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A Clinical Wake Up Call: Diagnostic Strategies and Novel Therapies in Idiopathic Hypersomnia

Supported by an educational grant from Jazz Pharmaceuticals

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Learning Objective 1

Recognize the QoL, functional, and clinical impact of IH to strengthen dialogues with patients

Audience Response

When evaluating a patient with idiopathic hypersomnia, how important is it to assess the quality of life and functional impact of IH?

A. Not important at all
B. Somewhat important
C. Important
D. Extremely important

Voice of the Patient:

The Impact of IH

Excessive Daytime Sleepiness vs. Hypersomnia

	Excessive Daytime Sleepiness	Hypersomnia
Complaint	**Excessive Daytime Sleepiness** Inability to stay awake during the day • Feeling of daytime sleepiness most of the day • Sleep attacks • Naps (planned or not) • Automatic behaviour, attention problems…	**Hypersomnia** Increased need for sleep • At night: > 9-10h ? • During day: > 1h ? • Night and Day: >11h ? • Sleep inertia
Causes	NT1, NT2, IH, OSAS, sleep deprivation…	IH, long sleepers, depression? …

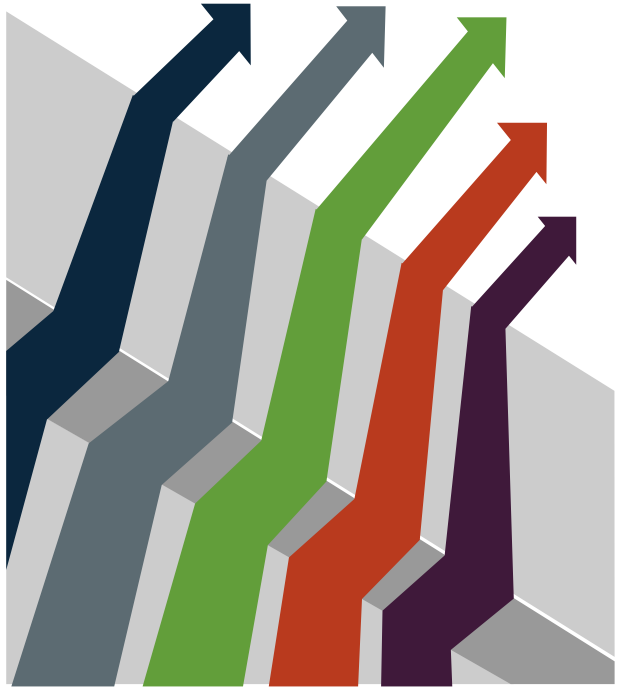
IH = idiopathic hypersomnia; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2; OSAS = obstructive sleep apnea syndrome

Daily Symptoms Reported by Patients with IH with and without Long Sleep Time

	Idiopathic hypersomnia with long sleep (n = 240)	Idiopathic hypersomnia without long sleep (n = 228)	*p* value
Excessive daytime sleepiness	235 (97.9%)	222 (97.4%)	.70
Intentional napping	154 (64.2%)	96 (42.1%)	< .0001
Unintentional daytime sleep	95 (39.8%)	74 (32.5%)	.10
Requiring multiple alarms to awaken	186 (77.5%)	140 (61.7%)	.0002
Having trouble waking up and functioning with normal alertness	211 (88.3%)	158 (69.3%)	< .0001
Brain fog (being unable to think clearly or concentrate at any time throughout the day)	205 (86.9%)	175 (78.1%)	.01
Difficulty remembering things	170 (73.3%)	156 (70.3%)	.48
Automatic behaviors	54 (23.8%)	46 (21.6%)	.58

Trotti LM, et al. *Sleep Med*. 2020;75:343-349.

The Impact of IH on the Individual



35% Do not feel they receive support from friends or family

26% Dismissed from their jobs or forced to relocate due to their symptoms

21% Do not feel they have autonomy over their work schedule

13% Divorced or broke up with a partner because of their condition

Trotti LM. *Sleep Med Clin*. 2017;12(3):331-344.; Arnulf I, et al. *Sleep Med Clin*. 2019;14(3):333-350.

Voice of the Family:

The Impact of IH

The Impact of IH on the Family and Society

Inability to wake up, maintain energy for chores/responsibilities alone creates sense of dependence

Responsibilities requiring unscheduled waking (i.e., caring for infants at night) can be extremely difficult

Sleep inertia can affect family routines (i.e., waking/ dressing children for school)

Risk of falling asleep at the wheel may make driving uncomfortable and increase risk of accidents

Arnulf I, et al. *Sleep Med Clin*. 2019;14(3):333-350.; Trotti LM, et al. *Sleep Med Clin*. 2020;75:343-349.; Billiard M, et al. *Sleep Med Rev.* 2016;29:23-33.; Pizza F, et al. *PLoS One.* 2015;10(6):e0129386.

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Learning Objective 2

Apply best practices to accurately diagnose IH

Audience Response

How confident are you in accurately diagnosing idiopathic hypersomnia?

A. Not confident at all
B. Somewhat confident
C. Confident
D. Extremely confident

Voice of the Patient:

The Diagnostic Journey

Differential Diagnosis of IH

- Narcolepsy (NT2)
- Delayed sleep-wake phase disorder
- Obstructive sleep apnea
- Long sleepers

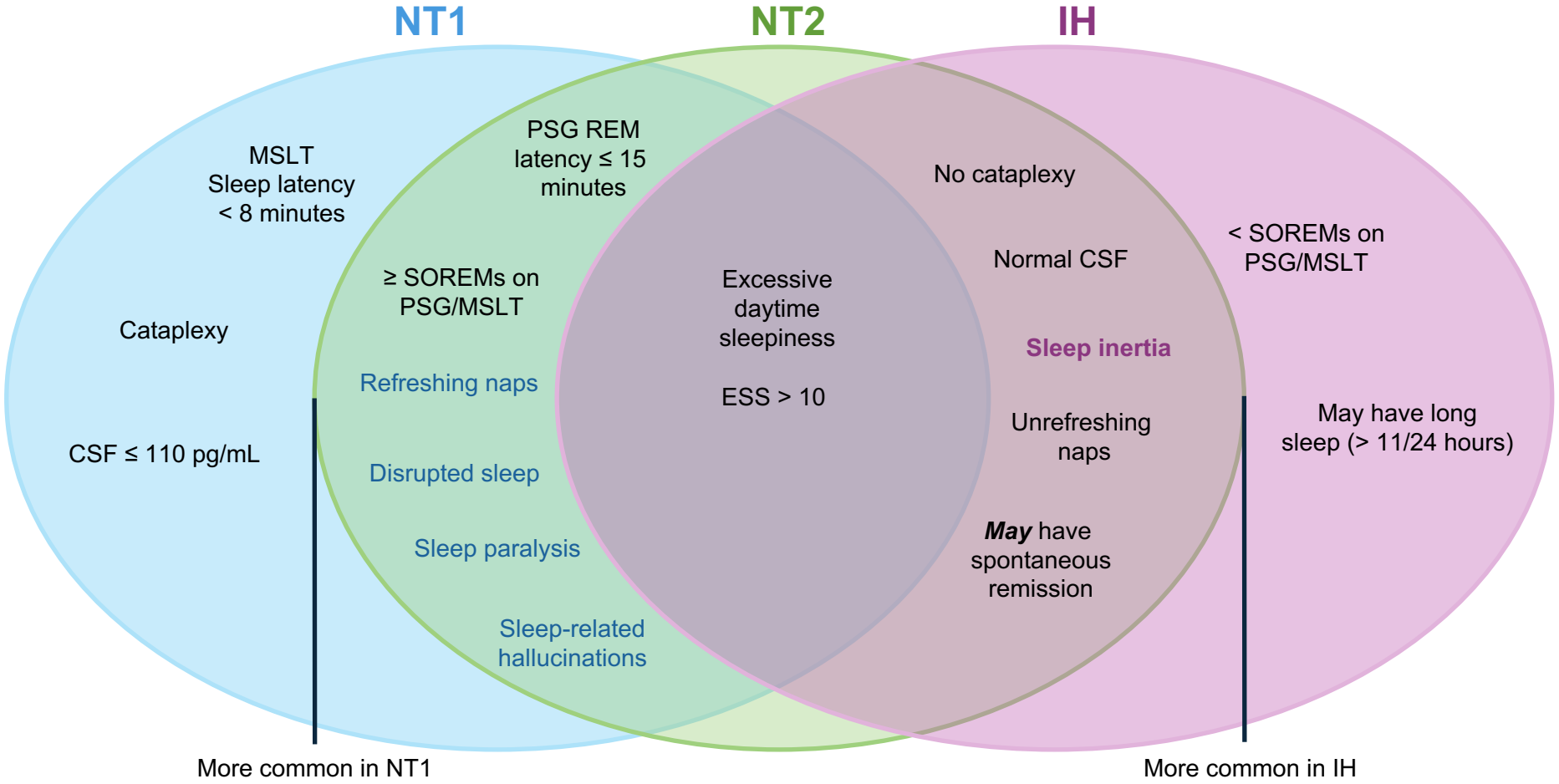
- Mood disorders
- Somatoform disorders
- Sedative, hypnotic, anxiolytic use disorder

