CMHC
Cardiometabolic Health Congress

EXPERT PERSPECTIVES AND DISCUSSIONS

COMPLIMENTARY
CME DINNER SYMPOSIUM

New Hope on the Horizon: Advances in the Diagnosis and Treatment of IDIOPATHIC HYPERSOMNIA

Supported by an educational grant from Jazz Pharmaceuticals, Inc.

Faculty

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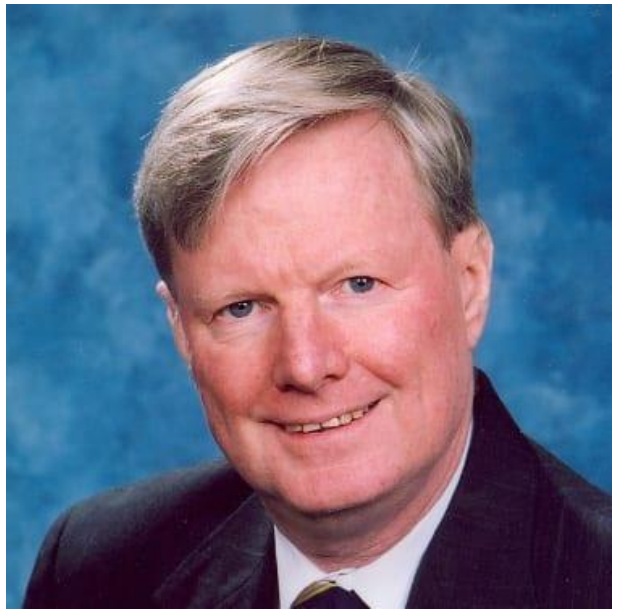
Bronx, NY



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Announcements

- This activity is jointly provided by Partners for Advancing Clinical Education and Cardiometabolic Health Congress.
- Supported by an educational grant from Jazz Pharmaceuticals, Inc.
- All CME/CE information and faculty disclosures can be found on your iPads and online.
- Presentations may contain discussions of non-FDA approved products and/or off-label discussion of products.

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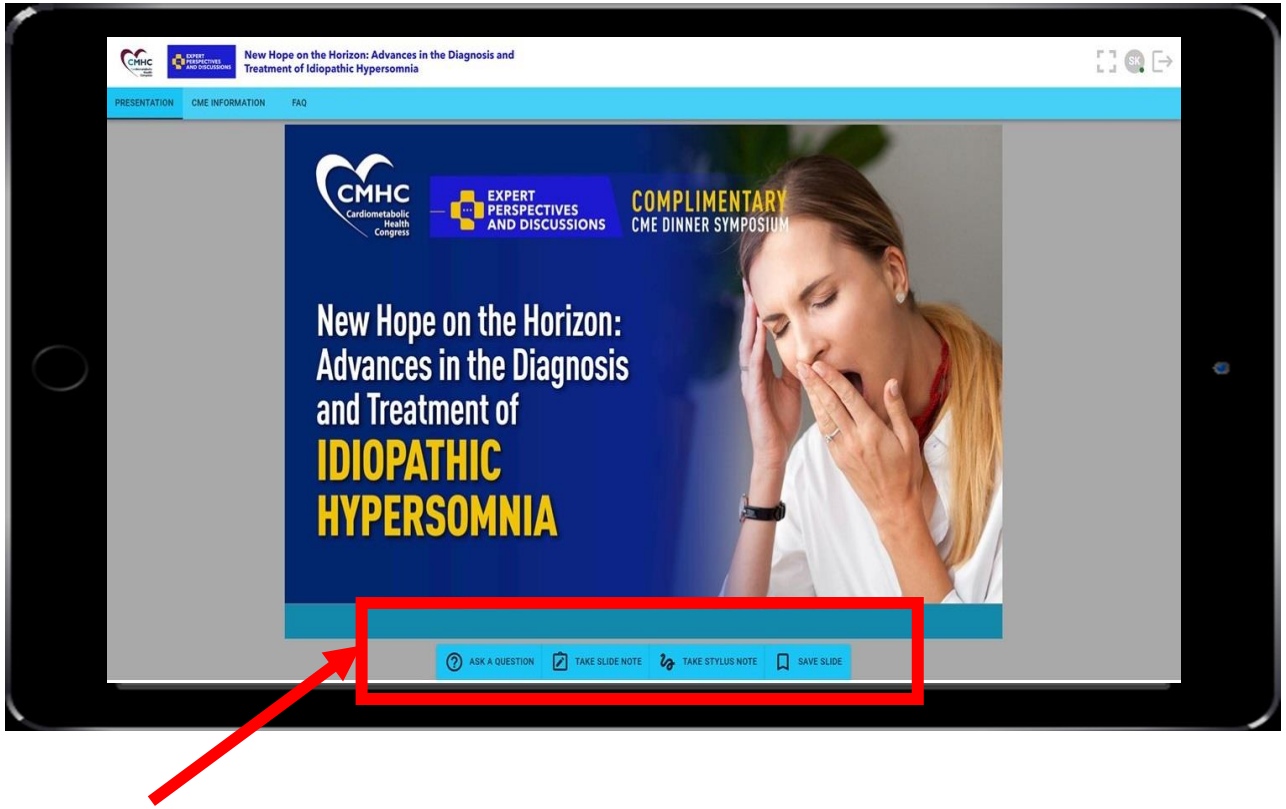
iPads Available for All Attendees

- Follow along during the presentations
- Participate in live polling and interactivity questions
- Take notes and save slides
- Submit your questions to faculty



Agenda

- IH: Overview, Symptoms, and Disease Burden (Michael Thorpy, MD)
- Diagnosis of IH (Yves Dauvilliers, MD, PhD)
- Current IH Treatment (Michael Thorpy, MD)
- New and Emerging Treatment Options (Yves Dauvilliers, MD, PhD)

Before we begin, an audience assessment

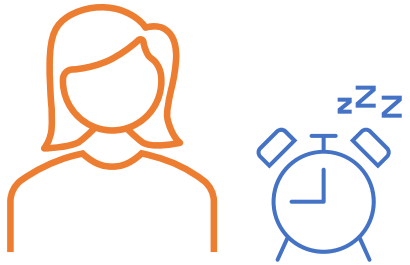
- Please select your degree
  - MD/DO
  - PhD
  - PharmD
  - RN
  - NP
  - PA
  - Other

Before we begin, an audience assessment

- In the past 5 years, how many patients have you diagnosed with idiopathic hypersomnia (IH), or have many patients with IH have you come across?

  - 0
  - 1-10
  - 11-20
  - 21-30
  - >30
  - Not applicable

Hypersomnia Case



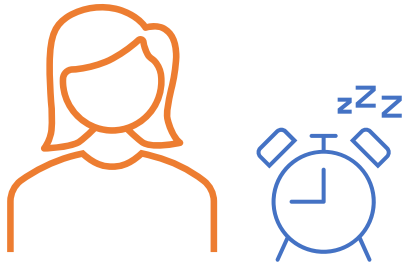
- 26-year-old female
- Weekdays Bedtime: 10pm Out of bed 9am
  - Weekends: BT 2 am OOB 12 noon
- Symptoms: Difficulty awakening, tired confused, disoriented upon awakening

  Sleepy after awakening takes a couple of naps during day.

  Sleep is sound but has vivid dreams and occasional nightmares, dreams in morning naps..

  Mild snoring and morning headaches
- BMI: 31
- On O/Cs
- Mild depression/anxiety on fluoxetine 40mg/day

ARS #1



What is your main initial impression of the diagnosis?

1. Delayed sleep phase syndrome
2. Narcolepsy Type 2
3. Idiopathic Hypersomnia
4. Obstructive sleep apnea syndrome
5. Depression

IH: Overview, Symptoms, and Disease Burden

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Which of the following is TRUE about the features of IH?

a. It is more common in males
b. Estimates suggest a prevalence of 50 per hundred thousand
c. Onset of symptoms & diagnosis is typically between 10-30 years of age
d. It associated with low CSF hypocretin

Symptoms of Idiopathic Hypersomnia

- Sleepiness
- Long nocturnal sleep duration
- Naps
- Difficulty awakening
- Sleep inertia
- Cognitive impairment
- Brain Fog

Maness C, et al. *J Sleep Res* 2018;e12689
Vernet C, et al. *J Sleep Res* 2010;19:525-534
Miglis MG, et al. *J Clin Sleep Med* 2020

Sleep Inertia

Definition:

A temporary disorientation and decline in performance and/or mood after awakening from sleep, often with slower reaction time, poorer short-term memory, and slower speed of thinking, reasoning, remembering, and learning.

Rosenthal R et al; JCSM In press

Brain Fog

Brain fog in hypersomnia disorders features:

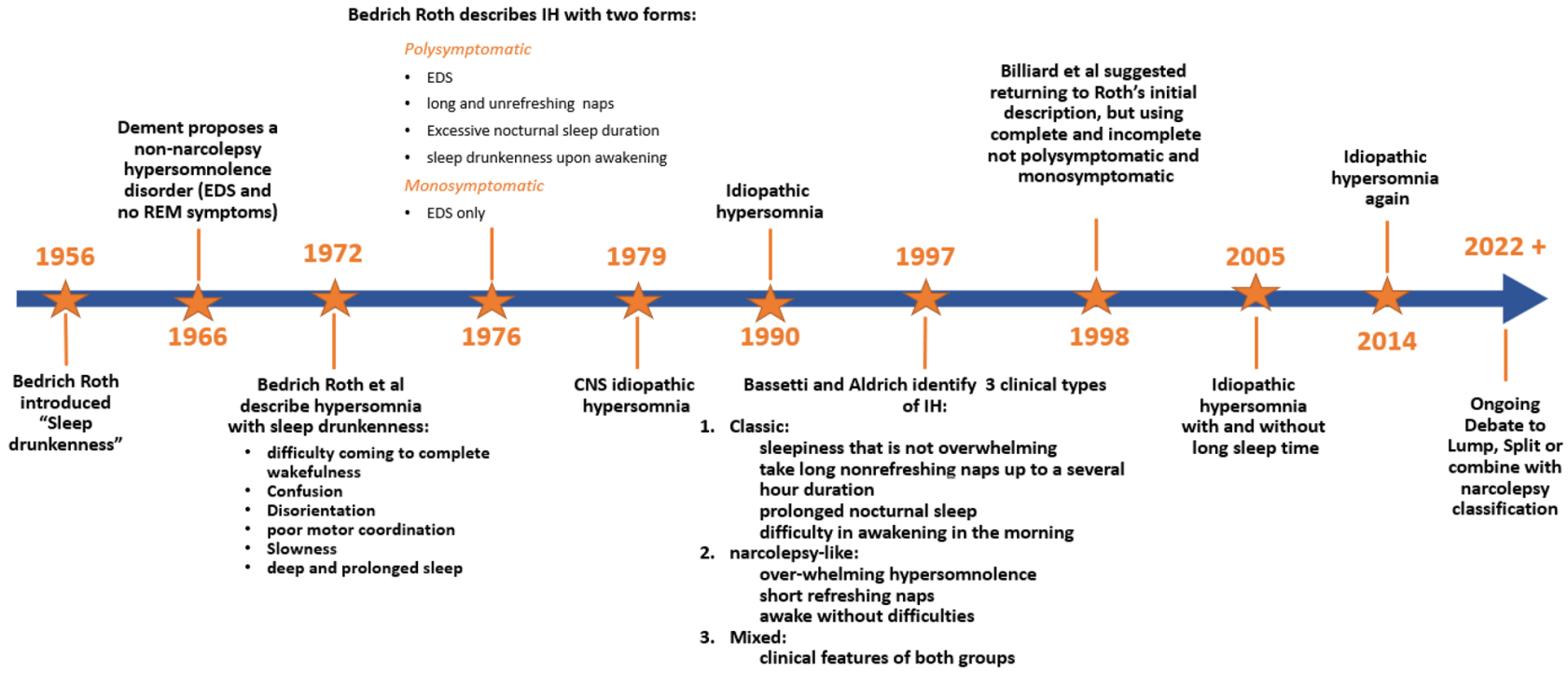
- Cognitive dysfunction
- May or may not be linked with excessive sleepiness
- Possibly related to an underlying inflammatory process
- Reduces concentration
- Impairs information processing
- Leading to a complaint of lack of clarity of thinking and awareness

Rosenthal R et al; JCSM In press

Idiopathic Hypersomnia: A Distinct Neurologic Sleep Disorder

Idiopathic hypersomnia (IH) is a chronic debilitating neurologic sleep disorder characterized by nonrestorative sleep despite normal or longer than normal periods of sleep

- IH classification has evolved from ”sleep drunkenness” in 1956 to “idiopathic hypersomnia” in 2014
- There is an ongoing debate to further classify IH based on advances in neurologic and pathophysiologic understanding of sleep disorders



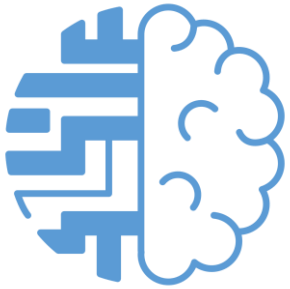
Lammers GJ. *Sleep Medicine Reviews*. 2020; 52:101306

Emerging Hypotheses that Explain Potential Causes of IH

Circadian rhythm dysfunction

Autonomic dysregulation

GABAergic dysregulation



Dysregulation of brain regional connectivity and metabolism

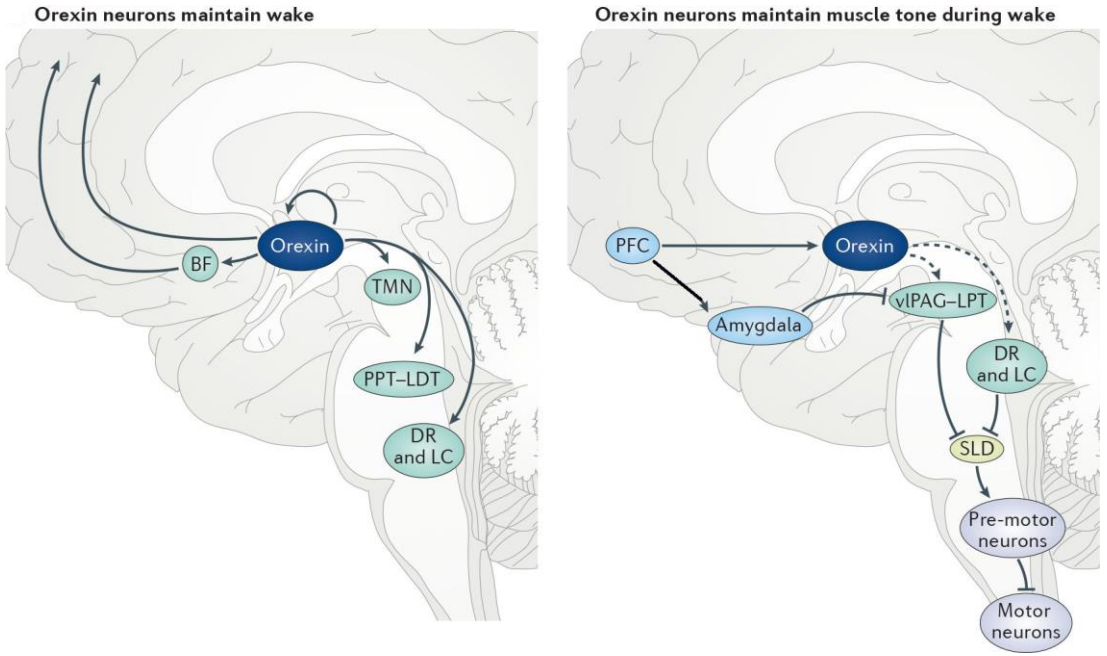
Altered orexin signaling

Dauvilliers Y et al. Annals of Neurology 2016; 80.2: 259-268; Lammers GJ. *Sleep Medicine Reviews*. 2020; 52:101306
Morse AM and Naik S. *CNS Drugs*. 2023;37(4):305-322; Miyagawa T, et al. *NPJ Genom Med*. 2022;7(1):29. Trotti LM et al. Neurotherapeutics (2021); 18: 20-31

