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Psychometric Evaluation of the Idiopathic Hypersomnia Severity Scale

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Introduction

- Idiopathic hypersomnia is a debilitating neurologic sleep disorder characterized by chronic excessive daytime sleepiness (EDS; the inability to stay awake and alert during the day, resulting in the irrepressible need to sleep or unplanned lapses into sleep or drowsiness).[1-3] In addition to EDS, symptoms may include severe sleep inertia (prolonged difficulty waking with frequent reentries into sleep, confusion, and irritability), a core symptom of idiopathic hypersomnia, as well as prolonged nighttime sleep, cognitive impairment, and long and unrefreshing naps[2,3]
- The Idiopathic Hypersomnia Severity Scale (IHSS) is a 14-item instrument that assesses the severity and impact of idiopathic hypersomnia symptoms. Items are scored using a 3- or 4-point Likert-type scale. Prior research demonstrated that the tool is sensitive to clinical changes following treatment[4,5]
  - The IHSS was developed in French and validated in French-speaking participants; subsequently, an English translation was developed, necessitating validation in a broader population[4]
- Change in IHSS total score during a randomized withdrawal period was a key secondary endpoint in a phase 3, double-blind, placebo-controlled study of lower-sodium oxybate (LXB) in adults with idiopathic hypersomnia (NCT03533114)[5]

Objectives

- Evaluate the psychometric properties of the IHSS total score
- Inform a meaningful within-patient change (MWPC) threshold for the IHSS total score

Methods

- The psychometric analysis used data from the phase 3 clinical trial evaluating the efficacy and safety of LXB in the treatment of idiopathic hypersomnia,[5] but was conducted independently of the trial's outcomes
- The phase 3 clinical study design included an open-label titration and optimization period (OLT; 10–14 weeks), a stable-dose period (SDP; 2 weeks), a double-blind randomized withdrawal period (DBRWP; 2 weeks), and an open-label extension (24 weeks)[5]
  - Clinical outcome assessments included in these analyses, besides the IHSS, were the Epworth Sleepiness Scale (ESS); Patient Global Impression of Change (PGIc); Clinical Global Impression of Change (CGIc); Functional Outcomes of Sleep Questionnaire, short version (FOSQ-10); and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)
- The IHSS total score, calculated as the sum across the 14 items, ranges from 0 to 50, with higher scores reflecting more severe symptoms and impacts from idiopathic hypersomnia[4]
  - In these analyses, the IHSS total score at a given timepoint was recorded as "missing" for participants with ≥4 missing item responses at that timepoint; for participants with ≤3 missing item responses, scores for the missing items were imputed
- The psychometric analysis population (PsAP; blinded to treatment) comprised clinical study participants (18–75 years of age; idiopathic hypersomnia diagnosis) from the modified intent-to-treat population (participants who were randomized to LXB or placebo, received ≥1 dose of randomized study drug, and had ≥1 set of post-randomization scores for ESS, IHSS, and PGIc) who had ≥1 non-missing response on the IHSS at any assessment time point (baseline, OLT week [W]1 and W8, end of OLT [eOLT], eSDP, and eDBRWP)
- Psychometric analyses were conducted to evaluate reliability (internal consistency and test-retest reliability) and construct-related validity (convergent/discriminant validity, known-groups methods, and ability to detect change) of the IHSS total score across assessment timepoints
- Distribution- and anchor-based analyses were conducted to inform MWPC interpretation thresholds related to worsening of idiopathic hypersomnia symptoms

Results

Table 1. IHSS Total Score Reliability Estimates

Internal Consistency						
Cronbach's alpha	**Baseline n=115**	**OLT W1 n=114**	**OLT W8 n=114**	**eOLT n=115**	**eSDP n=115**	**eDBRWP n=115**
	0.82	0.86	0.90	0.89	0.89	0.90
Test-Retest Reliability						
ICC estimate (95% CI)[a]	**Baseline to OLT W1 n=59[b]**		**Beginning of SDP to eSDP n=98[b]**		**eSDP to eDBRWP n=62[b]**	
	0.90 (0.81, 0.95)		0.89 (0.83, 0.93)		0.81 (0.69, 0.89)	

CI, confidence interval; eDBRWP, end of double-blind randomized withdrawal period; eOLT, end of open-label titration and optimization period; eSDP, end of stable-dose period; ESS, Epworth Sleepiness Scale; ICC, intraclass correlation coefficient; IHSS, Idiopathic Hypersomnia Severity Scale; OLT, open-label titration and optimization period; SDP, stable-dose period; W, week.
[a]ICCs were computed using single-measurement, absolute-agreement, 2-way mixed-effects models.
[b]A stable population was defined as participants with the same ESS severity level at both timepoints included in each retest analysis (ie, baseline to OLT W1, beginning of SDP to eSDP, and eSDP to eDBRWP).