- Sedating medications
- Withdrawal from amphetamines or other stimulants

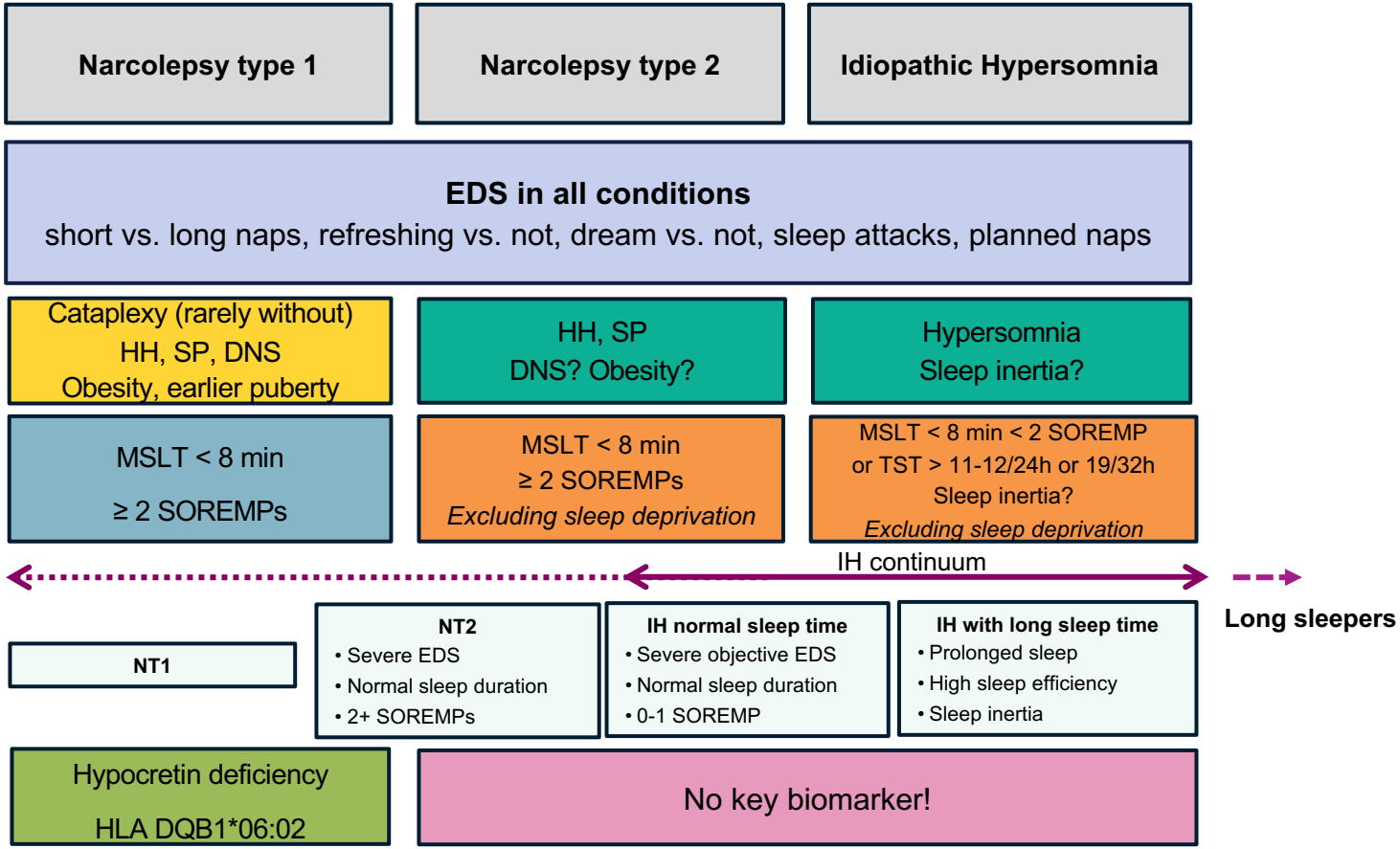
- Traumatic brain injury
- Chronic fatigue syndrome

Trotti LM. *Sleep Med Clin*. 2017; 12(3):331–344.

Differentiating IH from Narcolepsy Type 1 and Type 2



CSF = cerebrospinal fluid; ESS = Epworth Sleepiness Scale; MSLT = Multiple Sleep Latency Test; PSG = polysomnography; REM = rapid eye movement; SOREMs = sleep onset REM



Courtesy of Yves Dauvilliers, MD, PhD

DNS = disrupted nighttime sleep; HH = hypnagogic hallucinations; SP = sleep paralysis; TST = total sleep time

IH Diagnosis: ICSD-3 Criteria

A. **Daily periods of irrepressible need to sleep or daytime lapses into sleep, present for at least 3 months**

B. Fewer than two SOREMPs on MSLT
(or fewer than one if nocturnal REM latency was ≤ 15 min)

C. No cataplexy

D. At least one of the following:

1. Mean sleep latency ≤ 8 min on MSLT
2. **Total 24-h sleep time ≥ 660 min on 24-h PSG or wrist actigraphy (averaged over ≥ 7 days)**

