n = 104), n (%)	*P*	< 20 (n = 164), n (%)	≥ 20 (n = 43), n (%)	*P*	≥ 60 (n = 134), n (%)	< 60 (n = 62), n (%)	*P*
Sex			.49			.10			.75
Men	35 (29.17)	26 (25.00)		52 (31.71)	8 (18.60)		36 (26.87)	18 (29.03)	
Women	85 (70.83)	78 (75.00)		112 (68.29)	35 (81.40)		98 (73.13)	44 (70.97)	
Age, in years	31.72 (± 12.53)	32.63 (± 12.07)	.58	33.40 (± 12.11)	29.87 (± 11.66)	.09	32.92 (± 12.03)	32.88 (± 12.62)	.98
Disease duration, y	13.88 (± 10.94)	13.99 (± 11.88)	.94	14.67 (± 10.99)	12.52 (± 11.85)	.26	15.23 (± 11.33)	13.08 (± 11.83)	.23
Treatment			.008			.14			
No	79 (65.83)	85 (81.73)		119 (72.56)	36 (83.72)		96 (71.64)	46 (74.19)	.71
Yes	41 (34.17)	19 (18.27)		45 (27.44)	7 (16.28)		38 (28.36)	16 (25.81)	
IHSS total score[a]	25.90 (± 9.23)	34.01 (± 7.70)	< .0001	28.52 (± 9.45)	35.23 (± 7.12)	< .0001	28.16 (± 8.90)	34.35 (± 7.83)	< .0001
Weighted IHSS total score[a]	15.97 (± 13.22)	32.68 (± 10.06)	< .0001	57.48 (± 52.30)	112.56 (± 32.36)	.002	459.03 (± 456.79)	957.31 (± 471.86)	< .0001

[a]Quantitative variables are expressed as mean (± SD). BDI-II = Beck Depression Inventory II, EQ-5D = European Quality of Life-5 Dimensions questionnaire, ESS = Epworth Sleepiness Scale, IHSS = Idiopathic Hypersomnia Severity Scale, VAS = visual analog scale.

(n = 13, 5.31%); moderate 13–25 (n = 49, 21.88%); severe 26–38 (n = 119, 53.13%); very severe 39–50 (n = 43, 19.20%). The IHSS score category distribution was associated with treatment status: 79.34% of untreated patients were in the severe/very severe categories, but only 20.66% of treated participants (P = .01). The risk of having an ESS score ≥ 16, BDI-II score ≥ 20, and/or EQ-5D-VAS < 60 increased with the IHSS score level in the whole sample (86.05%, 40%, and 58.33%, respectively, for the very severe IHSS group), with similar results in the untreated and treated groups (**Table 6**). When the whole population was divided into 2 groups based on the IHSS score severity (mild/moderate and severe/very severe, using as cut-off a total score ≥ 26), women reported severe/very severe symptoms more frequently than men (73.8% vs 61.3%, P = .02), with no association with age, age at disease onset, disease duration, body mass index, mean sleep latency on the Multiple Sleep Latency Test, and long TST (ie, on the 24- or 32-hour bed-rest recording). A similar analysis in the untreated and treated groups did not highlight any significant difference, except for higher severity score in women in the treated group. Patients with long nighttime sleep (sleep duration > 9 hours or 11 hours; item 1 of the IHSS scale) had higher IHSS total score and total score without item 1, and more frequently severe/very severe symptoms than patients with normal sleep duration in the whole population, and also in untreated and treated patients (data not shown).

DISCUSSION

Our findings indicated that the IHSS is a valid, reliable tool and responsive to treatment in patients with IH, with significantly different numbers of symptoms and IHSS total scores between untreated and treated patients. The estimated MCID for the IHSS score was 4 points. The 4 different IHSS severity levels allowed confirmation of differences in symptom severity as a function of the treatment status and their association with EDS, depression, and health status. Our results also showed that IHSS item weighting is not necessary to show between-group differences. This study also confirmed that IHSS has adequate psychometric properties, and factor analysis indicated a 3-component solution.

IH severity can be variable in terms of symptom (EDS, prolonged nighttime sleep, and sleep inertia) intensity and frequency and their consequences on the daily life. The IHSS[15] allows quantification of symptom severity and their functional consequences in a comprehensive way during the baseline assessment and for monitoring changes in response to treatment. The present study (n = 226 patients with IH, among whom 126 did not participate in the first study) confirmed the good psychometric properties of the IHSS with adequate internal consistency in patients with IH. Unlike the previous study that included patients with IH, narcolepsy, and controls, the present factor analysis indicated a 3-component solution: component I on daytime functioning, component II on long sleep duration and sleep inertia, and component III on napping. IHSS total score, and the components I, II, and III scores correlated with the ESS, BDI-II, and EQ-5D-VAS scores.