Etiology and Pathogenesis of IH are not Well Understood

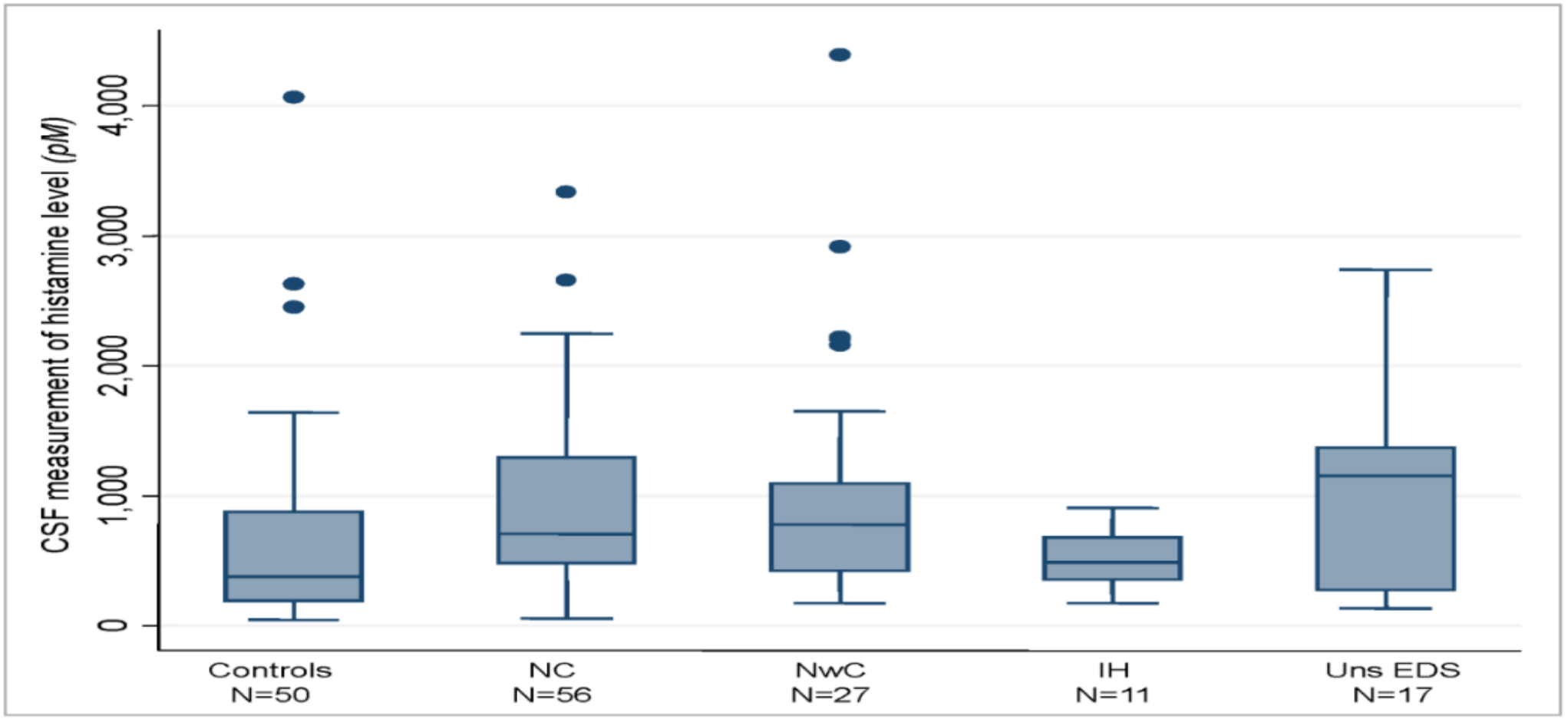
- Evidence indicate that IH is caused by a defect in the arousal CNS system rather than hyperactivity of sleep centers
- Impairment in the neurotransmission of orexin (a neuropeptide produced mainly by neurons in the lateral hypothalamus) is the hallmark pathology in narcolepsy with cataplexy (narcolepsy type 1)
- Recent evidence suggest that disruption of orexin-mediated neurotransmission is involved in the disease pathogenesis of subpopulations of patients with IH

Orexin Network is an Important Component of the Sleep-Wake Cycle



Dhillon K, et al. [Updated 2022 Dec 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023; Mahoney CE, et al. *Nat Rev Neurosci*. 2019;20(2):83-93.

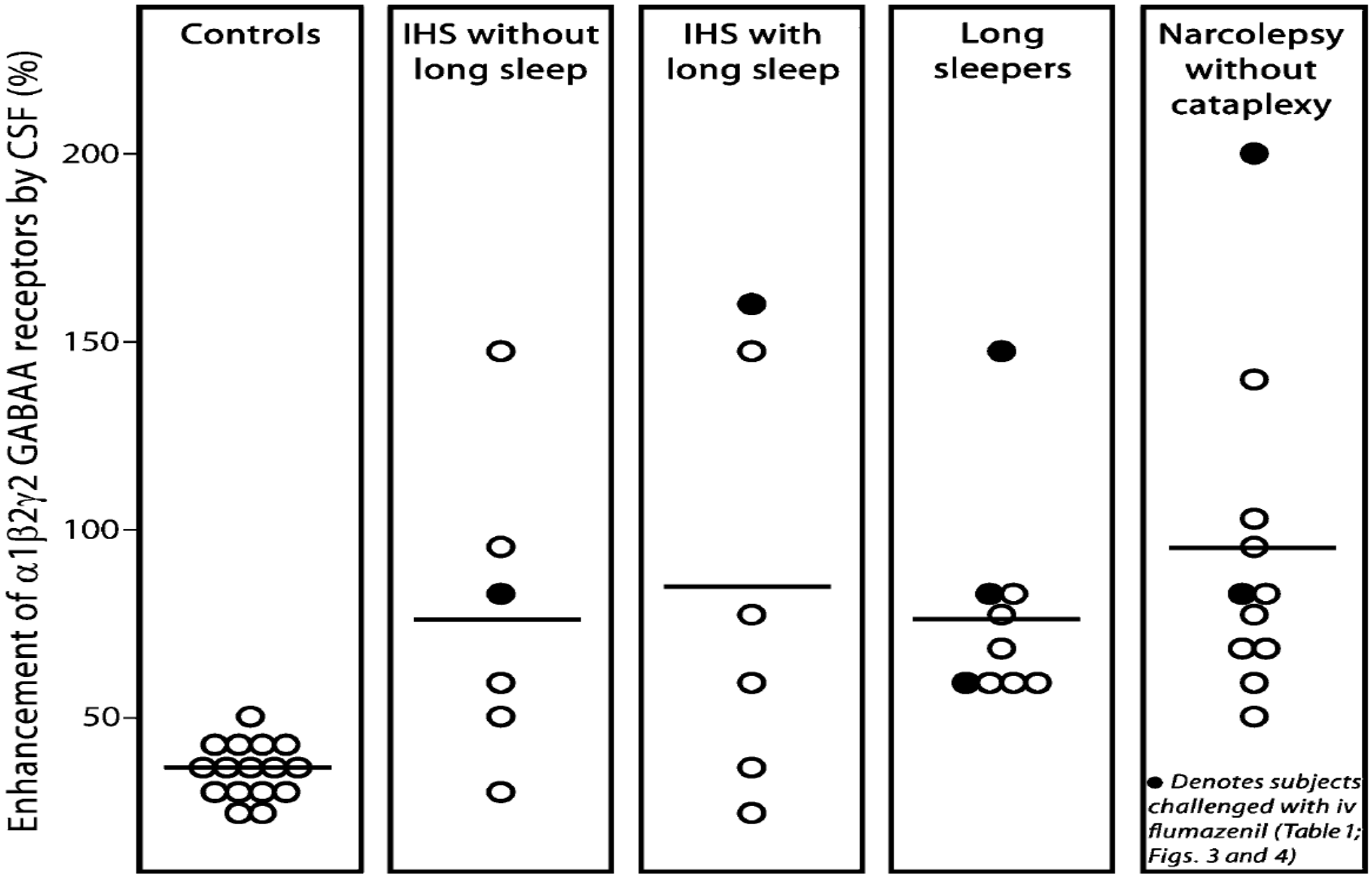
Pathophysiology of IH - Histamine



No differences between csf Histamine/telemethylHA between patients and controls

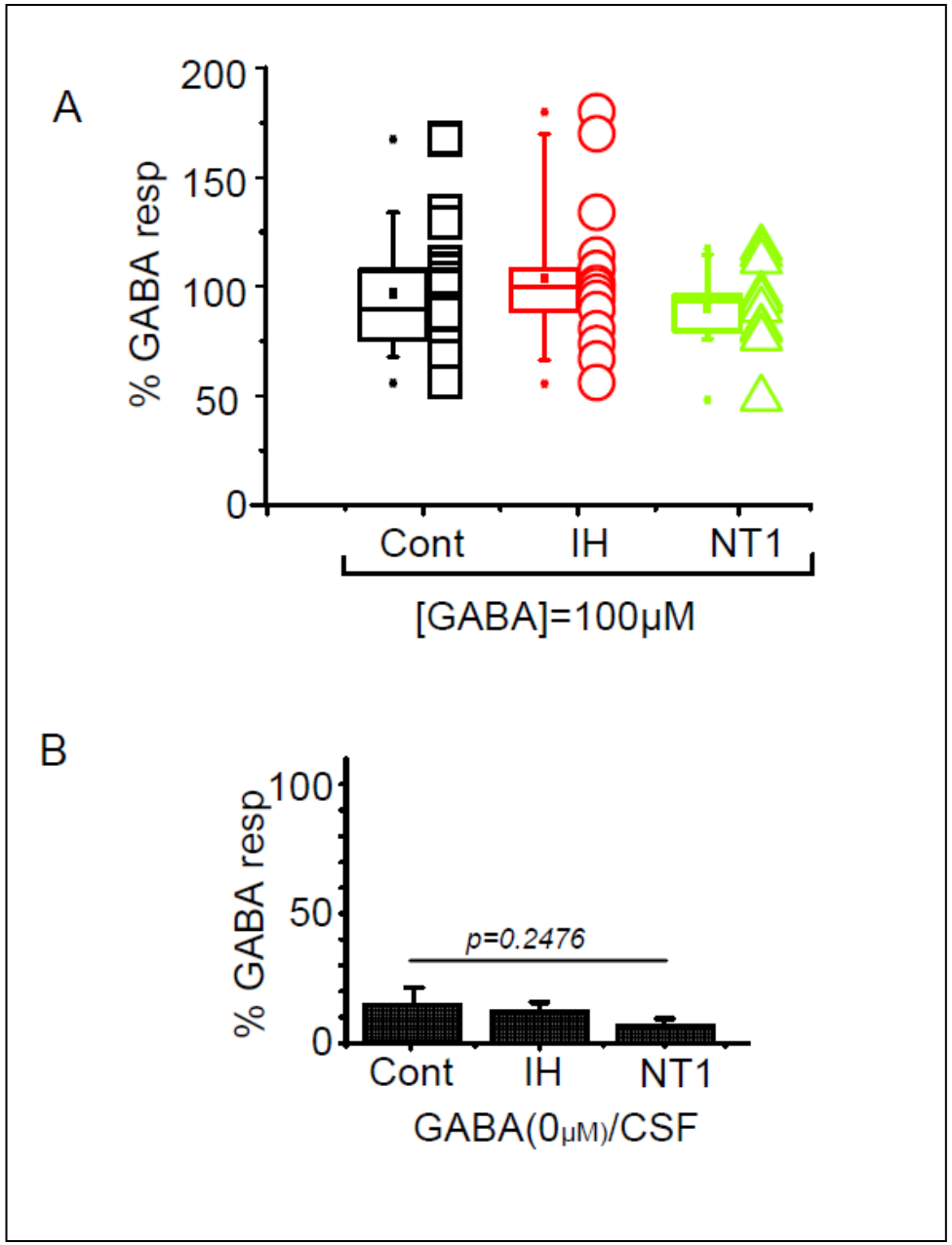
Dauvilliers Y, Delallée et al. *Sleep* 2012; 35.10: 1359-1366

Modulation of GABA-A Receptor Activity in Hypersomnias



Rye DB, et al. Sc
Transl Med 201
4.16:

Absence of GABA-A receptor potentiation in Hypersomnias



Dauvilliers Y, et al. Ann Neurol 80(2): 259-68

Csf Monoamines in Central Disorders of Hypersomnolence

11 biogenic amines/metabolites and 5 trace amines were measured in CSF of 94 drug-free subjects

39 NT1, 31 NT2 (7 with IH with LST), 24 without objective sleepiness

No differences among groups in CSF monoamines

CSF monoamine and metabolites levels	NSH N = 24	IH/NT2 N = 31	NT1 N = 39	Model 1	Model 2
	n(%)	*n*(%)	*n*(%)	*p*	*p*
Serotonergic system					
Serotonin (nM)					
≤0.02	18(75.00)	26(83.87)	27(69.23)	0.38	0.51
>0.02	6(25.00)	5(16.13)	12(30.77)		
5-HIAA (nM)*	58.60 (20.60;155.00)	55.60 (19.80; 113.00)	65.40 (27.70; 214.00)	0.09	0.20
Dopaminergic system					
Dopamine (nM)					
≤0.0868	10(41.67)	10(32.26)	12(30.77)	0.83	0.93
]0.0868–1.32]	8(33.33)	11(35.48)	12(30.77)		
>1.32	6(25.00)	10(32.26)	15(38.46)		
HVA (nM)*	35.20 (14.90;155.00)	43.30 (10.30; 294.00)	46.90 (17.00; 633.00)	0.46	0.60
DOPAC (nM)					
≤0.5	8(33.33)	11(35.48)	13(33.33)	0.19	0.14
]0.5–2.795[	12(50.00)	10(32.26)	9(23.08)		
≥2.795	4(16.67)	10(32.26)	17(43.59)		
3-MT (nM)					
≤0.125	21(87.50)	30(96.77)	37(94.87)	0.38	0.72
>0.125	3(12.50)	1(3.23)	2(5.13)		
OMD (nM) *	15.75 (9.92; 25.70)	13.20 (9.27; 22.40)	13.20 (5.76; 45.10)	0.29	0.19
Noradrenergic system					
Norepinephrine (nM)*	0.29 (0.02; 0.86)	0.36 (0.15; 1.01)	0.38 (0.08; 2.05)	0.24	0.46
MHPG (nM) *	52.60 (28.20; 86.00)	51.90 (36.20; 69.40)	52.00 (21.30; 138.00)	0.39	0.54
MHPG/norepinephrine*	177.71 (57.38; 4193.33)	127.15 (60.59; 457.33)	140.16 (40.54; 423.22)	0.31	0.57
Epinephrine (nM)					
≤0.02	10(41.67)	10(32.26)	13(33.33)	0.45	0.55
]0.05–0.1190[	10(41.67)	9(29.03)	11(28.21)		
≥0.1190	4(16.67)	12(38.71)	15(38.46)		
VMA (nM)					
≤0.125	23(95.83)	29(93.55)	33(84.62)	0.30	0.49
>0.125	1(4.17)	2(6.45)	6(15.38)		
Trace amines					
β-Phenylethylamine (nM)					
≤0.125	19(79.17)	31(100.00)	34(87.18)	NA	NA
>0.125	5(20.83)	0(0.00)	5(12.82)		
Tyramine (nM)					
≤0.025	21(87.50)	28(90.32)	32(82.05)	0.60	0.62
>0.025	3(12.50)	3(9.68)	7(17.95)		

* Continuous variables are expressed as median with minimum value and maximum value.
Model 1: crude association.
Model 2: adjustment for gender and BMI.