E. Insufficient sleep syndrome is ruled out

F. The hypersomnolence and/or MSLT findings are not better explained by other causes

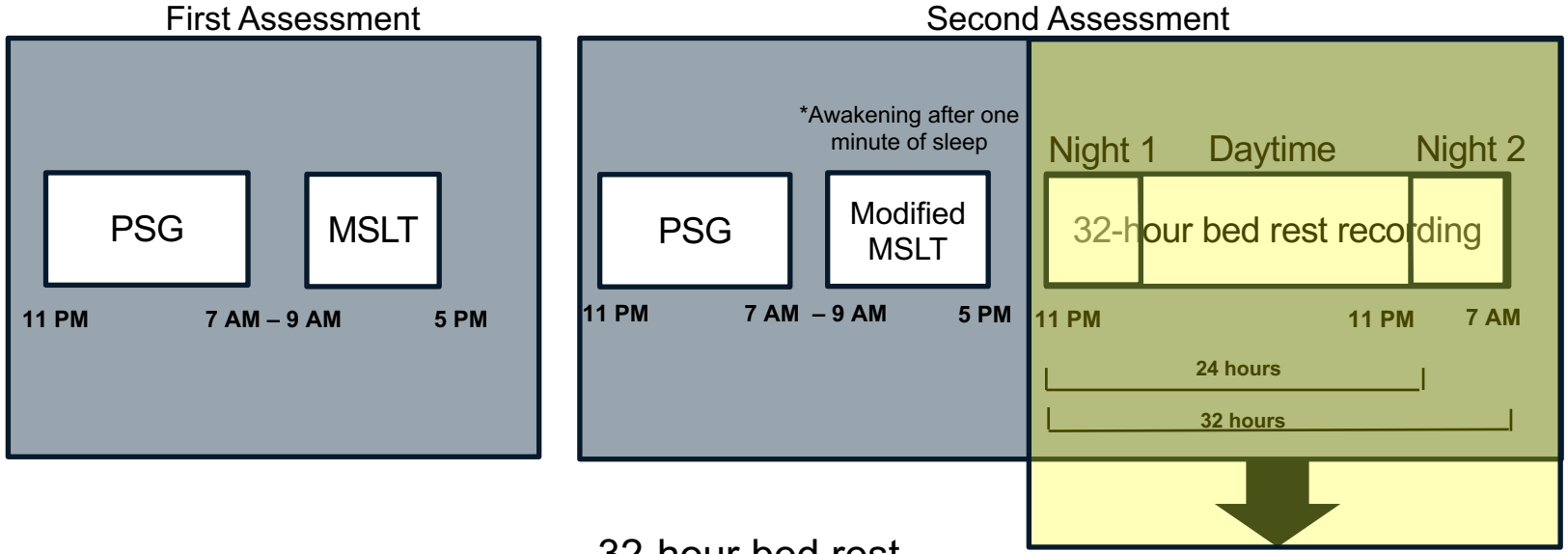
Sateia MJ. *Chest.* 2014;146(5):1387-1394.

IH Diagnostic Challenges

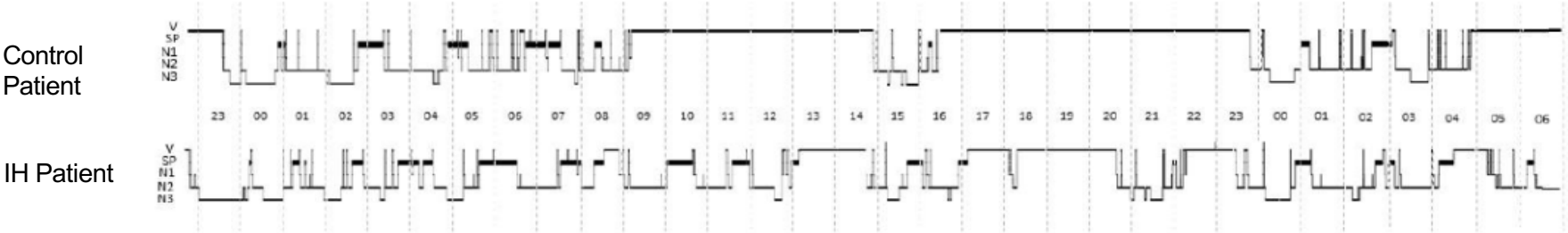
- IH vs. narcolepsy
  - Daily periods of irrepressible need to sleep or daytime lapses into sleep present for at least 3 months → same in IH, NT1, and NT2 (ICSD-3)
- SOREMPS are variable between tests
- Diagnostic tools
  - PSG is rarely performed to measure maximal sleep amount
  - MSLT assesses daytime sleep propensity, not sleep inertia / long sleep time
  - Challenges in how to assess sleep inertia
  - Wrist actigraphy accuracy may vary by degree of sleep efficiency; most accurate when sleep efficiency is high
- Few studies recorded patients with 24-hr protocol recording
  - With different protocols, it is not always standardized
  - Limitations in defining a pathological threshold for IH

Sateia MJ. *Chest.* 2014;146(5):1387-1394.; Lopez R, et al. *Sleep*. 2017;40(12); Alakuijala A, et al. *Front Neurol*. 2021;12:629709.; Pizza F, et al. *J Sleep Res*. 2013;22(1):32-40.; Evangelista E, et al. *Sleep*. 2022;45(1):zsab220.

32-Hour Assessment of Idiopathic Hypersomnia



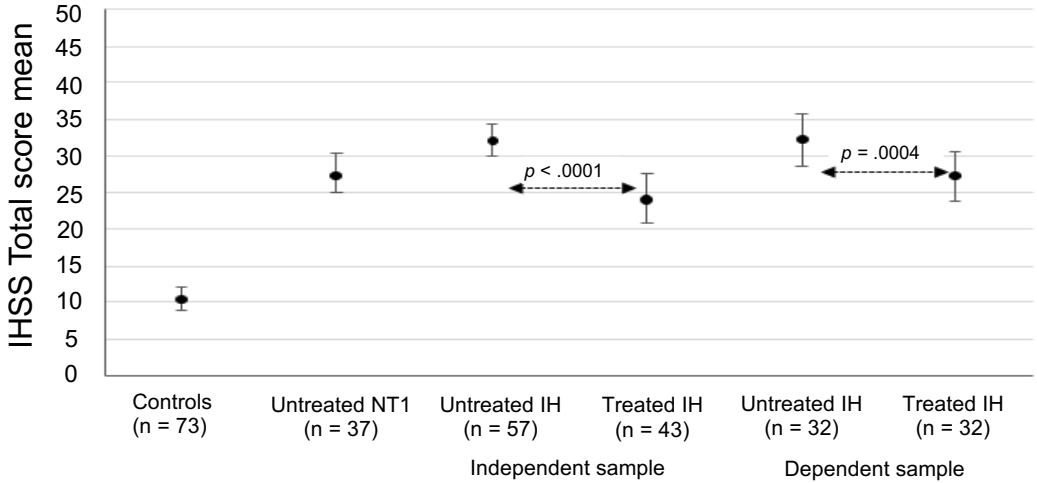
32-hour bed rest



TST cutoff to discriminate IH to controls was **19 hours over 32-hour recording**

Idiopathic Hypersomnia Severity Scale (IHSS)

- 14-item questionnaire that assesses the severity of IH
  - 5 on nighttime sleep symptoms and related sleep inertia
  - 4 on daytime sleep symptoms and related sleep inertia
  - 5 on daytime function
- Total score 0 to 50, higher score indicating more severe and frequent symptoms



- Higher scores in drug-free patients with IH than NT1 and controls
- No ceiling effect
- **Cut off to discriminate IH and controls: 22**
  Sensitivity: 91.1%
  Specificity: 94.5%
- **Untreated and treated IH: 26**
  Sensitivity: 55.8%
  Specificity: 78.9%
- **Treatment difference:**
  5-8 units

IHSS is a reliable, valid clinical tool for the quantification of IH symptoms; sensitive enough to detect clinical changes in symptoms following treatment!

Dauvilliers Y, et al. *Neurology*. 2019;92(15):e1754-e1762.

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Voice of the Family:

The Diagnostic Journey

IHSS: Clinically Relevant Score Ranges

Goal:

- To confirm its psychometric properties and responsiveness of IHSS to medications
- To estimate the minimum clinically important difference
- To report clinically relevant score ranges

Component I: 7 items on daytime functioning

Component II: 5 items on long sleep duration and sleep inertia

Component III: 2 items on napping

IHSS total score was lower in treated than untreated patients; between-group differences related to treatment. Probability of having severe EDS, high BDI, low QoL increased with the severity level.