Table 6—Probability of having excessive daytime sleepiness, depressive symptoms, and low health status according to the IHSS total score category.

	Whole Sample (n = 226)				Untreated Patients (n = 166)				Treated Patients (n = 60)			
IHSS Total Score	**n**	**%**	**ESS Score ≥ 16 (n)**	**Risk % [95% CI]**	**n**	**%**	**ESS Score ≥ 16 (n)**	**Risk % [95% CI]**	**n**	**%**	**ESS Score ≥ 16 (n)**	**Risk % [95% CI]**
0–12	13	5.80	2	15.38 [1.92–45.45]	6	3.66	1	16.67 [0.42–64.12]	7	11.67	1	14.29 [0.36–57.87]
13–25	49	21.88	9	18.37 [8.76–32.02]	30	18.29	9	30.00 [14.73–49.40]	19	31.67	0	–
26–38	119	53.13	56	47.06 [37.85–56.42]	94	57.32	46	48.94 [38.48–59.46]	25	41.67	10	40.00 [21.13–61.33]
39–50	43	19.20	37	86.05 [72.07–94.70]	34	20.73	29	85.29 [68.94–95.05]	9	15.00	8	88.89 [51.75–99.72]
IHSS Total Score	n	%	BDI-II Score ≥ 20 (n)	Risk % [95% CI]	n	%	BDI-II Score ≥ 20 (n)	Risk % [95% CI]	n	%	BDI-II Score ≥ 20 (n)	Risk % [95% CI]
0–12	11	5.31	1	0.91 [0.23–41.28]	5	3.23	1	20.00 [0.51–71.64]	6	11.54	0	–
13–25	45	21.74	2	4.44 [0.54–15.15]	26	16.77	1	3.85 [0.10–19.64]	19	36.54	1	5.26 [0.13–26.03]
26–38	111	53.62	24	21.62 [14.37–30.44]	91	58.71	21	23.08 [14.89–33.09]	20	38.46	3	15.00 [3.21–37.89]
39–50	40	19.32	16	40.00 [24.86–56.67]	33	21.29	13	39.39 [22.91–57.86]	7	13.46	3	42.86 [9.90–81.59]
IHSS Total Score	n	%	EQ-5D-VAS Score < 60 (n)	Risk % [95% CI]	n	%	EQ-5D-VAS Score < 60 (n)	Risk % [95% CI]	n	%	EQ-5D-VAS Score < 60 (n)	Risk % [95% CI]
0–12	9	4.59	1	11.11 [2.80–48.25]	4	2.82	1	25.00 [0.63–80.59]	5	9.26	0	–
13–25	41	20.92	7	17.07 [7.15–32.06]	24	16.90	3	12.50 [2.66–32.36]	17	31.48	4	23.53 [6.81–49.90]
26–38	110	56.12	33	30.00 [21.63–39.48]	85	59.86	24	28.24 [19.00–39.04]	25	46.30	9	36.00 [17.97–57.48]
39–50	36	18.37	21	58.33 [40.76–74.49]	29	20.42	18	62.07 [42.26–79.31]	7	12.96	3	42.86 [9.90–81.59]

BDI-II = Beck Depression Inventory II, CI = confidence interval, EQ-5D = European Quality of Life-5 Dimensions questionnaire, ESS = Epworth Sleepiness Scale, IHSS = Idiopathic Hypersomnia Severity Scale, VAS = visual analog scale.

Although all IHSS items are assumed to be equal, some patients may consider some items/symptoms more important than others, and this could place in question the ordinality of the IHSS dimension scores. Currently, the number of IHSS items per symptom is different as well as the scoring per item. Therefore, we determined here whether the different IHSS items need to be weighted to best assess IH symptoms. As previous studies showed that patients with IH have severe EDS, depressive symptoms, decreased quality of life, and work and social functioning impairments,[8,19] we asked whether IHSS items should be weighted to highlight IH burden by assessing the strength of the association of each item with other meaningful clinical outcomes (ie, ESS ≥ 16, BDI-II score ≥ 20, and EQ-5D-VAS score < 60). We found that IHSS total score and total weighted score were associated with these clinical outcomes in the unadjusted model and after adjustment for age and treatment group, or disease duration and treatment group. However, the weight of these associations largely varied in the different comparisons, and this did not allow us to establish a robust weighted IHSS score. Thus, IHSS item weighting is not mandatory to highlight between-group differences and to better describe IH severity.