Barateau et al, Sleep, 2021 1-9

Epidemiology of Idiopathic Hypersomnia

- Rare disease, with unknown prevalence
- Estimates suggest a prevalence of 15 per 100,000 population
- Onset of symptoms is typically between 10-30 years old

  Diagnosis is typically delayed until between 28-35 years old
- Often familial cases ?
- A higher prevalence in females has been seen clinically
- Spontaneous remissions reported in some patients

Trotti LM et al. Neurotherapeutics (2021); 18: 20-31

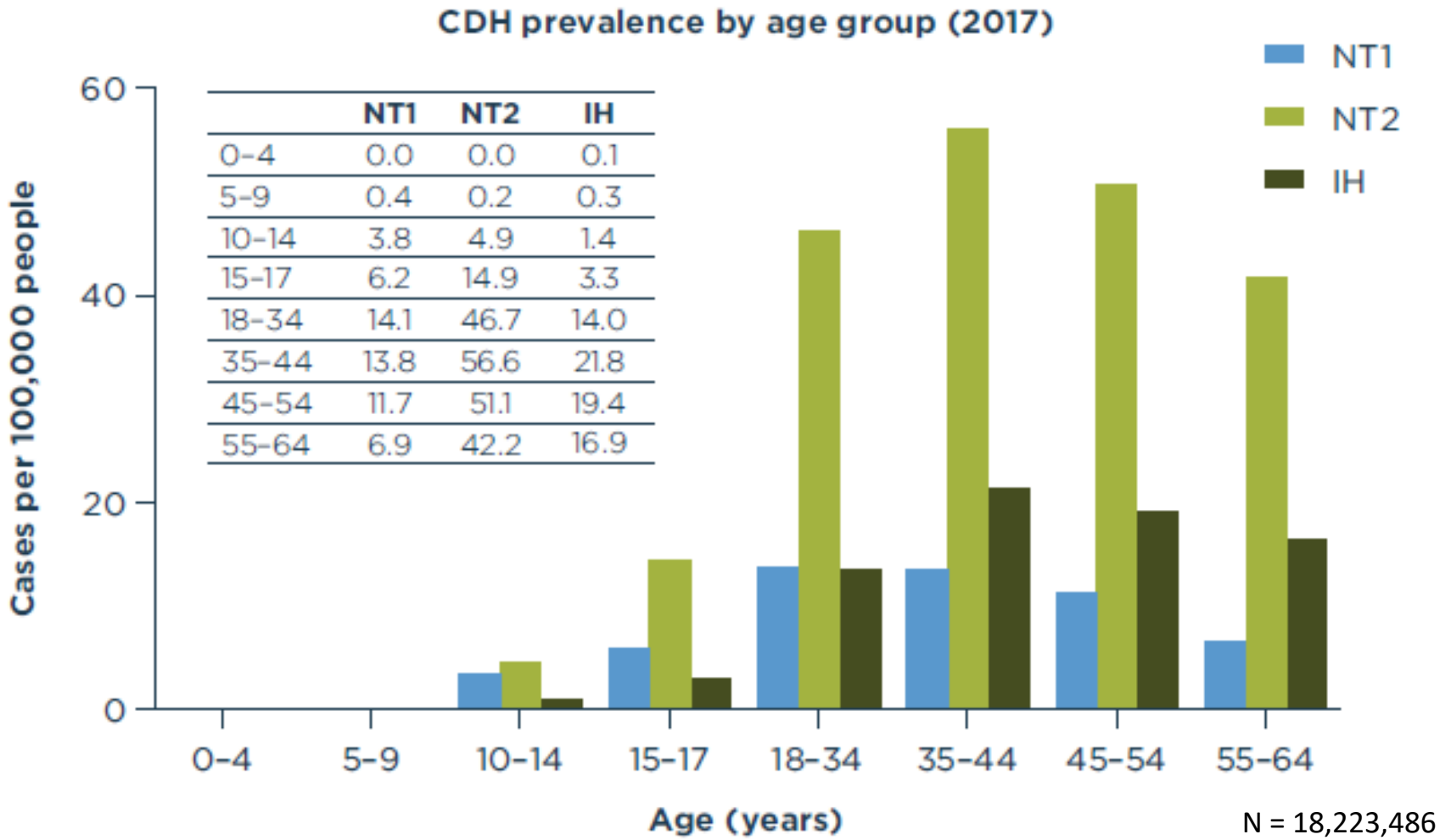
Prevalence of NT1, NT2 and IH in 2017

Overall Prevalence per 100,00 (2017):

9.7

38.8

13.9



	NT1	NT2	IH
0–4	0.0	0.0	0.1
5–9	0.4	0.2	0.3
10–14	3.8	4.9	1.4
15–17	6.2	14.9	3.3
18–34	14.1	46.7	14.0
35–44	13.8	56.6	21.8
45–54	11.7	51.1	19.4
55–64	6.9	42.2	16.9

N = 18,223,486

CDH: central disorders of hypersomnolence; IH: idiopathic hypersomnia; NT1: narcolepsy type 1; NT2: narcolepsy type 2

Assessment of the diagnosed prevalence of narcolepsy and idiopathic hypersomnia in the United States using real world data . Abioye I et al. World Sleep Symposium, Rome 2022

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Symptoms of Idiopathic Hypersomnia

Excessive daytime sleepiness (EDS)

Long sleep time

Sleep inertia

Unrefreshing naps

Cognitive dysfunction & brain fog

Lammers GJ. *Sleep Medicine Reviews*. 2020; 52:101306
Trotti LM et al. Neurotherapeutics (2021); 18: 20-31

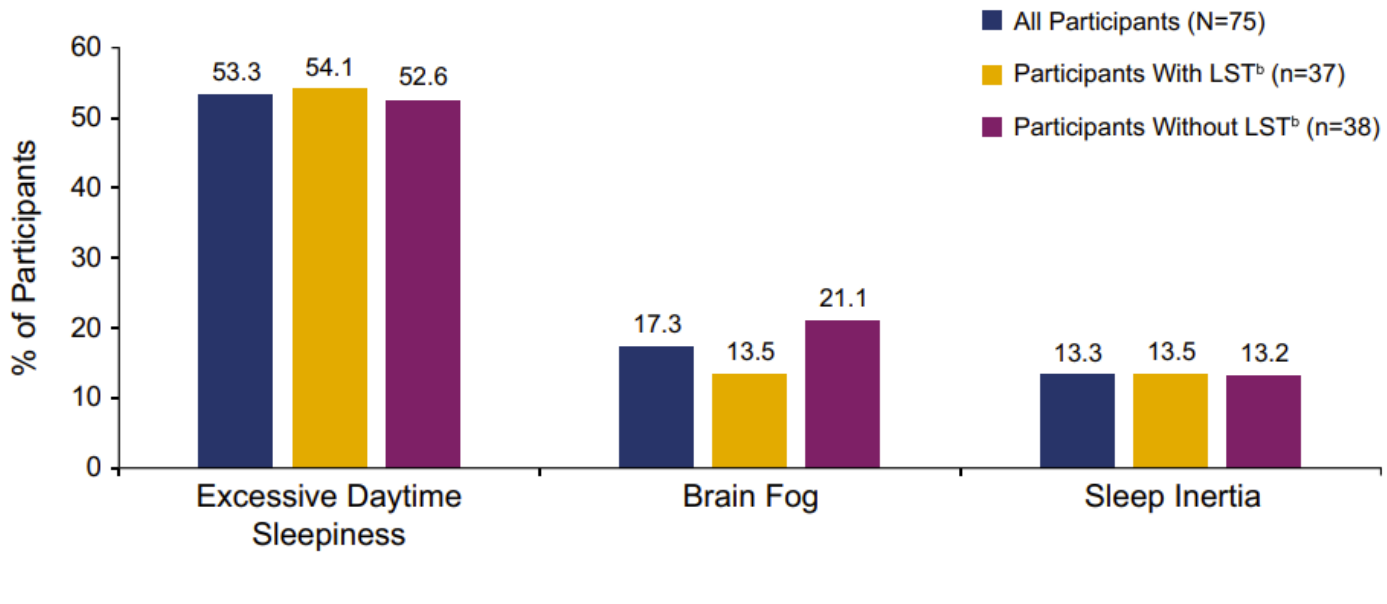
Daily Symptoms Reported by Patients with IH With and Without Long Sleep Time

	Idiopathic Hypersomnia with Long Sleep Time	Idiopathic Hypersomnia without Long Sleep	P-Value
Excessive Daytime Sleepiness	235 (97.9%)	222 (97.4%)	0.70
Intentional Napping	154 (64.2%)	96 (42.1%)	<0.0001
Unintentional Daytime Sleep	95 (39.8%)	74 (32.5%)	0.10
Requiring Multiple Alarms to Awaken	186 (77.5%)	140 (61.7%)	0.0002
Having Trouble Waking Up and Functioning with Normal Alertness	211 (88.3%)	158 (69.3%)	<0.0001
Brain Fog (Being Unable to Think Clearly or Concentrate at Any Time throughout the Day	205 (86.9%)	175 (78.1%)	0.01
Difficulty Remembering Things	170 (73.3%)	156 (70.3%)	0.48
Automatic Behaviors	54 (23.8%)	46 (21.6%)	0.58

Trotti LM et al. Neurotherapeutics (2021); 18: 20-31

Symptoms of IH can be Difficult to Treat

The Real-World Idiopathic Hypersomnia Outcomes Study (ARISE), which included 75 patients with IH, showed that the most difficult to treat symptoms associated with IH are EDS (53.3%), brain fog (17.3%), and sleep inertia (13.3%)



EDS, excessive daytime sleepiness

Schneider LD, et al. *Nat Sci Sleep*. 2023;15:89-101.

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

Trotti LM et al. *Sleep Med Clin* (2017); 2(3):331-344; Trotti LM et al. *Sleep Med* (2020); 75: 343-349; Jennum P et al. Europ J Health Economics (2014); 15:303-311

According to real-world data, what percentage of IH patients with long sleep time reported brain fog?

a. 83%
b. 50%
c. 32%

Patients with IH Experience Negative Impact on Cognitive Functions

Patients with IH may experience attention difficulties, which negatively impact their memory causing mistakes in a habitual activities and tasks

Patients often describe their difficulties with attention and cognition as “brain fog”

Based on data from the Hypersomnia Foundation’s online registry

83% of patients with IH experienced brain fog

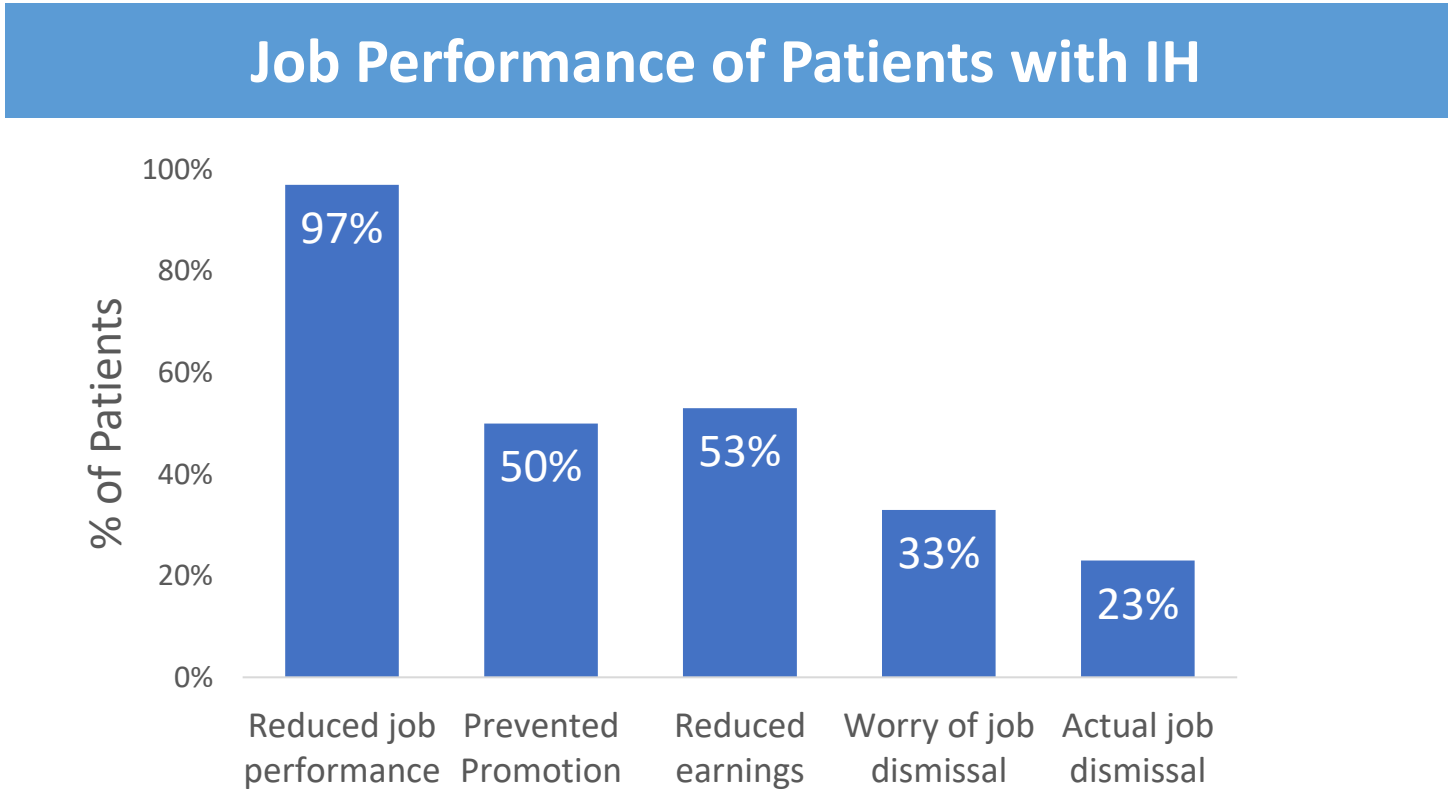
54% of patients with IH who received a treatment experienced brain fog within the past 30 days

84% of patients with IH who received a treatment experienced brain fog daily when symptoms worsened

Trotti LM, et al. *Sleep Med*. 2020;75:343-349; Maski K, Schneider L. Recognizing the Unique Burden of Idiopathic Hypersomnia in Your Patients. https://www.sleepcountshcp.com/pdf/IH_Medical_Expert_Panel_Overview.pdf

Job Performance of Patients with IH is Negatively Impacted by IH

In a study that used a questionnaire of patients with IH (n=30), patients reported negative impact of IH on several aspects of their life, including job performance, career success, and the risk of getting fired