Clinically relevant score ranges
Mild = 0-12
Moderate = 13-25
Severe = 26-38
Very severe = 39-50

These findings should stimulate the use of the IHSS in clinical settings and in research studies

BDI = Beck Depression Index; ESS = excessive daytime sleepiness; QoL = quality of life

Rassu AL, et al. *J Clin Sleep Med*. 2022;18(2):617-629.

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Learning Objective 3

Analyze the efficacy and safety of novel therapies for IH addressing the unmet needs of people with IH

Audience Response

How confident are you in developing safe, effective treatment strategies to optimally manage idiopathic hypersomnia?

A. Not confident at all
B. Somewhat confident
C. Confident
D. Extremely confident

Impact of Treatment on IH: Hypersomnia Foundation Registry

Comparison of symptoms within the last 30 days and symptoms at their worst

	Number (%) endorsing symptom at least daily, within the last 30 days	Number (%) endorsing symptom at least daily, when symptoms were at their worst	*p* value
Excessive daytime sleepiness	243 (64.1%)	370 (97.6%)	< .0001
Long sleep durations	52 (13.7%)	195 (51.5%)	< .0001
Intentional napping	52 (13.7%)	206 (54.4%)	< .0001
Unintentional daytime sleep	23 (6.1%)	140 (36.9%)	< .0001
Requiring multiple alarms to awaken	227 (60.2%)	265 (70.3%)	< .0001
Having trouble waking up and functioning with normal alertness	228 (61.1%)	301 (80.7%)	< .0001
Brain fog (being unable to think clearly or concentrate at any time throughout the day	201 (54.0%)	311 (83.6%)	< .0001
Difficulty remembering things	189 (51.8%)	262 (71.8%)	< .0001
Automatic behaviors	42 (12.4%)	88 (26.0%)	< .0001

- 82% taking medication within last 30 days
- 51% at least 1 stimulant
- 38% modafinil or armodafinil
- 11% combo modafinil/armodafinil + stimulant
- 12% melatonin
- 6% flumazenil
- 5% clarithromycin
- 3% sodium oxybate

Trotti LM, et al. *Sleep Med*. 2020:75: 343–349.

Strategies for the Treatment of IH

- Lower-sodium oxybate (LXB) is the first and only drug approved for the treatment of IH in adults
- Prior treatment approaches for EDS in IH similar to narcolepsy
- AASM 2021 draft guideline updates recommends the following for IH in adults:
  - ✓ modafinil (**strong**)
  - ✓ clarithromycin (conditional)
  - ✓ methylphenidate (conditional)
  - ✓ pitolisant (conditional)
  - ✓ sodium oxybate (conditional)

*LXB was not available when the AASM guideline for the Treatment of Central Disorders of Hypersomnolence was printed.

AASM = American Academy of Sleep Medicine
Maski K, et al. *J Clin Sleep Med*. 2021;17(9):1881-1893.

Overview of Pharmacological Trials in IH*

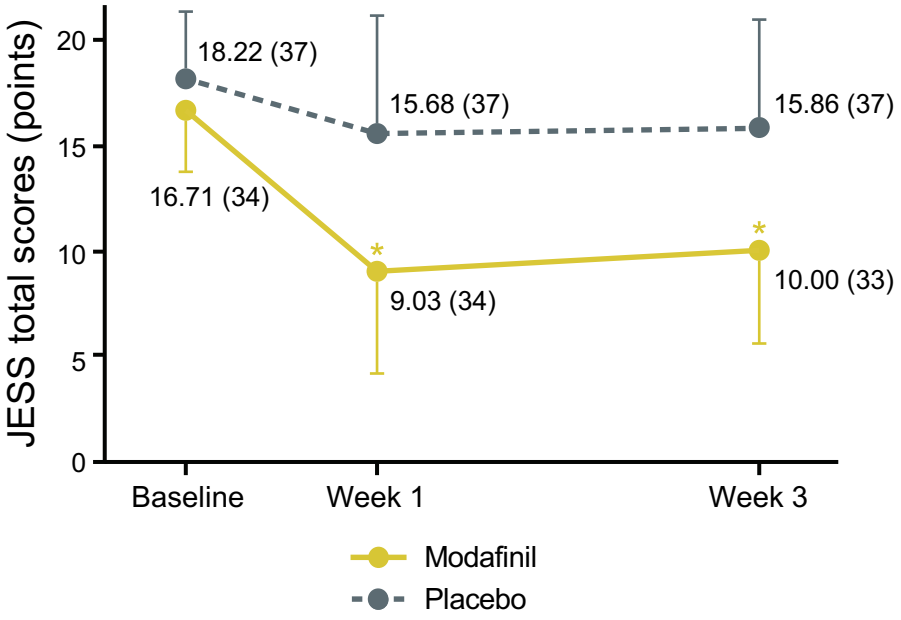
Treatment	Author	Patient population	Conclusion
Modafinil	Mayer et al. 2015	IH without long sleep time (n = 31)	Improvement on ESS: 6.0 points; on CGI: 1.0 point
Methylphenidate	Thakrar et al. 2018	IH (n = 9); NT1 (n = 70), NT2 (n = 47)	Improvement on ESS: 3.1 points
Dextroamphetamine	Ali et al. 2009	IH (n = 2)	0% complete or partial response
Sodium oxybate	Leu-Semenescu et al. 2016	Treatment-refractory IH (n = 46)	65% responders; improvement on ESS: 3.5 points
Pitolisant	Leu-Semenescu et al. 2014	Treatment-refractory IH (n = 65)	35% responders; improvement on ESS: 1.5 points
Mazindol	Nittur et al. 2013	Treatment-refractory IH (n = 37)	Improvement on ESS: 4.8 points
Flumazenil	Trotti et al. 2016	Refractory hypersomnolence (n = 153)	62.8% responders
Clarithromycin	Trotti et al. 2015	IH (n = 10); NT2 (n = 4); subjective hypersomnia (n = 6)	Improvement on ESS: 3.9 points
Transcranial direct current stimulation	Galbiati et al. 2016	IH (n = 8)	Improvement on ESS: 5.8 points

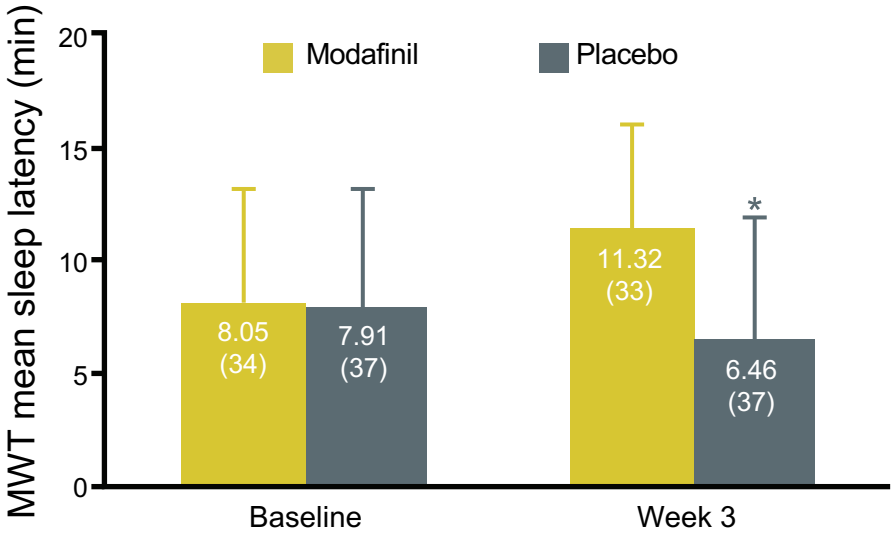
*These agents are not FDA-approved for the treatment of IH.