We found that 81% of untreated patients with IH had all 3 IH symptoms, 13% 2 symptoms (EDS with prolonged nighttime sleep or sleep inertia), and 6% only 1 symptom (EDS). Moreover, the number of symptoms was lower in treated than untreated patients, especially EDS. This result was expected because EDS is often treated with off-label stimulants or wake-promoting agents that are used for narcolepsy management.[20,21] Conversely, sleep inertia and prolonged nighttime sleep are rarely targeted with pharmacological treatments.[22,23] We reported changes of IHSS total score before and after medication. IHSS total score was significantly lower (by 4–5 points) in the treated than untreated groups in the cross-sectional and longitudinal samples, with significant changes for components I and III scores in both samples and for component II in the longitudinal sample. Based on 2 distribution-based methods, we suggest use of an MCID of 4 points in patients with IH. Although MCID determination remains controversial with no consensus on the methodology,[24] our estimate may represent a minimum meaningful change considered beneficial and remains useful for interpreting IHSS score differences and for determining sample sizes in future clinical trials. However, we did not include the patient global impression or clinical global impression rating in this study, and we do not know whether treated patients necessarily considered the change with treatment as beneficial. Moreover, the IHSS score may drop further with a drug that treats EDS, prolonged nighttime sleep, and sleep inertia, and not just EDS. When considering each IHSS item, we found between-group differences for 7 and 6 items in the cross-sectional and longitudinal sample, respectively. However, again, as the impact of pharmacological treatments depends on the IH symptoms and the drug mechanisms of action, we do not support the use of a subset of IHSS items but favor its global evaluation for a comprehensive measurement of the multiple aspects of symptoms and consequences in patients with IH. Since the IHSS is sensitive to changes in symptom severity, the scale could potentially be useful in initial and follow-up evaluations to monitor and optimize management of IH.

We have also proposed 4 equal ranks to define disease severity categories as a function of the IHSS total score (mild, moderate, severe, and very severe) and to specify the heterogeneity of the population and the percentage of patients in these categories according to their treatment. Accordingly, the proportion of patients in these 4 groups differed between treated and untreated conditions in the cross-sectional and longitudinal samples, with higher numbers of untreated patients in the severe and very severe categories. However, additional research is needed to validate optimal cut-off scores to determine the clinical significance of treatment outcome. Also, the probability of having severe sleepiness, moderate-to-severe depressive symptoms, and low health status increased with the IHSS severity level. Patients with long nighttime sleep (self-reported duration > 9 hours or ≥ 11 hours per night) and women had higher IHSS total score and were more often in the severe/very severe categories. A recent clinical study showed that compared with men, women more frequently reported excessive quantity of sleep assessed by ≥ 9 hours per night or ≥ 11 hours per 24 hours during week-days and weekends.[25] Also, another study in the general population reported that a long sleep period was reported more frequently by women than men.[26] However, we did not find an association between objective assessment of long sleep duration, IHSS total score, and IHSS severity level.

Our results indicate that IHSS fits an unmet need for outcome measures, clinically and for research. IHSS is sensitive to changes in symptom severity in well characterized patients with IH evaluated and managed in a reference center for rare hypersomnolences. Nonpharmacological and pharmacological interventions are useful in patients with IH[19]; however, they do not fully treat IH symptoms, particularly in patients who receive only stimulants and wake-promoting agents. We hope that the self-reporting character of IHSS will help patients become actively involved in the assessment and quantification of the main complaints and in treatment decisions and goals. IHSS is restricted to the 3 main IH symptoms and does not include other symptoms of the IH spectrum, such as fatigue, brain fog, cognitive complaints, and depressive symptoms. Other complementary patient-reported outcome scales could be developed to take into account the full IH spectrum. The IHSS has been translated into English and validated, is hosted by the MAPI Research Institute, which distributes the scale and provides a central clearinghouse for all current and future copywrited translations, and may be used following appropriate permissions or licensure. More studies using the IHSS need to be carried out to quantify the severity and consequences of IH symptoms over time, after treatment, or relative to the disease natural history (long-term stability, worsening, or spontaneous improvement).[27–29] Additional research is needed to determine IHSS comprehensiveness and applicability and to validate optimal cutoffs to determine the clinical significance of the complaints and the minimal score change associated with successful treatment to other potentially less severe IH populations or those with comorbid conditions, and also in other sleep centers. Also, the IHSS should be tested in other central hypersomnolence

disorders, especially in narcolepsy type 2, that share some features with IH.[30,31]

In conclusion, the IHSS is a valid and reliable tool to quantify IH symptoms and their consequences, with 4 clinically relevant severity levels. The IHSS has adequate psychometric properties for continued use and the 14 items do not need to be weighted. IHSS is sensitive to detect clinical changes in symptoms after treatment. We recommend its use in clinical settings for initial and follow-up evaluations, to monitor and optimize IH management, and in future trials.

ABBREVIATIONS

BDI-II, Beck Depression Inventory II
EDS, excessive daytime sleepiness
EQ-5D-VAS, European Quality of Life-5 Dimensions visual analog scale
ESS, Epworth Sleepiness Scale
IH, idiopathic hypersomnia
IHSS, Idiopathic Hypersomnia Severity Scale
MCID, minimum clinically important difference
SD, standard deviation
TST, total sleep time

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DISCLOSURE STATEMENT

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