006 Characteristics and Disease Burden of Patients With Idiopathic Hypersomnia With and Without Long Sleep Time: The Real World Idiopathic Hypersomnia Outcomes Study (ARISE)

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Introduction

- Idiopathic hypersomnia is a debilitating neurologic sleep disorder characterized by chronic excessive daytime sleepiness (EDS).[1-3] In addition to EDS, symptoms may include severe sleep inertia (prolonged difficulty waking with frequent reentries into sleep, confusion, and irritability), as well as cognitive impairment, long and unrefreshing naps, and prolonged nighttime sleep[1,3]
- Limited information is available on the burden of symptoms in patients with idiopathic hypersomnia, and particularly how the experience may differ among those with long sleep time (LST; characterized as ≥11 hours in a 24-hour period in the *International Classification of Sleep Disorders*, 3rd Edition [ICSD-3])[1]
  - The ICSD-2 previously recognized a separate subtype of patients with idiopathic hypersomnia who sleep >10 hours at night, but this distinction was later removed in the ICSD-3, where criteria included patients both with and without LST[1,4]
- No treatment was US Food and Drug Administration (FDA) approved for idiopathic hypersomnia at the time of the study; low-sodium oxybate received FDA approval for adults with idiopathic hypersomnia in August 2021[5-8]
- The Real World Idiopathic Hypersomnia Outcomes Study (ARISE) evaluated the impact of idiopathic hypersomnia on patients' lives and patient perspectives regarding their current treatment

Objective

- To assess symptoms, functioning, quality of life, and treatment satisfaction in ARISE participants with idiopathic hypersomnia with or without LST

Methods

- Eligible ARISE participants included adults 21–65 years of age with idiopathic hypersomnia with or without LST (≥11 hours of sleep in a 24-hour period [self-reported])
- ARISE was a US-based virtual cross-sectional survey comprising multiple patient-reported outcome measures assessing:
  - Symptom severity (Epworth Sleepiness Scale [ESS]; Idiopathic Hypersomnia Severity Scale [IHSS])
  - Daily functioning (Functional Outcomes of Sleep Questionnaire, short version [FOSQ-10])
  - Quality of life (Neuro-QoL [Quality of Life in Neurological Disorders])
  - Cognition (British Columbia Cognitive Complaints Inventory [BC-CCI])
  - Depression (Patient Health Questionnaire-9 [PHQ-9])
  - Work/Activity impairment (Work Productivity and Activity Impairment Questionnaire: Specific Health Problem, v2.0 [WPAI:SHP])
  - Treatment satisfaction (Treatment Satisfaction Questionnaire for Medication, version II [TSQM-vII])
- Continuous variables were summarized with descriptive statistics (n, mean, standard deviation [SD], median, quartiles, minimum, and maximum). Frequency counts and percentage of participants within each category were provided for categorical data

References: 1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014. **2.** Billiard M, Sonka K. *Sleep Med Rev*. 2016;29:23-33. **3.** Trotti LM. *Sleep Med Clin*. 2017;12:331-44. **4.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders: Diagnostic and Coding Manual*. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005:98-105. **5.** XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals. **6.** Szarfman A, et al. *N Engl J Med*. 1995;333(19):1291. **7.** US Food and Drug Administration. Clinical Review for Binosto, NDA 202344. 2011. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf. **8.** US Food and Drug Administration. Quantitative Labeling of Sodium, Potassium, and Phosphorus for Human Over-the-Counter and Prescription Drug Products. Guidance for Industry. 2022. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quantitative-labeling-sodium-potassium-and-phosphorus-human-over-counter-and-prescription-drug. **9.** Johns MW. *Sleep*. 1991;14:540-5. **10.** Dauvilliers Y, et al. *Neurology*. 2019;92:e1754-e62. **11.** Chasens ER, et al. *Sleep*. 2009;32:915-9. **12.** National Institute of Neurological Disorders and Stroke (NINDS). *User Manual for the Quality of Life in Neurological Disorders (Neuro-QoL) Measures, Version 2.0*. Bethesda, MD: National Institute of Neurological Disorders and Stroke; 2015. **13.** Reilly MC, et al. *Pharmacoeconomics*. 1993;4:353-65. **14.** Reilly Associates. *WPAI Scoring*. 2022. Available at: http://www.reillyassociates.net/WPAI_Scoring.html. **15.** Atkinson MJ, et al. *Health Qual Life Outcomes*. 2004;2:12.