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders; ICSD = International Classification of Sleep Disorder

Schinkelshoek MS, et al. *Curr Sleep Medicine Rep*. 2019;5:207-214.; Evangelista E, et al. *Expert Opin Investig Drugs*. 2018;27(2):187-192.

Modafinil:† Efficacy in IH without Long Sleep Time





†Modafinil is not FDA-approved for the treatment of IH. * $p < .001$

JESS = Japanese version of the Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test

Inoue Y, et al. *Sleep Med*. 2021;80:315-321.

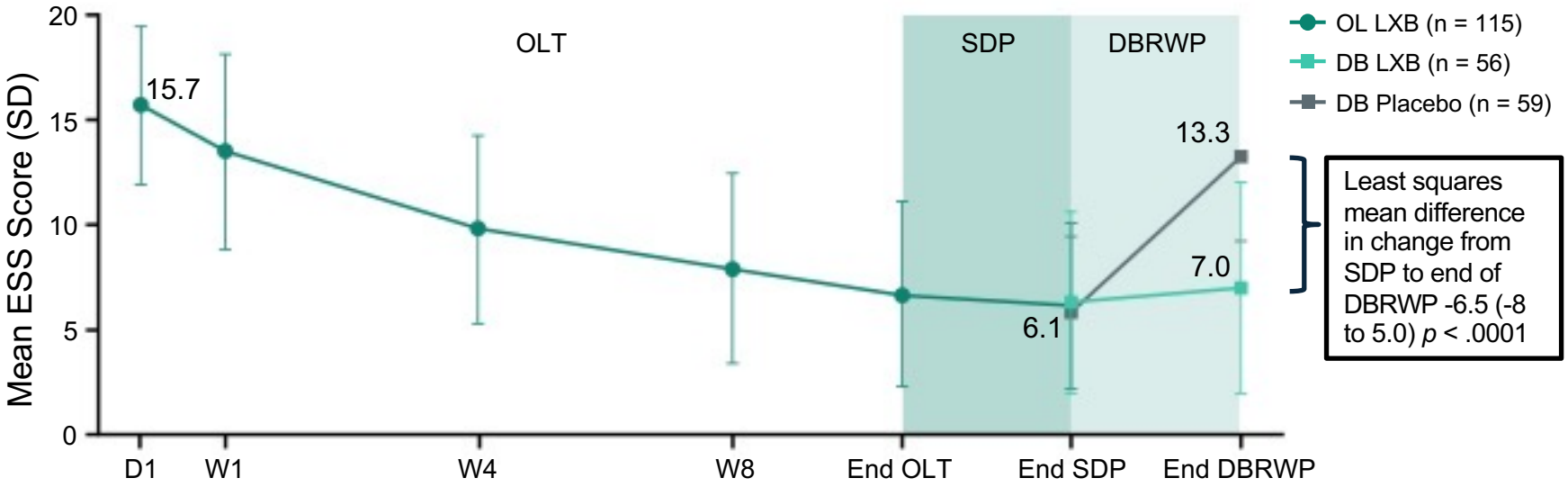
Pitolisant:*
Efficacy in IH with and without Long Sleep Time (Chart Review)

Patients with IH	With Long Sleep Time (n = 49)	Without Long Sleep Time (n = 16)	*p* value
Time on pitolisant (months)	4	7	0.85
ESS			
Score at baseline	17 (14-18)	17 (16-20.5)	0.23
Score with pitolisant	14 (12-17)	16 (13-17)	0.34
Responders, % (n)	37 (18)	31 (5)	0.69
Treatment stopped, % (n)	67.3 (33)	68.7 (11)	0.84
Reasons for stopping			
Lack of efficacy, % (n)	48.5 (16)	63.6 (7)	0.6
Adverse effects, % (n)	21.2 (7)	9.1 (1)	0.65
Loss of efficacy, % (n)	3 (1)	9.1 (1)	1

*Pitolisant is not FDA-approved for the treatment of IH.

Leu-Semenescu S, et al. *Sleep Med*. 2014;15(6):681-687.

LXB: Efficacy in IH – ESS



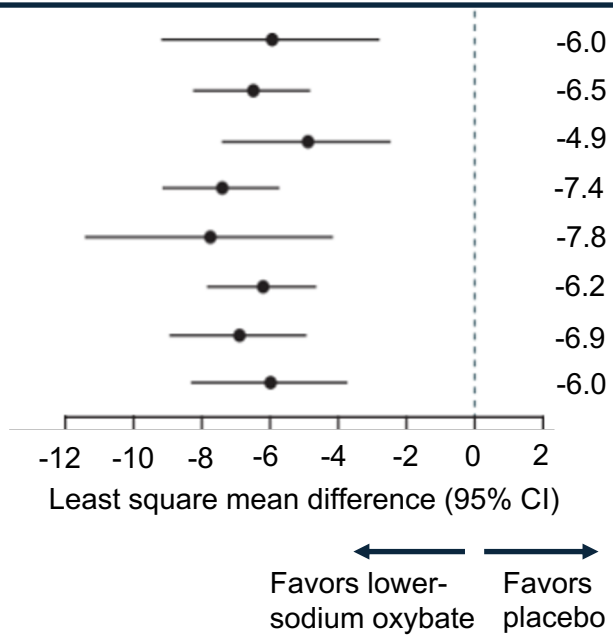
- Improvement in mean ESS score from study entry to end of SDP
- Worsening in mean ESS score from end of SDP to end of DBRWP with placebo; maintenance of improvement with LXB

DBRWP = double-blind, randomized withdrawal period; OLT = titration and optimization period; SDP = stable-dose period

Dauvilliers Y, et al. *Lancet Neurol*. 2022;21(1):53-65.

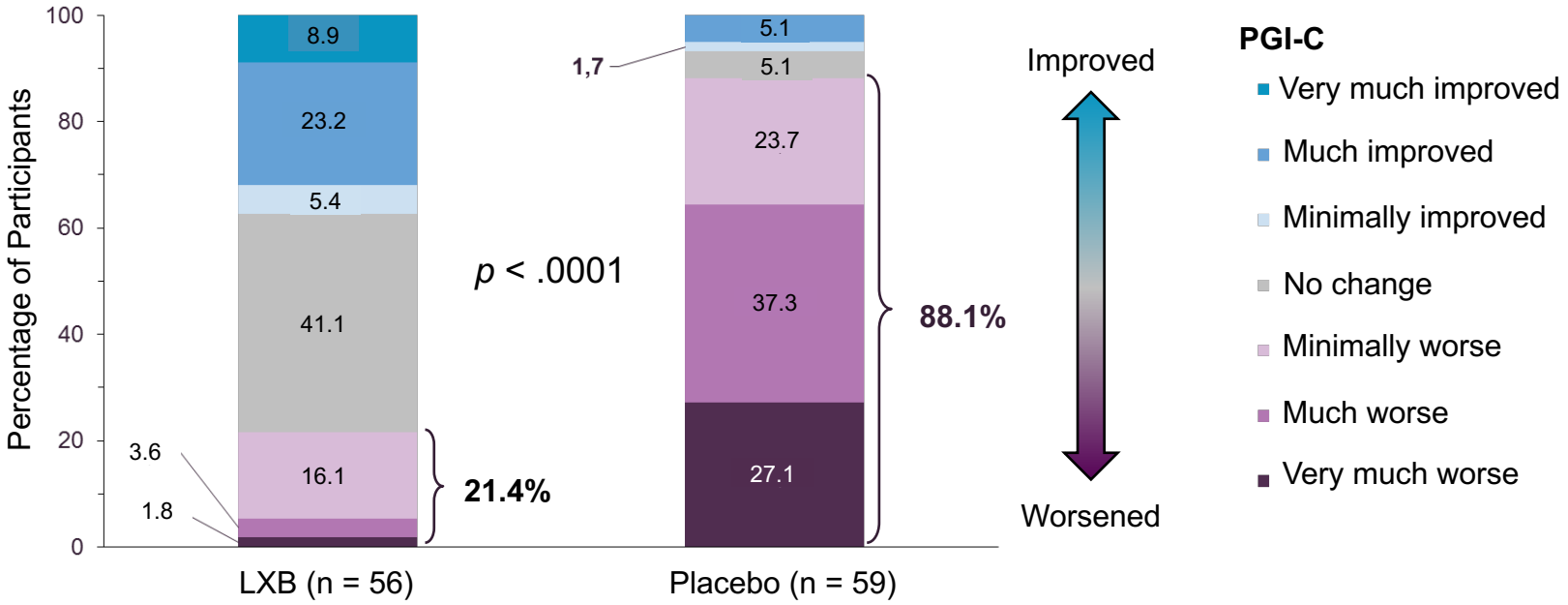
LXB: Efficacy in IH – Differences in ESS Scores Between Groups