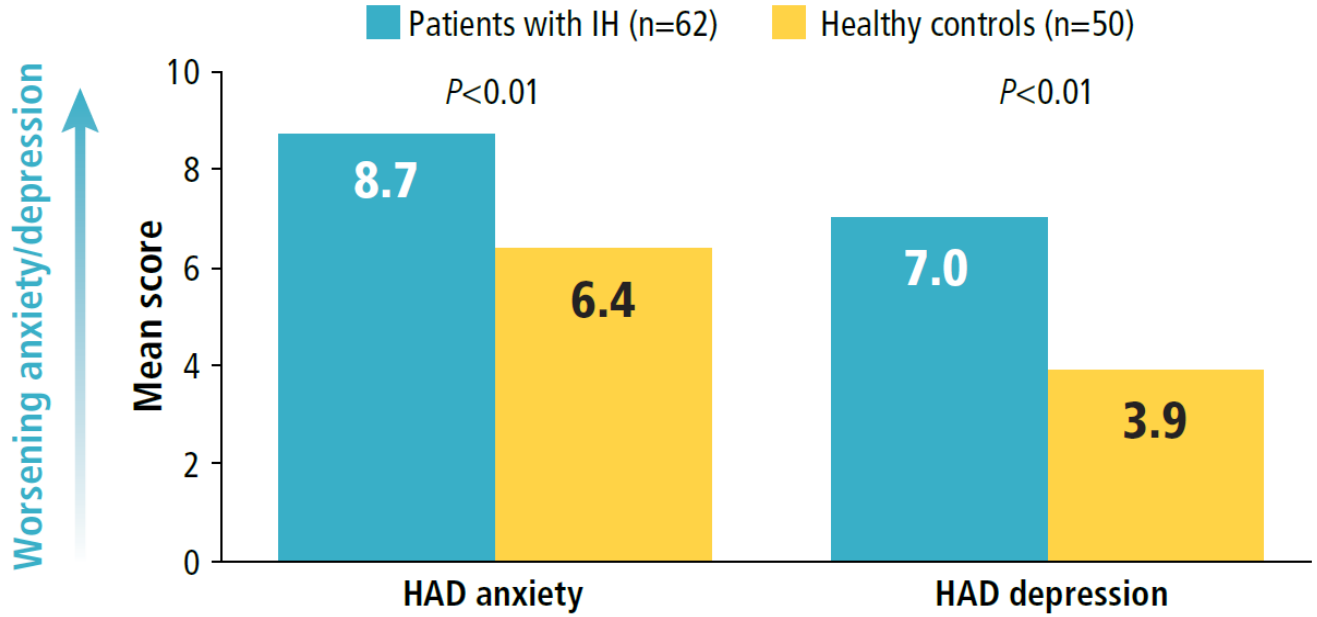


Broughton R, et al. *Sleep Res*. 1978;7:229-233; Maski K, Schneider L. Recognizing the Unique Burden of Idiopathic Hypersomnia in Your Patients. https://www.sleepcountshcp.com/pdf/IH_Medical_Expert_Panel_Overview.pdf

Mental Health of Patients with IH is Negatively Impacted

- Patients with IH may experience anxiety or depression
- Patients with IH described experiencing several mental health symptoms, including:
  - sad mood
  - lost interest
  - Irritability
  - social isolation
  - concentration issues
  - anxiety

HAD Scale Scores in Patients with IH Compared with Controls



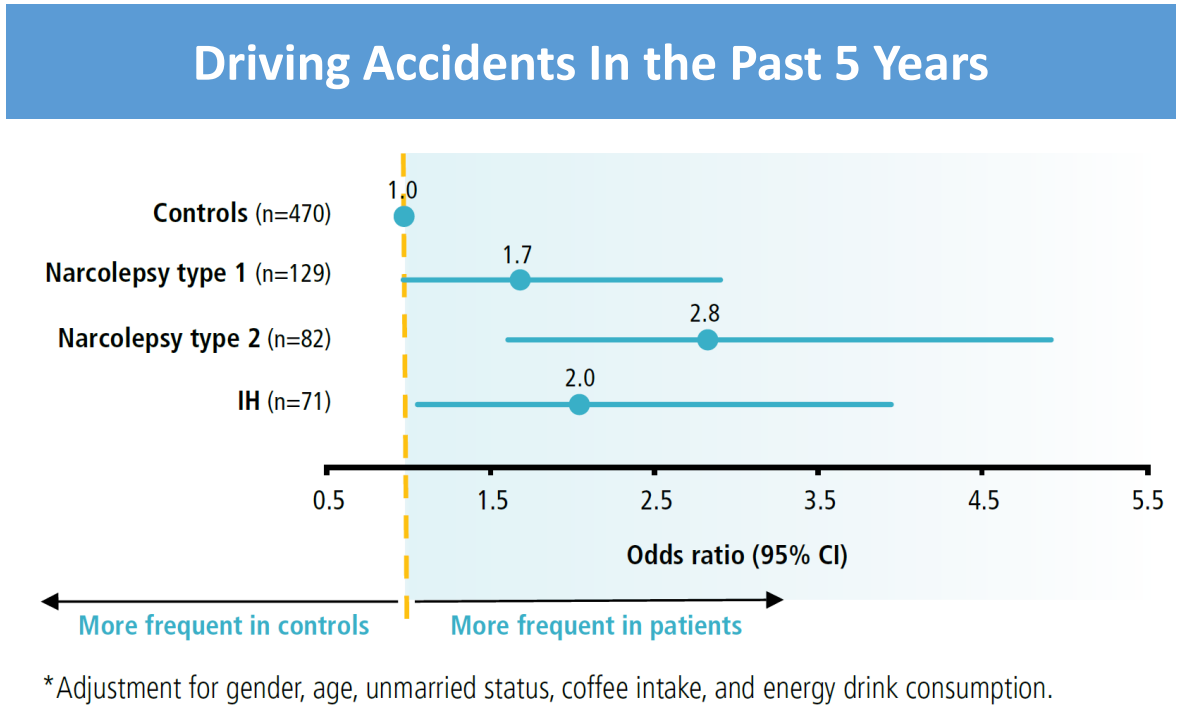
HAD, Hospital Anxiety and Depression.

*Conducted using an in-person interview and a standardized questionnaire for all patients being monitored for 48 hours with suspected IH in a single hospital between 2005 and 2008.

Vernet C, et al. *J Sleep Res*. 2010;19(4):525-534; Neikrug AB, et al. *Behav Sleep Med*. 2017;15(2):158-171; Maski K, Schneider L. Recognizing the Unique Burden of Idiopathic Hypersomnia in Your Patients. https://www.sleepcountshcp.com/pdf/IH_Medical_Expert_Panel_Overview.pdf

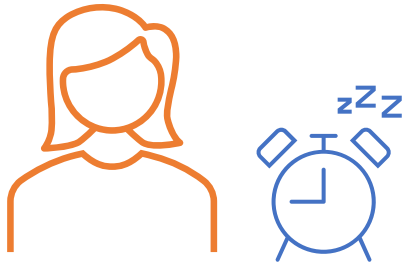
Patients with IH Experience Higher Prevalence of Driving Accidents than Healthy Individuals

A cross-sectional study of compared patients with IH with healthy controls reported that patients with hypersomnolence disorders have a significantly higher prevalence of driving accidents compared with healthy controls



Pizza F, et al. *PLoS One.* 2015;10(6):e0129386; Maski K, Schneider L. Recognizing the Unique Burden of Idiopathic Hypersomnia in Your Patients. https://www.sleepcountshcp.com/pdf/IH_Medical_Expert_Panel_Overview.pdf

Hypersomnia Case



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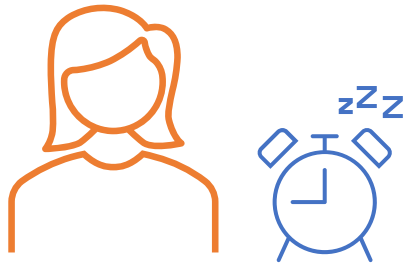
  - Weekends: BT 2 am OOB 12 noon
- Symptoms: Difficulty awakening, tired confused, disoriented upon awakening

  Sleepy after awakening takes a couple of naps during day.

  Sleep is sound but has vivid dreams and occasional nightmares, dreams in morning naps..

  Mild snoring and morning headaches
- BMI: 31
- On O/Cs
- Mild depression/anxiety on fluoxetine 40mg/day

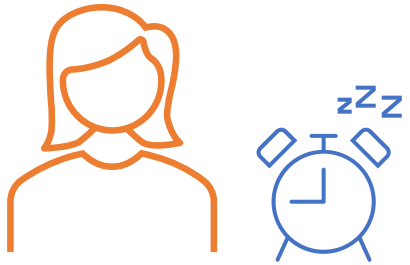
ARS #2



Which of the following would your regard as the most important first step following your consultation before starting diagnostic investigations?

1. Stop the fluoxetine
2. Evaluate suicide risk
3. Stop the O/Cs
4. Advise weight loss
5. Stabilize sleep pattern

ARS #3



Which evaluation would you initiate next?

1. Epworth Sleepiness Scale (ESS)
2. Idiopathic Hypersomnia Severity Scale (IHSS)
3. Sleep Diary and /or Actigraphy
4. Psychomotor vigilance test (PVT)
5. Polysomnography (PSG)
6. PSG and MSLT

How To Diagnose Idiopathic Hypersomnia

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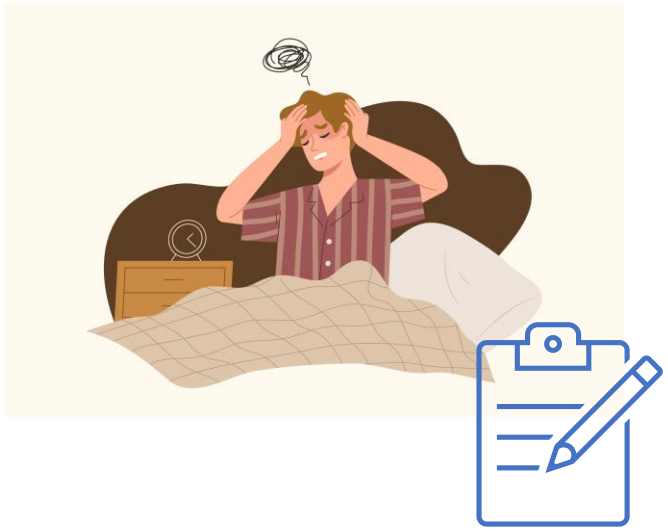


Which of the following is TRUE about the diagnosis of IH?

a. MSLT is the gold standard to diagnose IH
b. Diagnostic criteria include the presence of abnormal REM sleep phenomena.
c. MSLT has relatively low sensitivity for IH
d. Frequent association with HLADQB1*0602

Current Diagnostic Criteria of IH According to the International Classification of Sleep Disorders – 3rd edition

Idiopathic Hypersomnia

Criteria A-F must be met

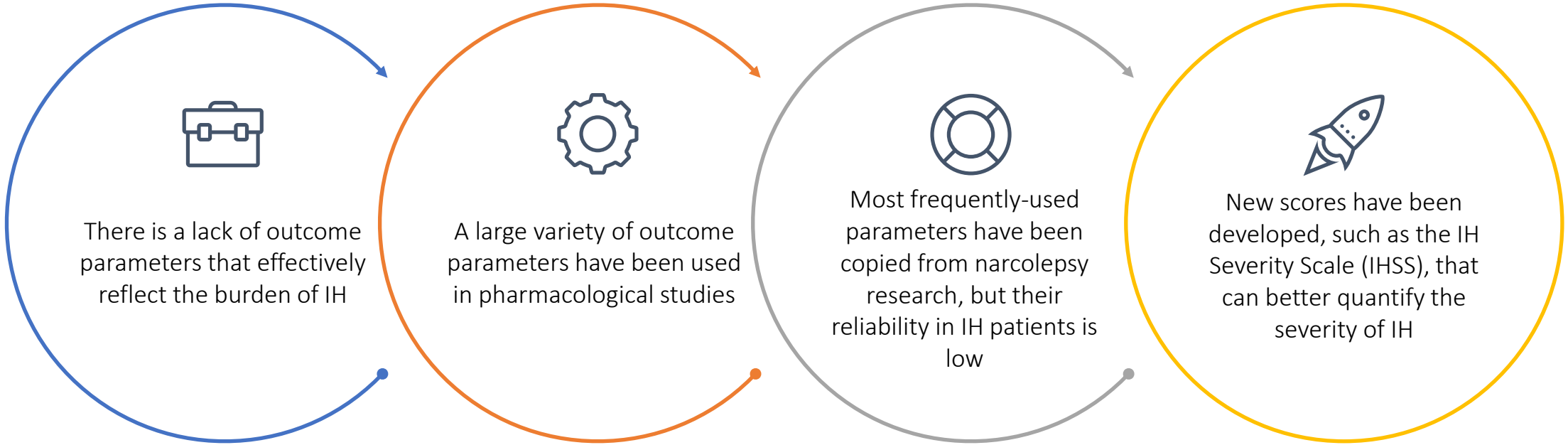
A. Daily periods of irrepressible need to sleep for ≥3 months
B. MSLT shows <2 SOREM
  a. SOREM within 15 min of PSG preceding MSLT can be used as one SOREM
C. Cataplexy is absent
D. MSLT shows a mean sleep latency ≤8 min, or the total sleep time is ≥660 min on a 24-h PSG
E. Insufficient sleep syndrome is ruled out
F. Symptoms and MSLT findings are not better explained by other causes

ICSD. International classification of sleep disorders. 3rd ed. American Academy of Sleep Disorders: Darien, IL, USA; 2014

Are you aware of the IHSS (Idiopathic Hypersomnia Severity Scale) and have you used it?

- Yes
- No

Challenges in Quantifying the Burden And Symptom Severity in IH



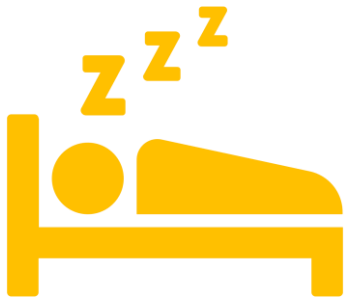
Schinkelshoek MS et al. *Current Sleep Medicine Reports* 5.4 (2019): 207-214; Dauvilliers et al. *Neurology* (2019); 92.15: e1754-e1762

The IHSS Scale is a recently developed tool to assess the symptom burden in IH. Which of the following is NOT one of the main objectives of this scale?

a. Prolonged, unrefreshing daytime and nighttime sleep
b. Brain Fog
c. Impaired daytime alertness
d. Sleep inertia

Idiopathic Hypersomnia Severity Scale (IHSS): An Emerging Tool to Assess Disease Severity and Burden

IHSS, which was developed in 2019, is a 14-item self-assessment questionnaire that measures the severity, frequency, and functional impact of the 3 key IH symptoms.



Prolonged, unrefreshing daytime and nighttime sleep

Impaired daytime alertness

Sleep inertia

Dauvilliers Y, et al. Neurology. 2019;92(15):e1754-e1762; Rassu AL et al. J Clin Sleep Med. 2022;18(2):617-629.