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Results

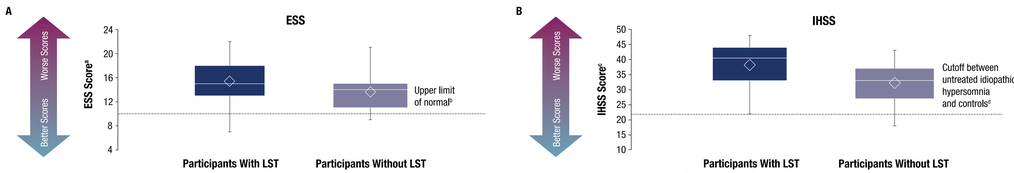
Table 1. Demographics and Participant Characteristics

Characteristic	Participants With LST (n=37)	Participants Without LST (n=38)	All Participants (N=75)
Age, years, mean (SD)	33.7 (10.7)	34.4 (10.9)	34.1 (10.7)
Female, n (%)	27 (73.0)	34 (89.5)	61 (81.3)
Time since idiopathic hypersomnia diagnosis, years, n (%)			
<2	5 (13.5)	7 (18.4)	12 (16.0)
2–4	20 (54.1)	14 (36.8)	34 (45.3)
5–9	8 (21.6)	10 (26.3)	18 (24.0)
≥10	4 (10.8)	7 (18.4)	11 (14.7)
Patient-reported sleep duration, mean (SD)			
Approximate hours of sleep in a typical 24-hour period	14.3 (2.7)	8.9 (1.1)	11.6 (3.4)
Approximate hours of sleep in a typical night	9.8 (1.7)	8.0 (0.8)	8.9 (1.6)
Approximate hours of sleep in a typical day	4.5 (2.9)	0.9 (1.0)	2.7 (2.8)
Taking off-label medications for idiopathic hypersomnia, n (%)	36 (97.3)	31 (81.6)	87 (89.3)

LST, long sleep time; SD, standard deviation.

- Seventy-five participants enrolled with a mean (SD) age of 34.1 (10.7) years; most were female and most were taking medications for idiopathic hypersomnia
- More participants with LST reported taking off-label medications than those without LST

Figure 1. Participants Reported High Levels of Sleepiness and Other Idiopathic Hypersomnia Symptoms on the (A) ESS and (B) IHSS, and Even Higher Levels Were Reported by Participants With LST

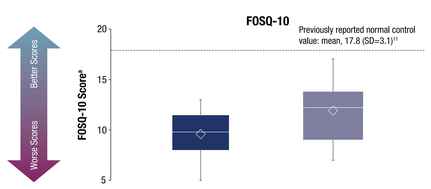


	Participants With LST	Participants Without LST
ESS		
n=	37	38
Mean (SD)=	15.4 (3.8)	13.6 (3.0)
Median (Q1, Q3)=	15.0 (13, 18)	14.0 (11, 15)
Min, max=	7, 22	9, 21
IHSS		
n=	36	37
Mean (SD)=	38.2 (7.1)	32.2 (7.0)
Median (Q1, Q3)=	40.5 (33, 44)	33.0 (27, 37)
Min, max=	22, 48	18, 43

The bottom and top edges of the box indicate Q1 and Q3, the line inside the box is the median, and the marker inside the box is the mean. The whiskers extending from the box indicate the minimum and maximum values.
[a]Range of possible ESS scores is 0–24; higher scores indicate greater sleepiness.
[b]ESS scores of >10 suggest pathologic sleepiness.[9]
[c]Range of possible IHSS scores is 0–50; higher scores indicate greater symptom severity.
[d]IHSS scores of ≥22 are a cutoff separating untreated patients with idiopathic hypersomnia from controls.[10]
ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; LST, long sleep time; Q1, first quartile; Q3, third quartile; SD, standard deviation.