	Placebo (n = 59)	Lower-sodium oxybate (n = 56)	Least squares mean difference (95% CI)	Nominal *p* value
Male	16	17	-6.0 (-9.2 to -2.8)	*p* = .0006
Female	43	39	-6.5 (-8.3 to -4.8)	*p* < .0001
Once nightly	11	15	-4.9 (-7.4 to -2.5)	*p* = .0004
Twice nightly	47	41	-7.4 (-9.2 to -5.7)	*p* < .0001
With long sleep	11	13	-7.8 (-11.4 to -4.2)	*p* = .0002
Without long sleep	48	43	-6.2 (-7.8 to -4.6)	*p* < .0001
Taking baseline IH medication	35	33	-6.9 (-8.9 to -4.9)	*p* < .0001
Treatment naïve	24	23	-6.0 (-8.3 to -3.7)	*p* < .0001



Dauvilliers Y, et al. *Lancet Neurol*. 2022;21(1):53-65.

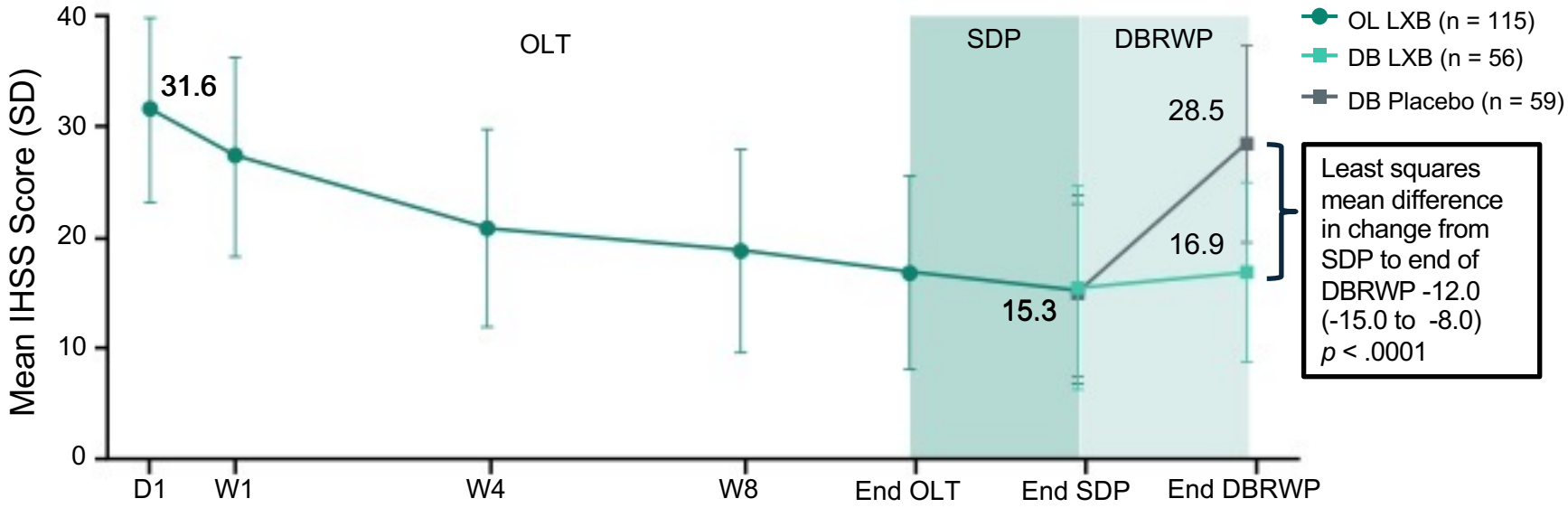
LXB: Efficacy in IH – PGI-C



At the end of DBRWP, significant worsening in PGI-C ratings was observed in participants randomized to placebo vs. LXB (88.1% vs. 21.4% rated minimally/much/very much worse)

PGI-C = patient global impression of change
Dauvilliers Y, et al. *Lancet Neurol*. 2022;21(1):53-65.

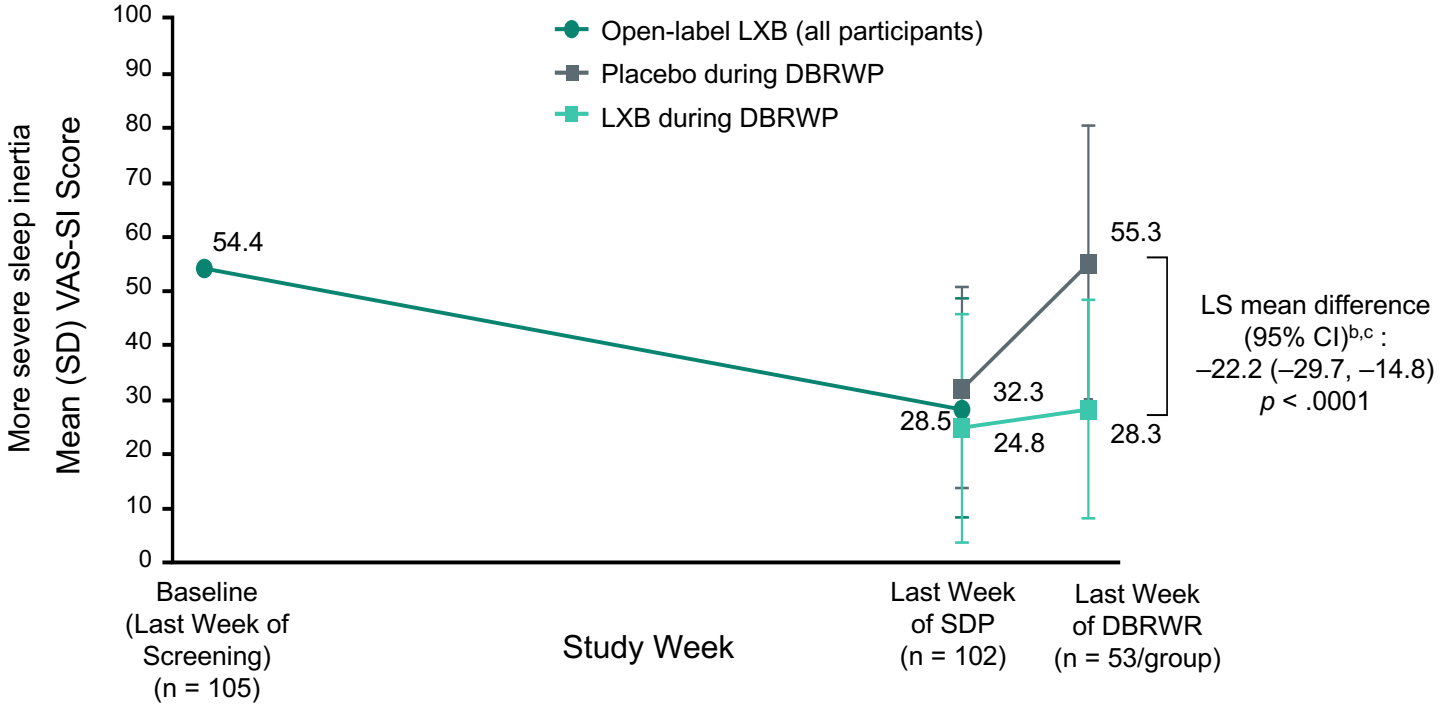
LXB: Efficacy in IH – IHSS



- Improvement in mean IHSS score from study entry to end of SDP
- Worsening in mean IHSS score from end of SDP to end of DBRWP with placebo; maintenance of improvement with LXB

Dauvilliers Y, et al. *Lancet Neurol*. 2022;21(1):53-65.