- The IHSS demonstrated good internal consistency (Cronbach's alpha ≥0.80 at all timepoints)
- The IHSS total score demonstrated acceptable test-retest reliability (intraclass correlation coefficients >0.8) for a stable population defined as participants with the same ESS severity level across selected timepoints

- The PsAP included 115 participants (mean [SD] age, 40.9 [13.9] years; 71.3% female; 80.9% White; 79.1% non-Hispanic)
- IHSS total scores decreased (indicating improvement) with open-label LXB treatment (baseline to eSDP), then increased during DBRWP in participants randomized to placebo but remained stable in participants randomized to continue LXB treatment[5]

Table 2. IHSS Total Score Convergent/Discriminant Validity

Concurrent Assessment	Spearman Correlation (Correlation Coefficient ρ) With IHSS Total Score at eDBRWP
ESS (n=115)	0.717
PGIc (n=115)	0.589
CGIc (n=115)	0.610
FOSQ-10 (n=112)	–0.835
WPAI:SHP percent of time missed (n=79)[a]	0.357
WPAI:SHP percent of impairment while working (n=80)[a]	0.783
WPAI:SHP percent of overall impairment (n=79)[a]	0.817
WPAI:SHP percent of activity impairment (n=112)	0.799

CGIc, Clinical Global Impression of Change; eDBRWP, end of double-blind randomized withdrawal period; ESS, Epworth Sleepiness Scale; FOSQ-10, Functional Outcomes of Sleep Questionnaire, short version; IHSS, Idiopathic Hypersomnia Severity Scale; PGIc, Patient Global Impression of Change; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.
[a]WPAI:SHP items relating to work productivity were completed by employed participants.

- Spearman correlations between IHSS total score and other efficacy measures within the trial were moderate to strong (>0.3 in expected directions), demonstrating acceptable convergent/discriminant validity

Table 3. IHSS Total Score Known-Groups Methods by Sleepiness Severity Level at eDBRWP

ESS Severity Group[a]	n	IHSS Total Score		
		Mean (SD)	Median	*P* Value[b]
Normal	58	16.3 (7.6)	15.0	<0.001
Mild/Moderate	37	28.0 (6.7)	28.0	
Severe	20	32.4 (9.9)	31.0	

eDBRWP, end of double-blind randomized withdrawal period; ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; SD, standard deviation.
[a]Normal (score 0–10), mild/moderate (11–15), severe (16–24).
[b]*P* value is from Kruskal-Wallis test comparing distributional differences among groups.

- Mean and median IHSS total scores in the normal ESS severity group were lower than those in the mild/moderate and severe ESS severity groups. The difference among groups was statistically significant, supporting acceptable known-groups validity

Table 4. IHSS Total Score Ability to Detect Change

eSDP, Mean (SD)	eDBRWP, Mean (SD)	Change, Mean (SD)	Cohen's *d*[a]
15.3 (8.5)	22.9 (10.3)	7.5 (9.8)	0.89

eDBRWP, end of double-blind randomized withdrawal period; eSDP, end of stable-dose period; IHSS, Idiopathic Hypersomnia Severity Scale; SD, standard deviation.
[a]Cohen's *d* effect size statistic is calculated by taking the mean change of the target assessment scores and dividing that by the SD of those scores at the earlier timepoint.

- High sensitivity of the IHSS total score was confirmed by a large effect size

- Anchor-based assessments showed that IHSS total scores were sensitive to MWPCs in ESS severity and CGIc and PGIc ratings
- Distribution-based assessments reflect appropriate between-group differences underpinned by differences that are the lesser of 0.5 multiplied by the baseline SD or by the standard error of measurement. The results (not shown) demonstrated that differences in IHSS total scores of 2 points or less are more likely to be due to random error than real change
- Distribution- and anchor-based assessments converged on an MWPC threshold of ≥3 points for IHSS total score

Conclusions

- The IHSS total score can be used to measure idiopathic hypersomnia symptom severity and change over time (eg, change with treatment)
- The IHSS total score is reliable and construct valid
- Converging evidence from distribution- and anchor-based analyses suggests that a 3-point change in the IHSS total score represents meaningful within-patient change for this scale

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