Idiopathic Hypersomnia Severity Scale

On the basis of your symptoms during the past month:

1. What for you is the ideal duration of nigh-time sleep (at the weekend or on holiday, for example)?

(3) 11 hours or more; (2) >9 hours and <11 hours; (1) Between 7-9 hours; (0) less than 7 hours

2. Do you feel that you have not had enough sleep?

(3) always; (2) often; (1) sometimes; (0) never

3. Is it extremely difficult, or even impossible to wake in the morning without several alarm calls or the help of someone close?

(3) always; (2) often; (1) sometimes; (0) never

4. How long does it take you to feel you are functioning properly after you get up?

(4) 2 hours or more; (3) more than 1 hour but less than 2 hours
(2) Between 30 minutes and 1 hour; (1) less than 30 minutes; (0) I feel I'm functioning properly as soon as I wake up

5. After waking up, do you ever do or say irrational things, and/or are you very clumsy?

(3) always; (2) often; (1) sometimes; (0) never

6. During the day, when circumstances allow, do you ever take a nap?

(4) Very often, 6-7 times/week; (3) often, 4-5 times/week; (2) sometimes, 2-3 times/week; (1) rarely, once a week; (0) never

7. What for you is the ideal length of naps?

(3) 2 hours or more; (2) more than 1 hour and less than 2 hours; (1) less than 1 hour; (0) no naps

8. In general, how do you feel after a nap?

(3) Very sleepy; (2) sleepy; (1) awake; (0) wide awake

9. During the day, while carrying out activities that are not very stimulating, do you ever struggle to stay awake?

(4) Very often, at least 2x/day; (3) often, 4-7x/week; (2) sometimes, 2-3x/week; (1) rarely, 1x/week or less; (0) never

10. Do you consider that your hypersomnolence has an impact on your general health?

(4) Very significant; (3) significant; (2) moderate); (1) minor; (0) no impact

11. Do you consider that your hypersomnolence is a problem in terms of your proper intellectual functioning?

(4) Very significant; (3) significant; (2) moderate); (1) minor; (0) no problem

12. Do you consider that your hypersomnolence affects your mood?

(4) Very severely; (3) severely; (2) moderately; (1) slightly; (0) not at all

13. Do you consider that your hypersomnolence prevents you from carrying out daily tasks properly?

(4) Very significantly; (3) significantly; (2) moderately; (1) slightly; (0) not at all

14. Do you consider that your hypersomnolence is a problem in terms of your driving a car?

(4) Very significant; (3) significant; (2) moderate; (1) minor; (0) no problem/I do not drive

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

IHSS: Clinically Relevant Score Ranges

Goal:
To confirm 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

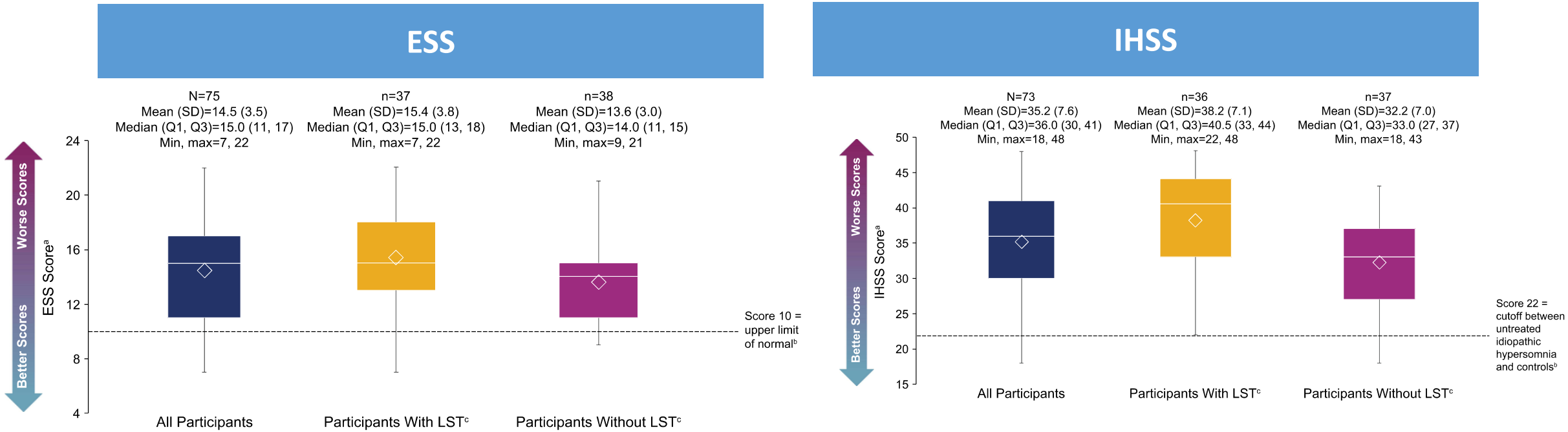
Cut off to discriminate IH and controls:
22

Sensitivity: 91.1%
Specificity: 94.5%

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

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

Burden of IH can be Assessed in Real World Using ESS and IHSS Tools

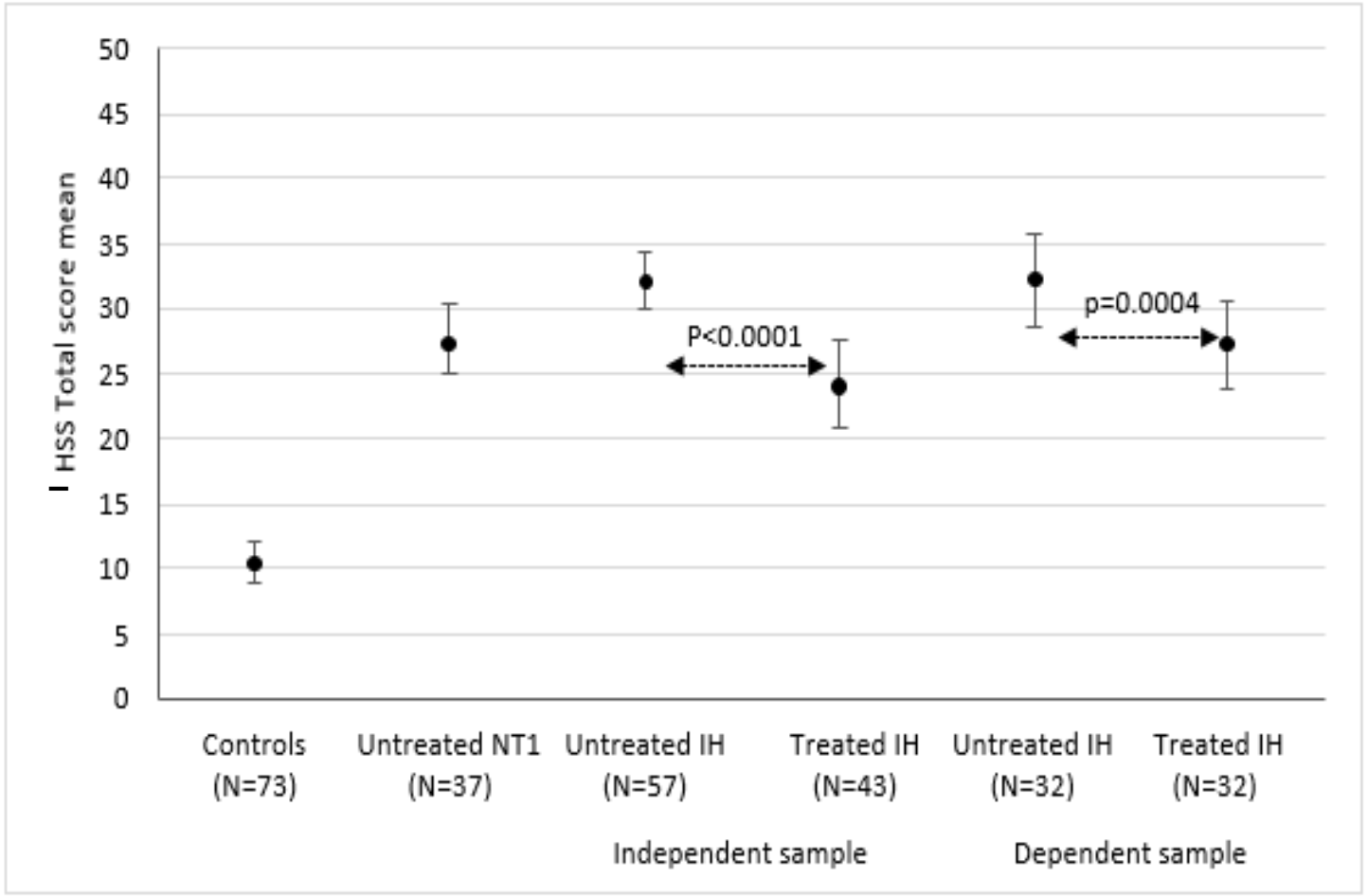


- The mean (SD) ESS score was 14.5 (3.5). For patients with and without LST, ESS scores were 15.4 (3.8) and 13.6 (3.0), respectively. Most patients (88.0%) scored >10, indicating pathological sleepiness; including patients with LST (89.2%) or without LST (86.8%)
- The mean (SD) IHSS score was in the severe range at 35.2 (7.6) for all patients, 38.2 (7.1) for patients with LST, and 32.2 (7.0) for those without LST

LST, long sleep time

Schneider LD, et al. *Nat Sci Sleep*. 2023;15:89-101.

Measurement of symptoms in idiopathic hypersomnia



212 subjects total completed IHSS
- 100 (57 untreated and 43 treated) IH
- 37 untreated NT1
- 73 controls without sleepiness

- Higher scores in drug-free IH patients 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

How to diagnose IH?

- **Clinic:**
  - EDS
  - Excessive quantity for sleep
  - Sleep inertia assessment: Need for standardized questions
  - Quantification of symptoms severity: IHSS
  - Age, gender

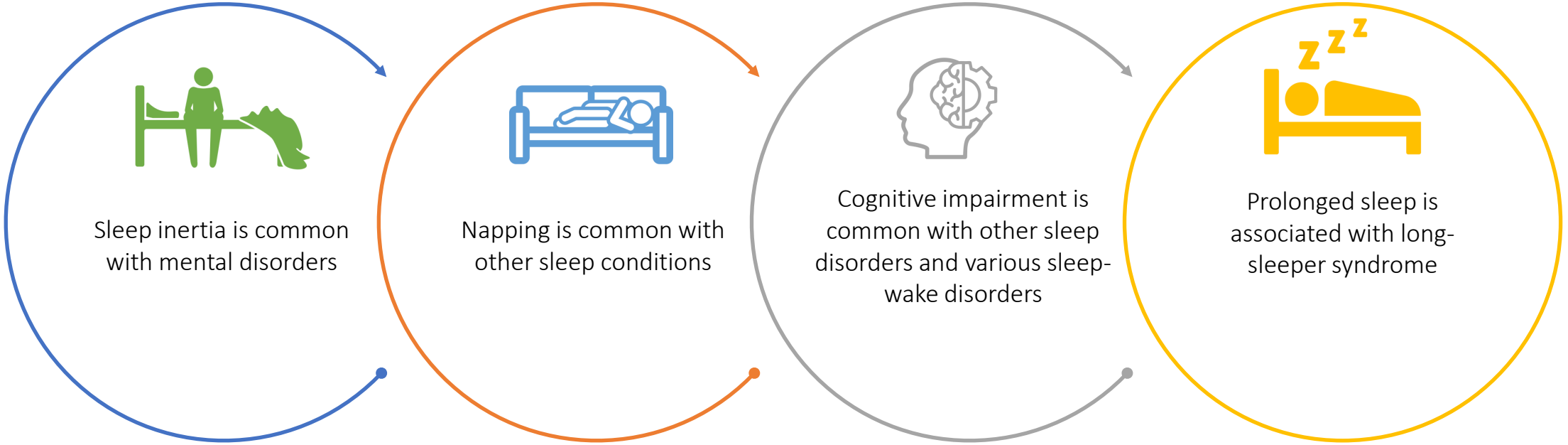
- **MSLT**:
  - Highly variable from test to test
  - Excluding narcolepsy spectrum…

- **Long TST recording:**
  - Poorly standardized assessment
  - Actigraphy-diary
  - Long-term **PSG** recording…

Dauvilliers Y et al. *Sleep Medicine Reviews* 2022: 101709
Lammers GJ. *Sleep Medicine Reviews*. 2020; 52:101306

Challenges of With the Current Diagnostic Parameters of IH

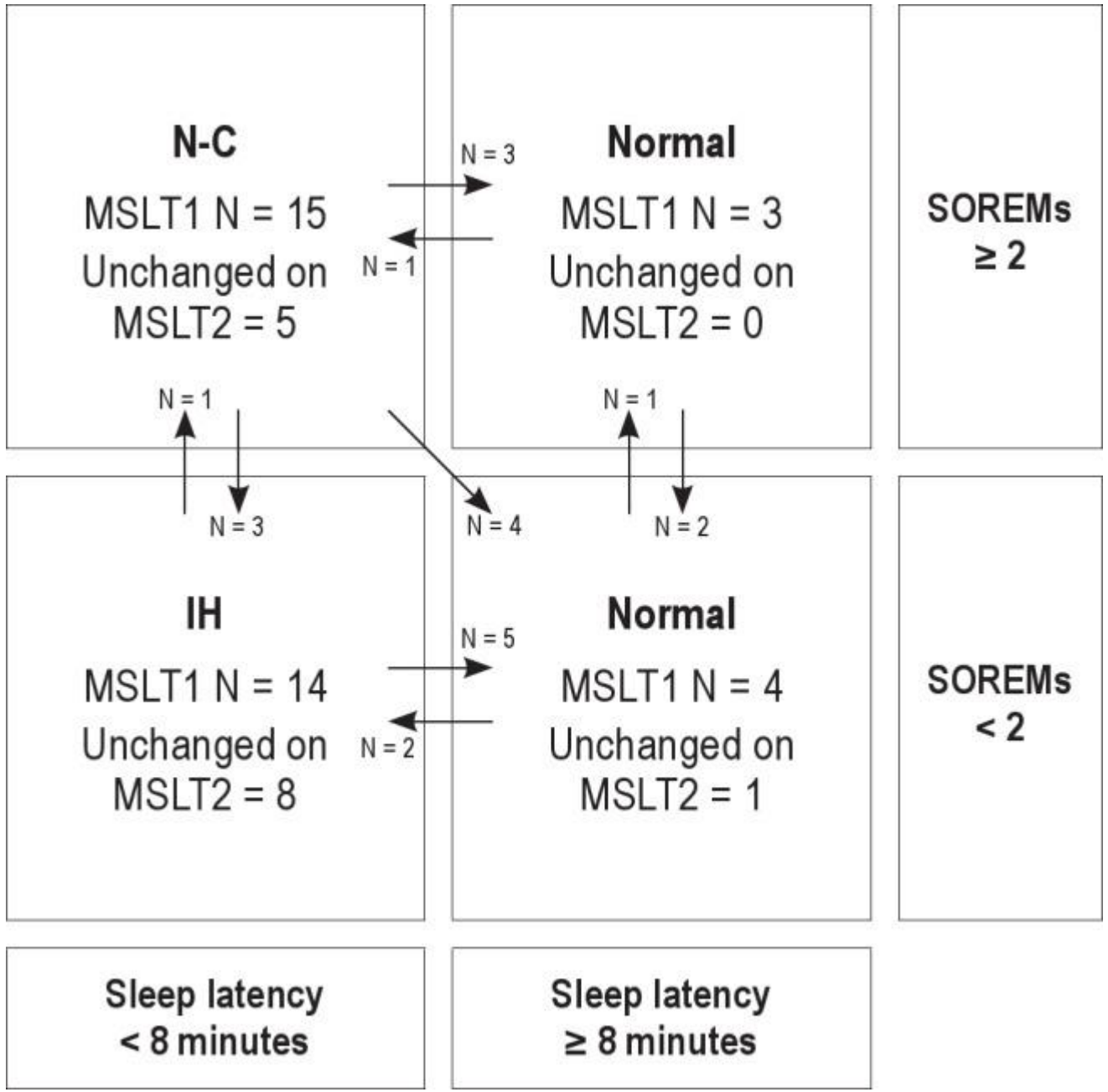
Other sleep and neurological disorders present with symptoms similar to IH



American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014;
Lammers GJ. *Sleep Medicine Reviews*. 2020; 52:101306 ; Trotti LM. *Sleep Med Rev*. 2017;35:76-84; Trotti LM nd Arnulf I. *Neurotherapeutics*. 2021;18(1):20-31.