LXB: Efficacy in IH – Sleep Inertia and Total Sleep Time



*LXB was also effective in reducing 24-hour TST, nocturnal sleep time, and nap duration in treatment naive patients and those taking alerting agents.

[a]Modified intent-to-treat population.
[b]Difference in change from end of SDP to end of DBRWP. [c]LXB, n = 49; placebo, n = 51.

VAS-SI = Visual Analog Scale for Sleep Inertia

Dauvilliers Y, et al. *Lancet Neurol*. 2022;21(1):53-65.; Bogan RK, et al. *Sleep*. 2021;44(Suppl 2):A192.; Morse AM, et al. Presented at 2022 World Sleep Congress. Poster #119.

Safety of Treatments for IH

Drug	Schedule	Common AEs (≥ 5%)
Modafinil*	IV	Anxiety, back pain, diarrhea, dizziness, dyspepsia, headache, insomnia, and nausea
Pitolisant*	–	Anxiety, insomnia, and nausea
SXB / LXB	III	Anxiety, decreased appetite, diarrhea, dizziness, headache, nausea, hyperhidrosis, parasomnia, and vomiting

*Modafinil and pitolisant are not FDA-approved for IH.

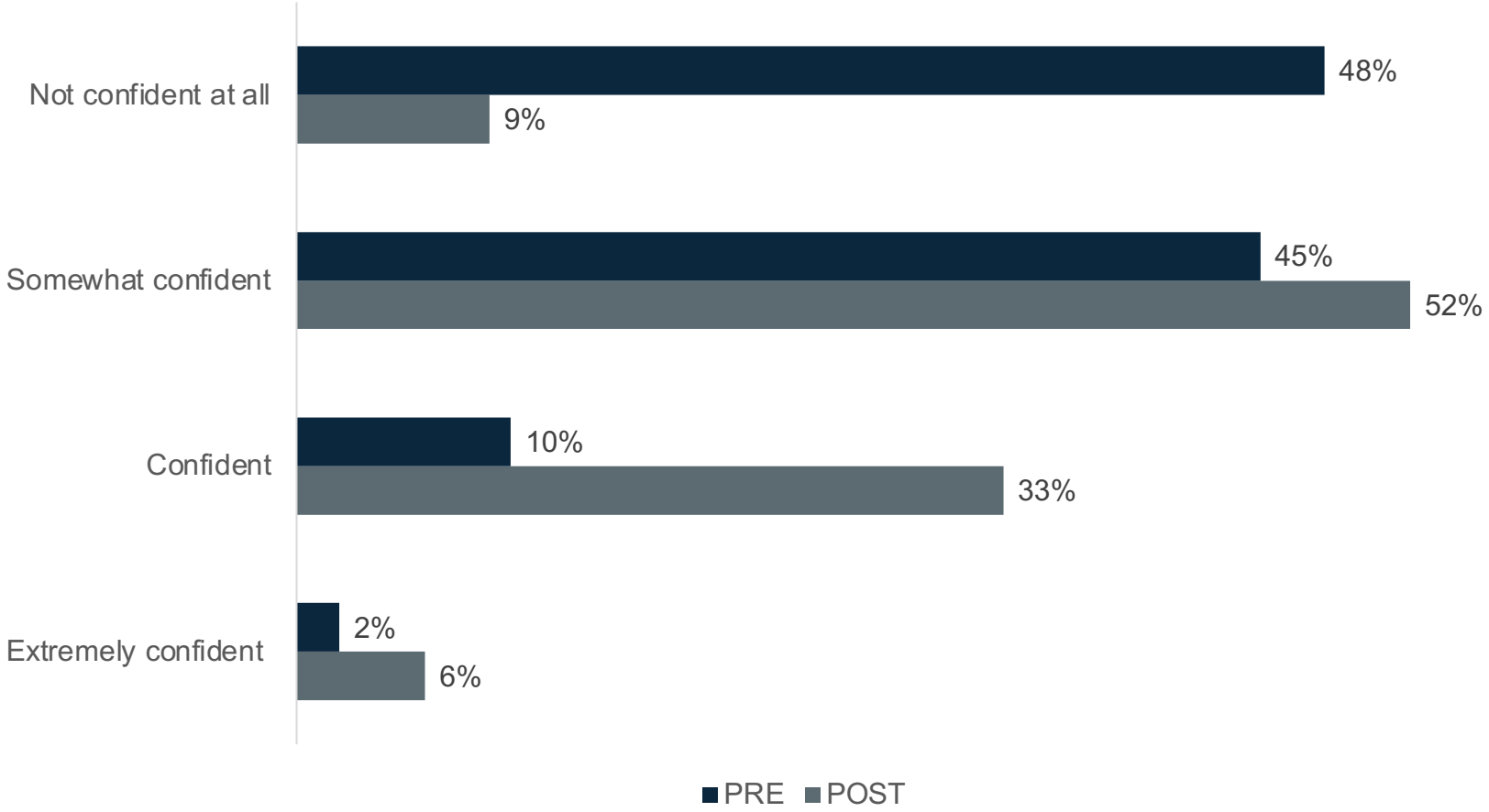
Drugs@FDA Website.

Audience Response

Now, how confident are you in developing safe, effective treatment strategies to optimally manage idiopathic hypersomnia?

A. Not confident at all
B. Somewhat confident
C. Confident
D. Extremely confident

How confident are you in developing safe, effective treatment strategies to optimally manage idiopathic hypersomnia?