- ESS scores >10 were reported by 89.2% of participants with LST and 86.8% of participants without LST
- IHSS scores ≥22 were reported by 100% of participants with LST and 91.9% of participants without LST

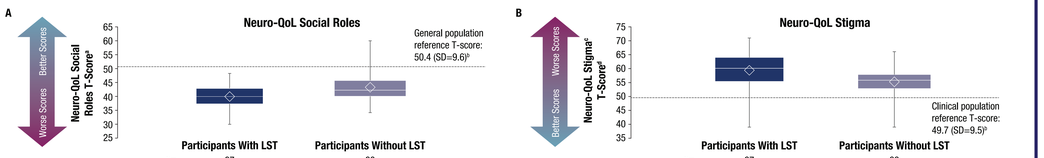
Figure 2. Participants Reported Impairments in Daily Functioning, Which Were Greater in Those With LST



	Participants With LST	Participants Without LST
n=	33	34
Mean (SD)=	9.6 (2.3)	11.9 (2.8)
Median (Q1, Q3)=	9.8 (8.0, 11.5)	12.2 (9.0, 13.8)
Min, max=	5, 13	7, 17

The bottom and top edges of the box indicate Q1 and Q3, the line inside the box is the median, and the marker inside the box is the mean. The whiskers extending from the box indicate the minimum and maximum values.
[a]Range of possible FOSQ-10 scores is 5–20; lower scores indicate worse impairment.
FOSQ-10, Functional Outcomes of Sleep Questionnaire, short version; LST, long sleep time; Q1, first quartile; Q3, third quartile; SD, standard deviation.

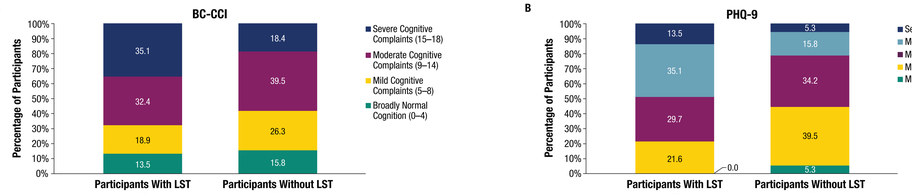
Figure 3. Participants Reported (A) a Low Ability to Participate in Social Roles and Activities and (B) a High Perception of Stigma; Participants With LST Reported Greater Impairment in These Domains



	Participants With LST	Participants Without LST
Neuro-QoL Social Roles		
n=	37	38
Mean (SD)=	39.8 (4.3)	43.0 (5.3)
Median (Q1, Q3)=	39.9 (37.1, 42.7)	42.0 (39.9, 45.3)
Min, max=	30, 48	34, 60
Neuro-QoL Stigma		
n=	37	38
Mean (SD)=	59.4 (6.1)	55.2 (4.9)
Median (Q1, Q3)=	60.1 (55.4, 64.0)	55.8 (52.8, 57.8)
Min, max=	39, 71	39, 66

The bottom and top edges of the box indicate Q1 and Q3, the line inside the box is the median, and the marker inside the box is the mean. The whiskers extending from the box indicate the minimum and maximum values.
[a]Range of possible T-scores for social roles is 24.1–60.2; higher scores indicate better outcomes.
[b]T-score distributions rescale raw scores into standardized scores with approximate mean (SD) of 50 (10).[12]
[c]Perceptions of self and publicly enacted negativity, prejudice, and discrimination as a result disease-related manifestations.
[d]Range of possible T-scores for stigma is 39.2–81.5; higher scores indicate worse outcomes.
LST, long sleep time; Neuro-QoL, Quality of Life in Neurological Disorders; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Figure 4. Participants, Especially Those With LST, Often Reported (A) Severe Cognitive Complaints and (B) Moderate to Severe Depressive Symptoms

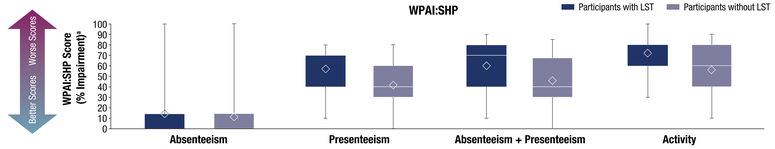


	Participants With LST	Participants Without LST
BC-CCI		
n=	37	38
Mean (SD)=	11.6 (4.9)	10.1 (4.6)
Median=	13.0	10.5
Min, max=	2, 18	2, 18
PHQ-9		
n=	37	38
Mean (SD)=	14.1 (5.2)	10.6 (5.1)
Median=	14.0	10.0
Min, max=	5, 26	2, 25

BC-CCI, British Columbia Cognitive Complaints Inventory; LST, long sleep time; PHQ-9, Patient Health Questionnaire-9; SD, standard deviation.