IH Diagnosis: MSLT cannot be the gold standard

- MSLT demonstrates poor test-retest reliability
- The PSG-MSLT measures and classification are not stable in patients with noncataplectic central disorders of hypersomnolence, particularly for NT2 and IH, compared with NT1
- MSLT is more reproducible and stable feature in NT1 vs. NT2



SOREMs, sleep onset REM periods. N-C, narcolepsy without cataplexy; IH, idiopathic hypersomnia.

Trotti LM et al. *J Clin Sleep Med* 2013; 9.8: 789-795
Lopez R et al. *Sleep* 2017; 40.12: zsx164
Ruoff C et al. *J Clinc Sleep Med* 2018; 14.1: 65-74

Test-Retest Reliability of Multiple Sleep Latency Test in Central Disorders of Hypersomnolence

Two PSG-MSLTs in untreated patients with central hypersomnolence (median: 1.9 y)
22 NT1 and 75 others: NT2 (22.7%), IH (26.7%) or unspecified EDS (50.6%).

Non-cataplectic central disorders of hypersomnolence		MSLT #2				Total
		Hypersomnia phenotype	Narcolepsy phenotype	REM dysregulation phenotype	Normal phenotype	
MSLT #1	Hypersomnia phenotype	5 (25.0%)[1]	5 (25.0%)	1 (5.0%)	9 (45.0%)	20
	Narcolepsy phenotype	0 (0.0%)	8 (47.1%)	1 (5.9%)	8 (47.1%)	17
	REM dysregulation phenotype	3 (13.6%)	5 (22.7%)	7 (31.8%)	7 (31.8%)	22
	Normal phenotype	6 (37.5%)	1 (6.2%)	0 (0.0%)	9 (56.2%)	16
Total		14	19	9	33	75

Narcolepsy type 1		MSLT #2				Total
		Hypersomnia phenotype	Narcolepsy phenotype	REM dysregulation phenotype	Normal phenotype	
MSLT #1	Hypersomnia phenotype	0 (0.0%)[1]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	Narcolepsy phenotype	1 (6.2%)	13 (81.3%)	2 (12.5%)	0 (0.0%)	16
	REM dysregulation phenotype	0 (0.0%)	1 (20.0%)	3 (60.0%)	1 (20.0%)	5
	Normal phenotype	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1
Total		1	15	5	1	22

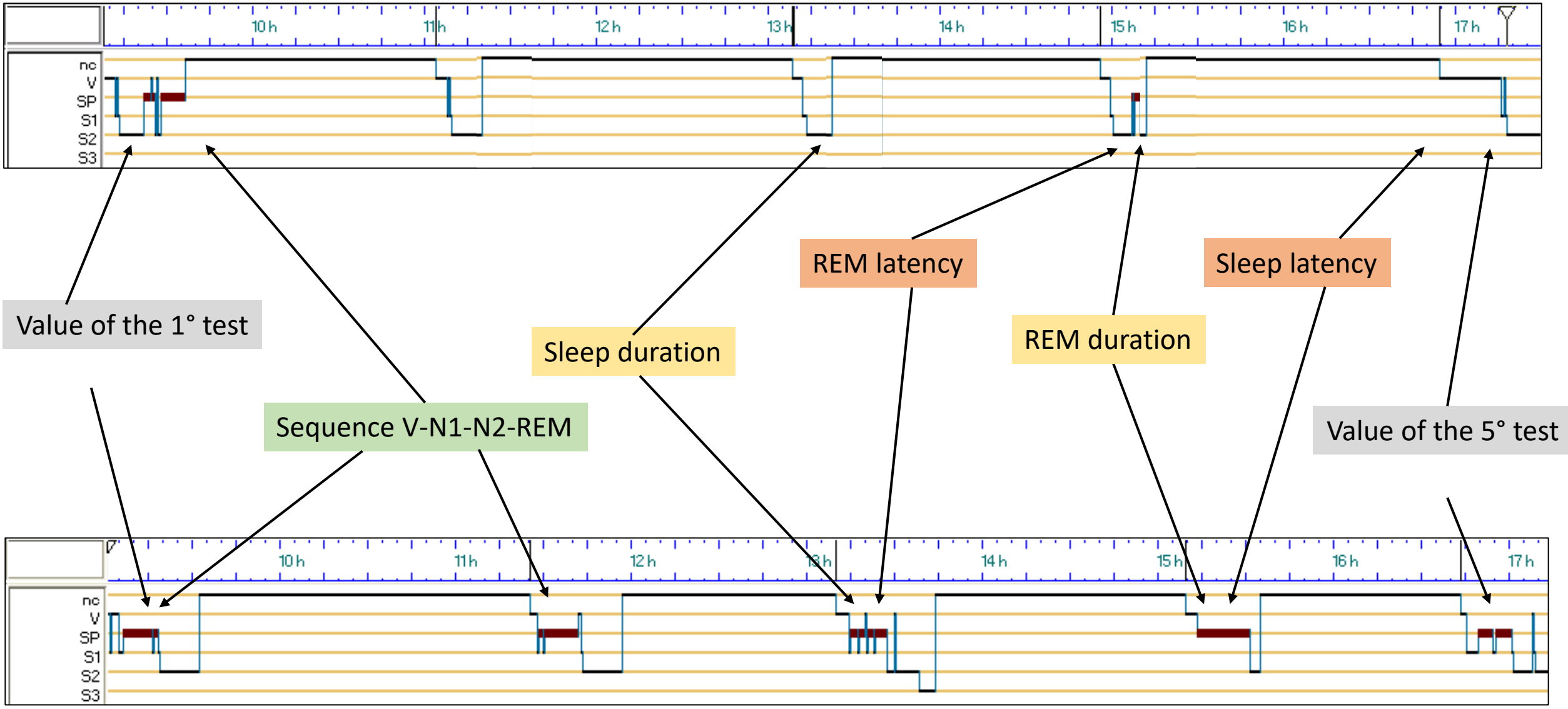
NT1: 43/53 81.1%
NT2: 9/30 30.0%

Instability of MSLT values: Change in classification in NT2 and IH / NT1
MSLT: To be perform twice to confirm the primary diagnosis of NT2 if stable criteria ?

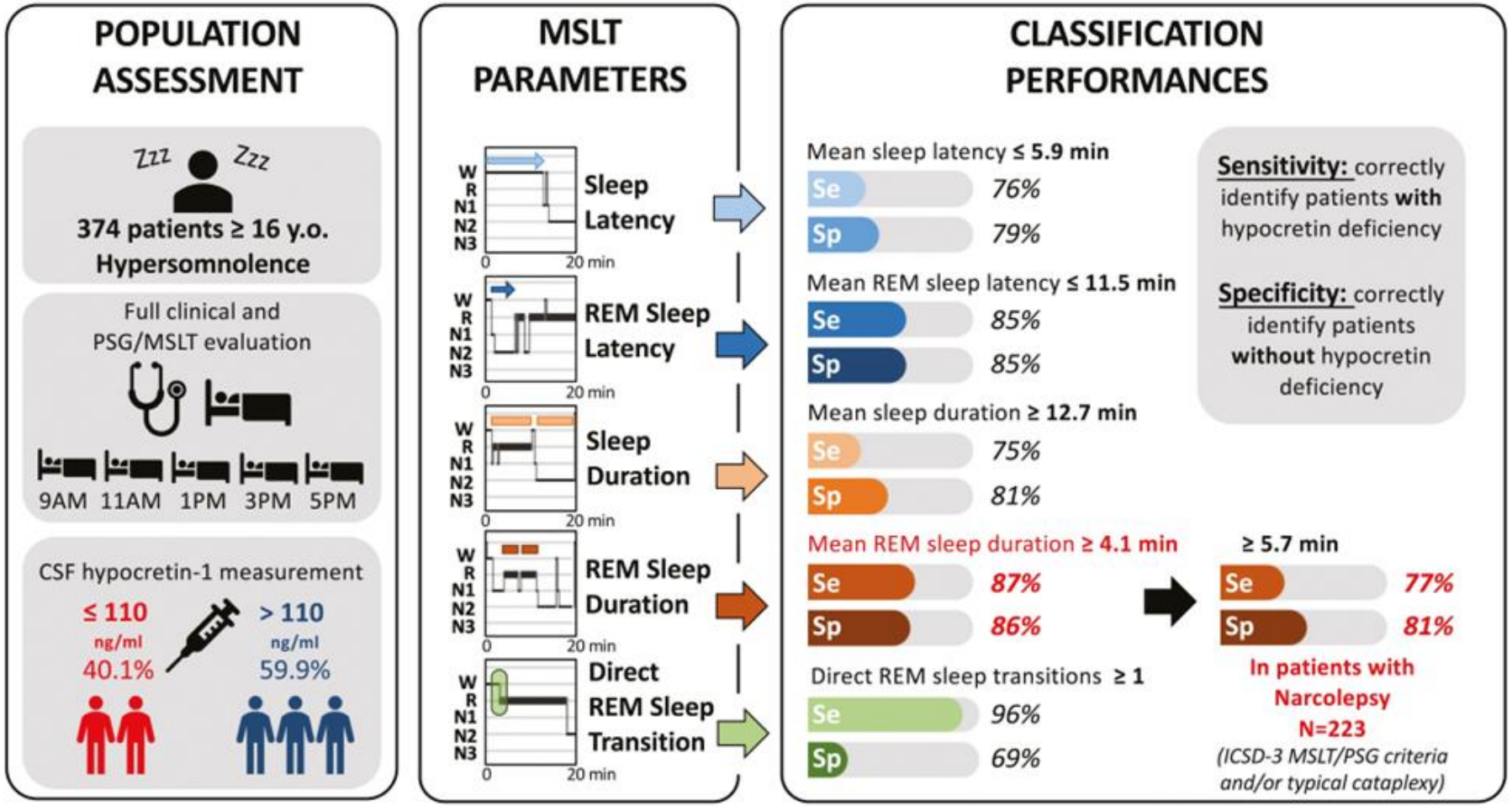
Lopez R et al. *Sleep* 2017; 40.12: zsx164

Rapid eye movement sleep duration during the multiple sleep latency test to diagnose hypocretin-deficient narcolepsy

Lopez R., …, Dauvilliers Y, *Sleep* 2023; 46.1: zsac247



Can the Multiple Sleep Latency Test identify hypocretin deficiency in patients with a complaint of hypersomnolence ?



Rapid Eye Movement Sleep Duration on the MSLT best predicts hypocretin deficiency in patients with hypersomnolence and in patients with narcolepsy

Lopez R., …, Dauvilliers Y, *Sleep* 2023; 46.1: zsac247

Few studies recorded patients with 24-h protocol recording

Idiopathic hypersomnia

M. Billiard[1] and Y. Dauvilliers[1]

Sleep Medicine Reviews, Vol. 5, No. 5, pp 351–360, 2001

Idiopathic Hypersomnia with and without Long Sleep Time: A Controlled Series of 75 Patients

Sleep 2009

Cyrille Vernet, MSc[1,2,3]; Isabelle Arnulf, MD, PhD[1,2,3]

Daytime continuous polysomnography predicts MSLT results in hypersomnias of central origin

FABIO PIZZA[1], KEIVAN K. MOGHADAM[1], STEFANO VANDI[1], STEFANIA DETTO[1], FRANCESCA POLI[1], EMMANUEL MIGNOT[2], RAFFAELE FERRI[3] and GIUSEPPE PLAZZI[1]

J Sleep Res 2013

Alternative Diagnostic Criteria for Idiopathic Hypersomnia: A 32-Hour Protocol

Elisa Evangelista, MD,[1,2,3] Régis Lopez, MD, PhD,[1,2,3] Lucie Barateau, MD,[1,2,3] Sofiene Chenini, MD,[1] Adriana Bosco, PhD,[1] Isabelle Jaussent, PhD,[2,3] and Yves Dauvilliers, MD, PhD[1,2,3]

ANN NEUROL 2018;83:235–247

Evaluation of pathological sleepiness by Multiple Sleep Latency Test and 24-hour polysomnography in patients suspected of idiopathic hypersomnia

Makoto Honda, MD, PhD,[1,2†] Shinya Kimura, Certified PSGT,[2†] Kaori Sasaki, Certified PSGT,[2†] Masataka Wada, MD[2,3†] and Wakako Ito, MD, PhD[2†]

Psychiatry and Clinical Neurosciences 75: 149–151, 2021

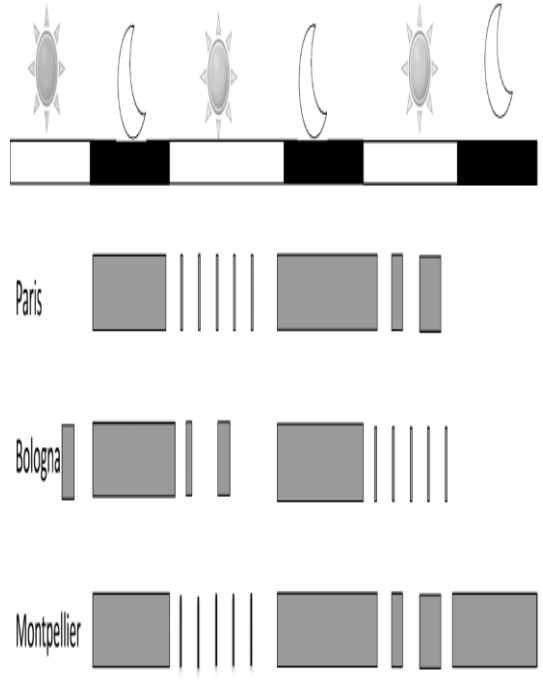
Variable inclusion criteria → Abnormal MSLT or total sleep time ≥11 hours

Lack of validation and standardization →

- Level of physical and social activity, lights…
- Variable duration: 20 or 24 hours
- Invitation to nap or free-running protocol
- Ambulatory vs in lab

Variable daytime sleep duration before recording →

MSLT preceding or following recording
Sleep duration during MSLT



Idiopathic Hypersomnia with and without Long Sleep Time: A Controlled Series of 75 Patients

Vernet C, and Arnulf, I. *Sleep*. 2009; 32.6:753-759.