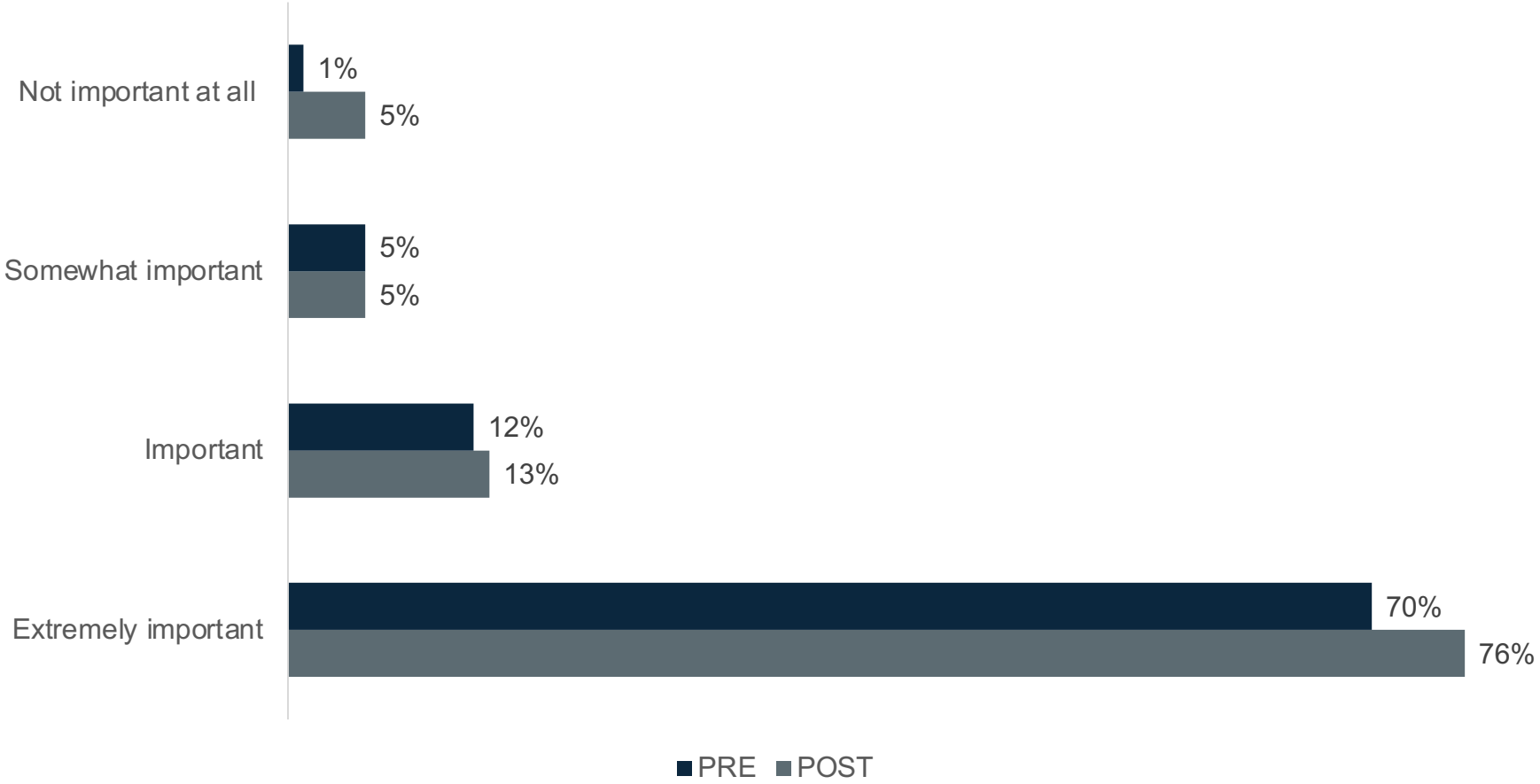
Results recorded March 31, 2022.

Audience Response

When evaluating a patient with idiopathic hypersomnia, now how important is to assess the quality of life and functional impact of IH?

A. Not important at all
B. Somewhat important
C. Important
D. Extremely important

When evaluating a patient with idiopathic hypersomnia, how important is it to assess the quality of life and functional impact of IH?



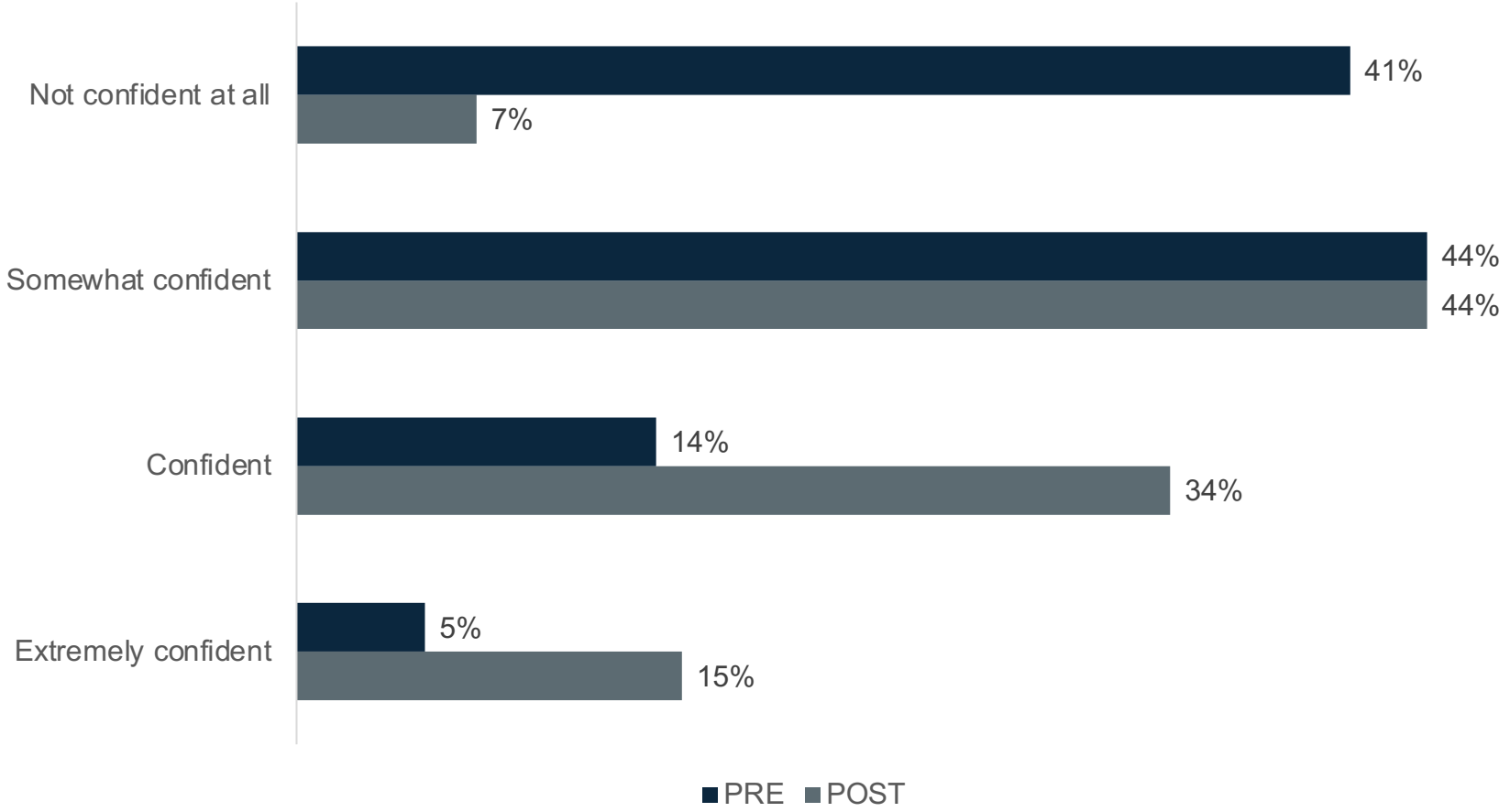
Results recorded March 31, 2022.

Audience Response

Now, how confident are you in accurately diagnosing idiopathic hypersomnia?

A. Not confident at all
B. Somewhat confident
C. Confident
D. Extremely confident

How confident are you in accurately diagnosing idiopathic hypersomnia?



Results recorded March 31, 2022.

Conclusions

- The burden of IH is extensive, encompassing diminished QoL, impaired cognitive functioning, poor workplace performance, mood changes, and psychosocial dysfunction.
- Accurately diagnosing IH can be a challenge.
- Currently, there is only one FDA-approved treatment for IH, and it has shown benefit across a variety of domains.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- At every visit, assess the burden of IH on patient's daily functioning, including its negative impact on work and psychosocial functioning and QoL.
- Use evidence-based strategies to facilitate the early, accurate diagnosis of IH.
- Incorporate into treatment planning, the latest clinical evidence on FDA-approved strategies for IH.

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AFTER THE SHOW

Questions & Answers

Question and Answer recorded on March 31, 2022

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