- Moderate to severe cognitive impairment was reported by 67.6% of participants with LST and 57.9% of participants without LST
- Moderate to severe depressive symptoms were reported by 78.4% of participants with LST and 55.3% of participants without LST

Figure 5. Participants Reported Presenteeism and Impairments in Overall Work Productivity (Absenteeism + Presenteeism) and Activity; Greater Impairments Were Reported by Those With LST

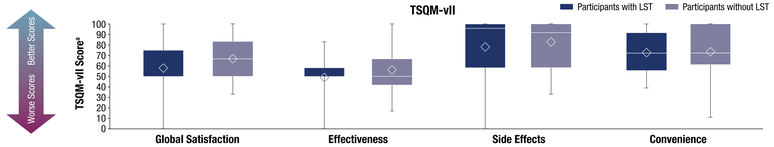


	Absenteeism		Presenteeism		Absenteeism + Presenteeism		Activity	
n=	22	34	21	33	21	33	37	38
Mean (SD)=	14.2 (26.5)	11.1 (21.8)	57.1 (21.9)	41.5 (21.4)	60.1 (24.1)	45.8 (23.8)	72.2 (17.3)	56.1 (23.2)
Median (Q1, Q3)=	0 (0, 14.3)	0 (0, 14.3)	70 (40, 70)	40 (30, 60)	70 (40, 80)	40 (30, 67.4)	80 (60, 80)	60 (40, 80)
Min, max=	0, 100	0, 100	10, 80	0, 80	10, 90	0, 85	30, 100	10, 90

The bottom and top edges of the box indicate Q1 and Q3, the line inside the box is the median, and the marker inside the box is the mean. The whiskers extending from the box indicate the minimum and maximum values.
[a]Range of possible scores for the WPAI:SHP is 0–100, with greater numbers indicating greater impairment.[13,14]
LST, long sleep time; Q1, first quartile; Q3, third quartile; SD, standard deviation; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

- Average absenteeism was >10%, which was lower than presenteeism; this suggests that work impairment in participants with idiopathic hypersomnia manifests as decreased productivity while at work rather than lost work time, although absenteeism greater than 10% is still a concern

Figure 6. Participants Reported Low Satisfaction With the Effectiveness of Off-label Treatments



	Global Satisfaction		Effectiveness		Side Effects		Convenience	
n=	36	31	36	31	36	31	36	31
Mean (SD)=	57.9 (21.4)	66.7 (20.3)	49.1 (16.6)	56.2 (19.7)	78.2 (27.6)	82.8 (21.7)	72.8 (20)	73.5 (22.3)
Median=	50	66.7	50	50	95.8	91.7	72.2	72.2
Q1, Q3=	50, 75	50, 83.3	50, 58.3	41.7, 66.7	58.3, 100	58.3, 100	55.6, 91.7	61.1, 100
Min, max=	0, 100	33, 100	0, 83	17, 100	0, 100	33, 100	39, 100	11, 100

The bottom and top edges of the box indicate Q1 and Q3, the line inside the box is the median, and the marker inside the box is the mean. The whiskers extending from the box indicate the minimum and maximum values.
[a]Range of possible scores is 0–100, with greater numbers indicating higher satisfaction; a poor appraisal of health was previously found to correspond to mean scores of 64.8 (global satisfaction), 63.3 (effectiveness), 75.8 (side effects), and 83.3 (convenience).[15]
LST, long sleep time; Q1, first quartile; Q3, third quartile; SD, standard deviation; TSQM-vII, Treatment Satisfaction Questionnaire for Medication, version II.

- Participants with LST reported lower average ratings on global satisfaction and treatment effectiveness scales than those without LST
- Treatment effectiveness was scored the lowest across all groups of participants

Conclusions

- ARISE participants with idiopathic hypersomnia reported high levels of sleepiness; impaired daily functioning, cognition, and mood; poor quality of life; and impaired work productivity/activity levels, despite the majority of participants taking off-label treatments
- In this survey, individuals with idiopathic hypersomnia reported substantial disease burden regardless of phenotype
- These findings from ARISE help to more clearly define the symptom burden of idiopathic hypersomnia, important for evaluating the impact of therapeutic options

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