75 patients with IH: Complaint of EDS, **MSLT < 8 min OR TST > 11 on long-term PSG monitoring (cut off pre-decided!)**
30 controls with MSL > 8 min
PSG – MSLT and then ad libitum PSG recording till 5 PM
Books, newpapers, watches, walking, daylight allowed, and invitation of two naps (before and after lunch)

Sleep measures	Patients	Controls	P
Number	75	30	
Nighttime sleep			
Total sleep time, min	579 ± 90	491 ± 77	< 0.0001
Sleep efficiency, %	90.9 ± 6.3	88.8 ± 7.3	0.18
Latency to, min			
Sleep onset	31.2 ± 41.6	32.0 ± 20.9	0.90
REM sleep	81.5 ± 48.0	84.2 ± 43.7	0.79
Sleep stages, % total			
stages 1-2	55.4 ± 9.1	53.8 ± 7.8	0.38
stages 3-4	20.8 ± 8.2	24.9 ± 6.5	0.01
REM sleep	23.7 ± 6.5	21.1 ± 4.6	0.02
Sleep fragmentation			
Arousals, n/h	8.7 ± 5.8	18.0 ± 8.9	< 0.0001
Periodic legs movements, n/h	8.5 ± 12.5	5.9 ± 20.7	0.54
Apnea/hypopnea, n/h	2.3 ± 3.7	4.4 ± 5.4	0.05
End of the night			
SWS after 06:00, % patients	60.6	36.7	0.03
Time of last SWS episode	8:44 ± 1:40	6:11 ± 1:45	< 0.0001
Sleep during 24-hour monitoring			
Total sleep time, min	695 ± 99	525 ± 87	< 0.0001
Sleep stages, % total			
stages 1-2	58.2 ± 9.0	55.8 ± 7.4	0.17
stages 3-4	19.7 ± 7.9	26.1 ± 8.5	0.0008
REM sleep	22.1 ± 6.0	20.0 ± 4.3	0.06

Table 6—Mean Sleep Onset Latency During Multiple Sleep Latency Tests in the Various Studied Groups

Subjects	Controls	Patients with idiopathic hypersomnia	P	Hypersomniacs without long sleep time	Hypersomniacs with long sleep time	P
No.	30	75		35	40	
Mean sleep latency (MSL) ± SE, min	15.8 ± 0.7	7.8 ± 0.5	< 0.0001	5.6 ± 0.3	9.6 ± 0.7	< 0.0001
Subjects with (%)						
MSL < 8 min	3.3	60.9	< 0.0001	100	28.6	< 0.0001
MSL between 8 and 10 min	0.0	9.4	< 0.0001	0.0	17	< 0.0001
MSL > 10 min	96.6	29.7	< 0.0001	0.0	54	< 0.0001

MSLT differs between IH and controls but cut off of 8 min insensitive

During 20-h recording:
Median sleep duration in IH: 672-718 min (40 with TST > 600 min)
Median sleep duration in controls: 522 min 95% IC:493-558: **9.3 hours**
So why 11 H ?

CMHC Cardiometabolic Health Congress

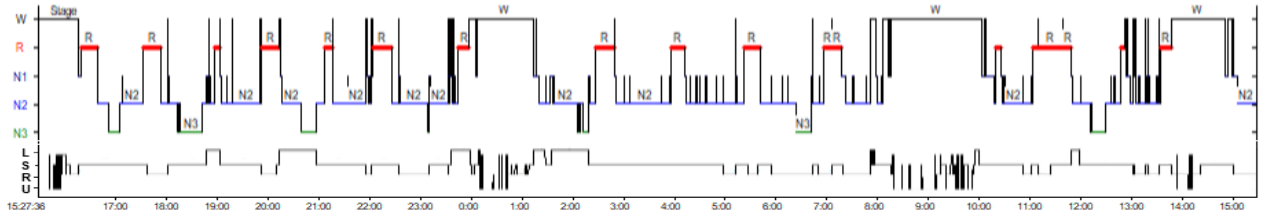
EXPERT PERSPECTIVES AND DISCUSSIONS

Evaluation of pathological sleepiness by Multiple Sleep Latency Test and 24-hour polysomnography in patients suspected of idiopathic hypersomnia

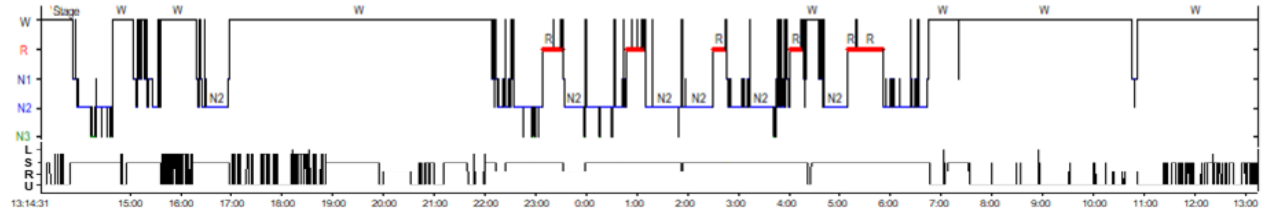
Honda M. et al. *Psychiatry Clin Neurosci* 2021; 75(4): 149-151

24-h PSG then PSG and MSLT
35 patients included: 27 with TST > 660 min, 6 with MSLT < 8 min (4 in common), 6 without criteria
Diagnosis: IH, NT2, subjective hypersomnolence…
NO controls

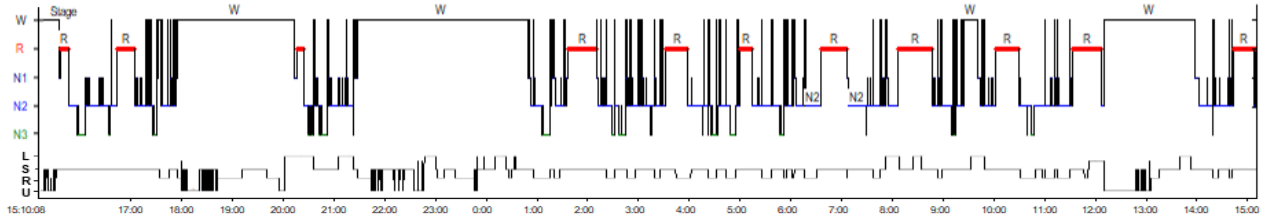
Subtype 1 24hr PSG-determined type 23F (24hr-PSG TST 1104 min, MSLT mSL 9.1 min, SOREMP 0/4)



Subtype 2 MSLT-determined type 32M (24hr-PSG TST 590 min, MSLT mSL 4.6 min, SOREMP 0/4)



Subtype 3 Mixed type 25F (24hr-PSG TST 906 min, MSLT mSL 4.5 min, SOREMP 3/4)



	Sensitivity	Specificity	Accuracy	Misclassification
MSLT	12%	80%	34%	79%
24 hour PSG	92%	60%	83%	

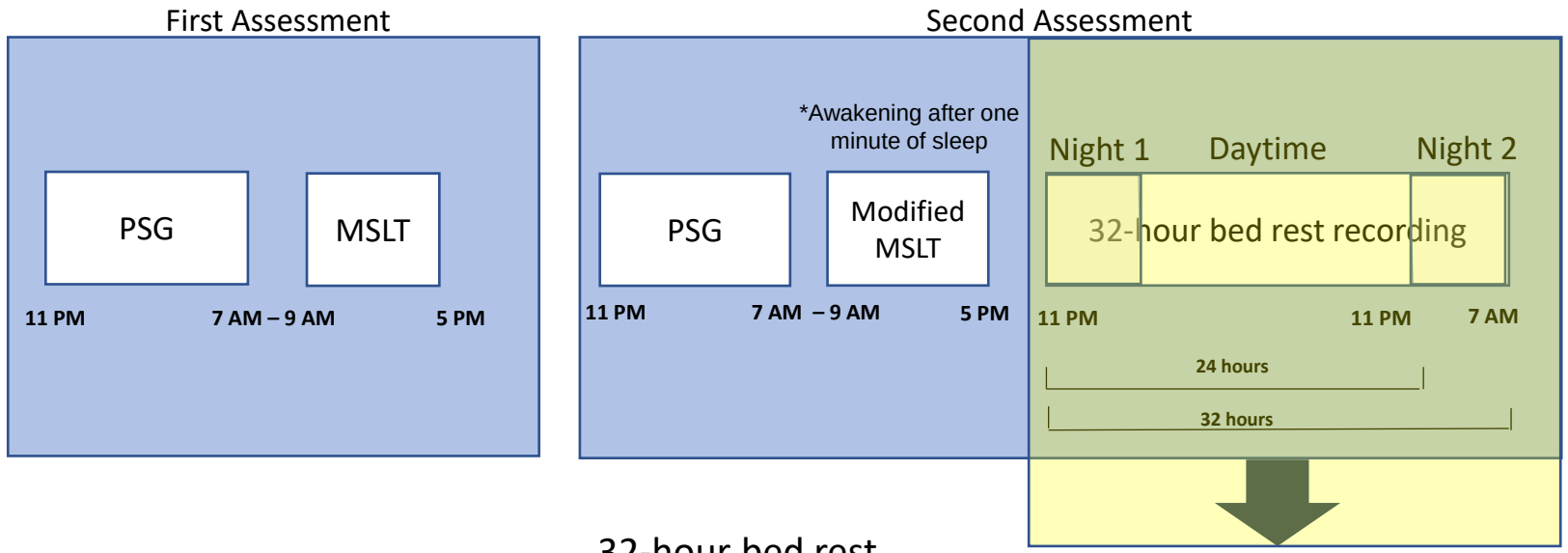
MSLT cannot diagnose IH patients with LST complaints
Bias: No patients included without complaint of long TST

Two dimensions of Hypersomnolence
- High sleep propensity
- Prolonged sleep

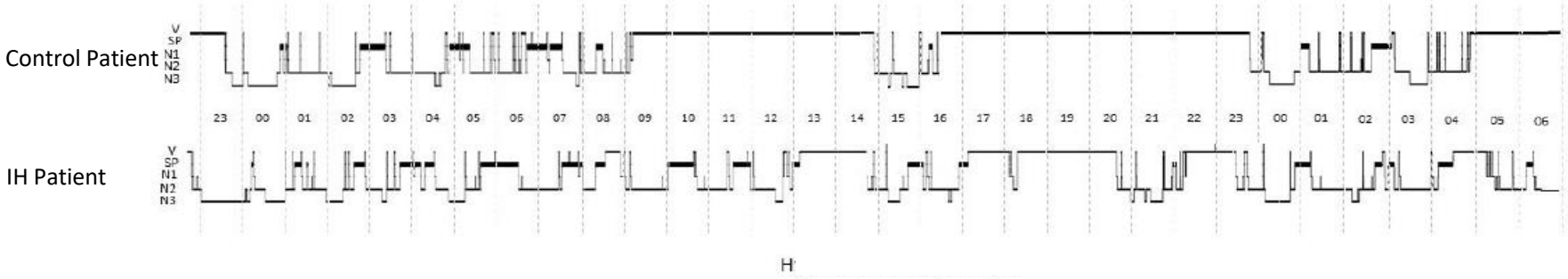
Different assessments, different pathophysiology ?

Alternative Diagnostic Criteria for Idiopathic Hypersomnia: A 32-Hour Protocol

Evangelista E. et al. *Ann Neurol* 2018; 83(2): 235-247



32-hour bed rest



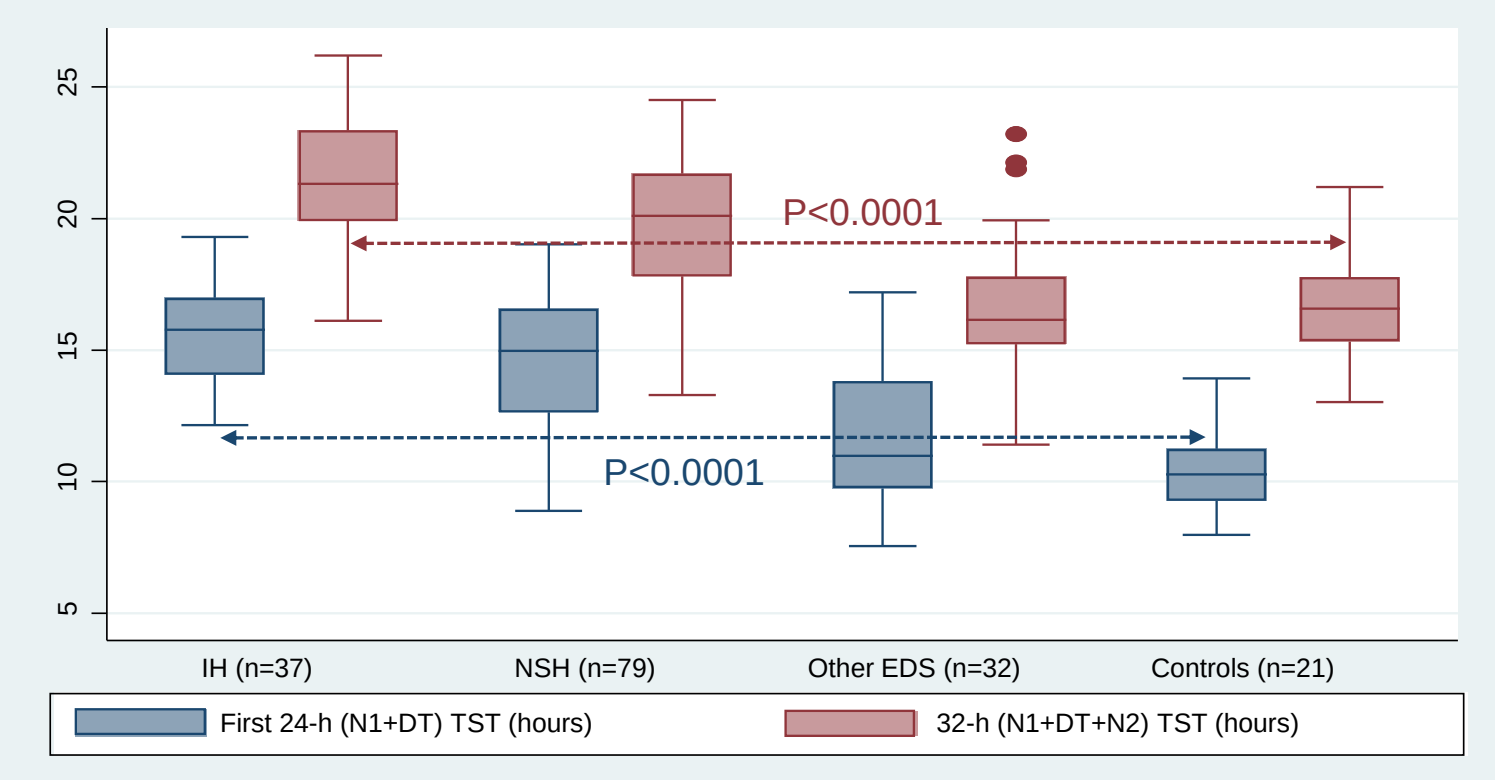
TST cutoff to discriminate IH to controls was **19 hours over 32-hour recording**

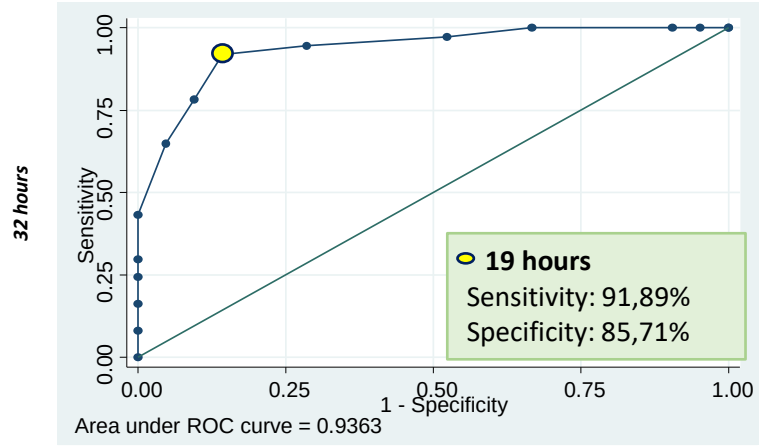
116 hypersomnolence complaint (EQS or EDS): no cataplexy, obesity, sleep-deprived, drug, depression/comorbidities

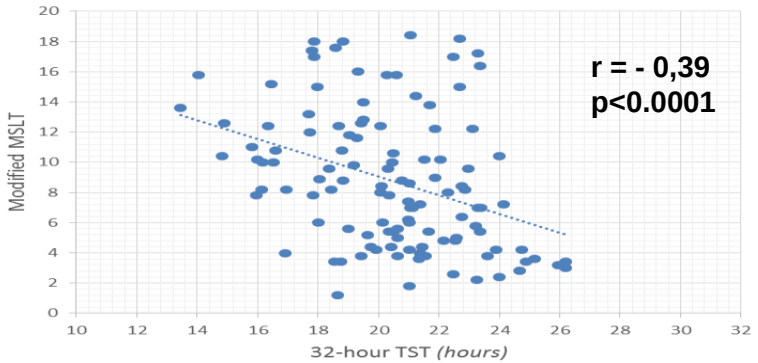
37 with MSLT<8min (IH) and 79 with MSLT >8 min (NSH)

32 other EDS (AHI>15, depression, PLMS>15, obesity)

21 controls: No sleep complaint or problems







TST cut off to discriminate IH to controls was **19h on 32-hour (12h on 24-h) controlled bed-rest protocol**

Better phenotype (TST>19h): Lower MSLT, more sleep inertia, overweight

KEY INTEREST for diagnosis and research purposes – Continuum between IH with / without LST

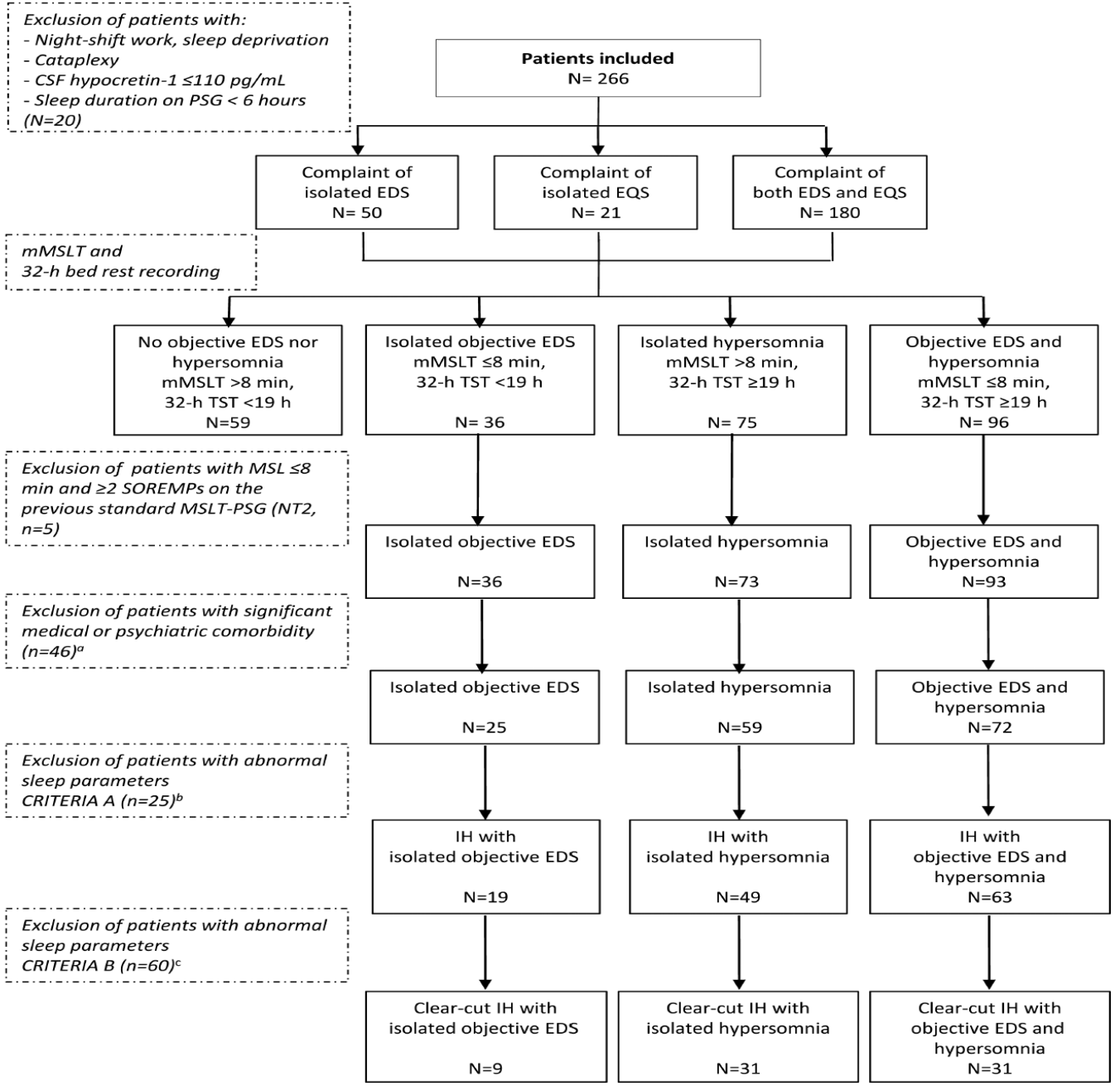
Characteristics associated with hypersomnia and excessive daytime sleepiness identified by extended polysomnography recording

- 266 drug-free patients with hypersomnolence (EDS 90%, EQS 80%) underwent PSG-mMSLT and 32-h bed rest PSG recording
- No sleep deprived, no cataplexy, no shift work, hcrt Nl….
- Categorization as function of 19-h TST and MSLT 8 min

Differentiation between
- Isolated objective EDS
- Isolated Hypersomnia
- Objective EDS and hypersomnia

N=71 with IH among 202 patients
51 women, age 24 [17-54]

Request to better understanding pathophysiology, biology, specific biomarkers, personalized management and health outcomes ?

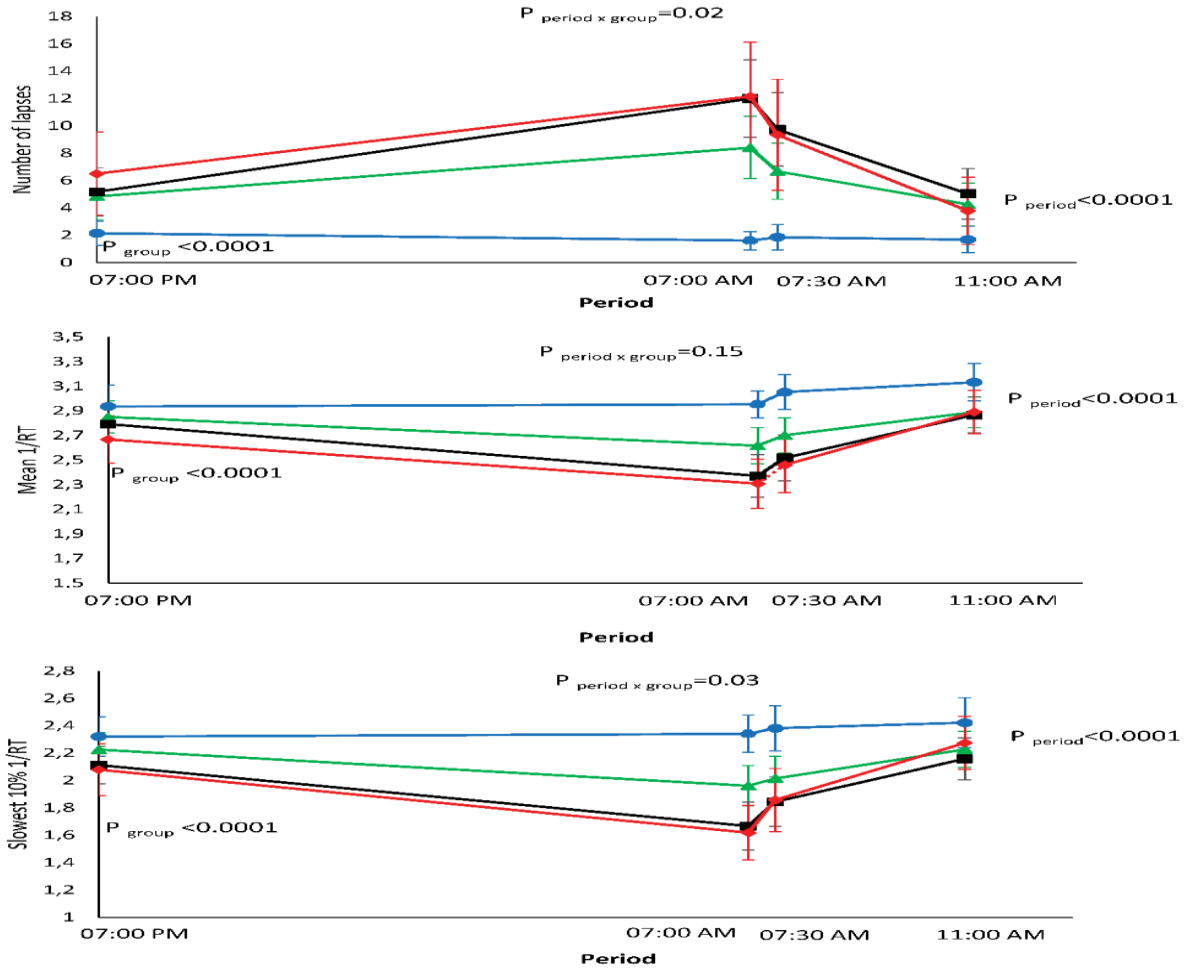


EDS= ESS >10; EQS= self reported sleep duration ≥9 h over the 24 hours during the week; NT2= Narcolepsy type 2
[a] i.e. Patients with body mass index ≥30 kg/m² or BDI-II score ≥20
[b] i.e. Patients with sleep efficiency <85%, AHI ≥10/h, PLMS ≥15/h
[c] i.e. Patients with N3% <15%, REM% <15%, micro-arousal index ≥15/h

Evangelista E. et al. *Sleep* 2021; 44.5: zsaa264

Sleep inertia measurement with the psychomotor vigilance task in idiopathic hypersomnia

Evangelista E. et al. *Sleep* 2022; 45(1): zsab220



Sleep inertia is frequent in IH but poorly defined and assessed
Self-reported questionnaire (IHSS, 3 questions) and 4 PVT (7 PM, 7-7:30-11 AM)
in 62 IH patients and 140 non IH (NT1, OSAS, NSH, insomnia)
Whether PVT can reliably measure sleep inertia

Sleep inertia was more frequent in IH patients (57% vs 43%)

Lapses number increases especially at 7 / 7:30 AM

- as function of SI severity
- regarless of sleep drunkenness and sleep disorders

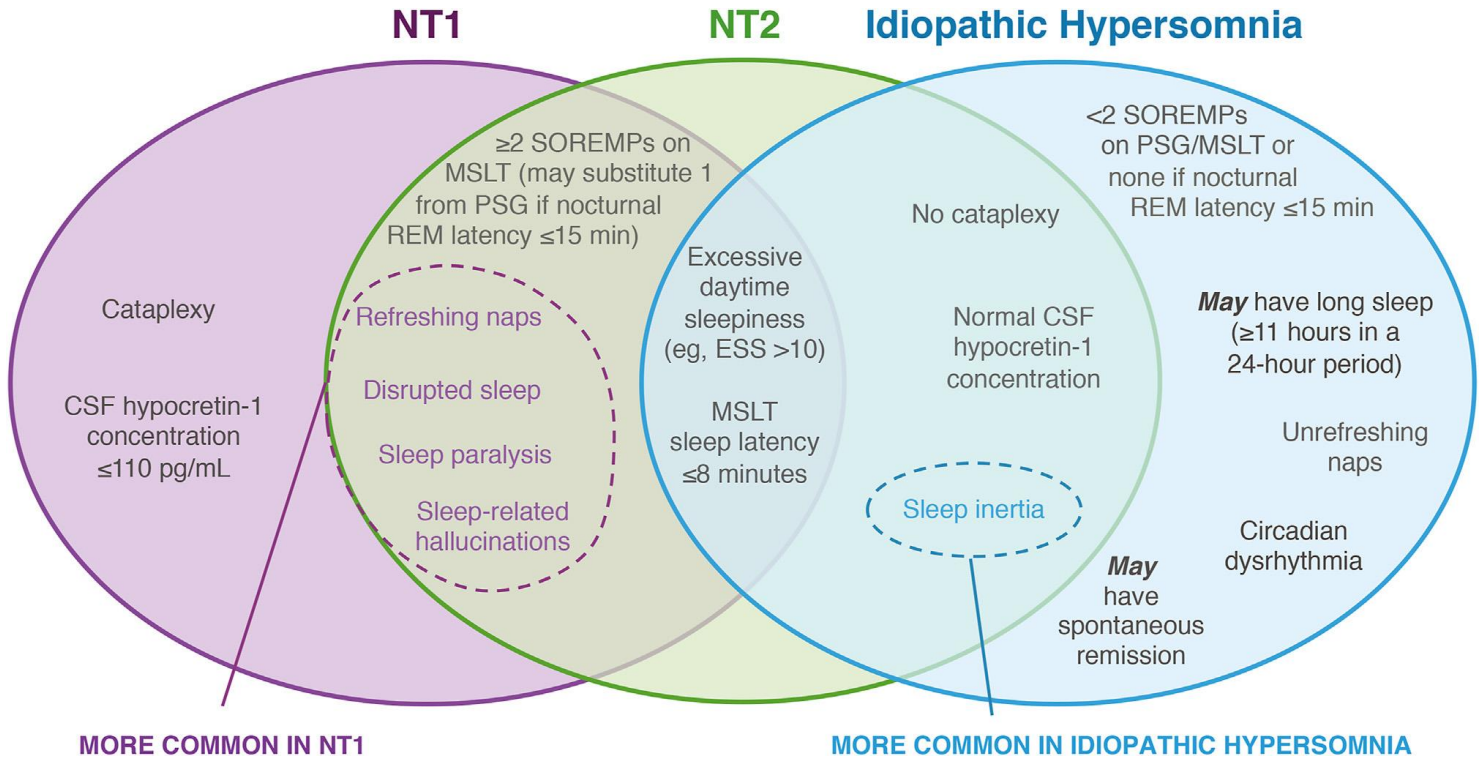
PVT is a reliable and objective measure of sleep inertia
PVT may help to optimize managment and follow-up

CMHC Cardiometabolic Health Congress

EXPERT PERSPECTIVES AND DISCUSSIONS

Differentiating IH from Narcolepsy Type 1 and Type 2

- Narcolepsy type 1 (NT1) and type 2 (NT2) share the same MSLT diagnostic criteria with IH but require two or more sleep onset rapid eye movement period (SOREMP)
- The presence of cataplexy or low cerebrospinal fluid (CSF) levels of hypocretin-1 are characteristics of NT1
- Distinguishing idiopathic hypersomnia from NT2 is more challenging
- Sleep inertia is more common and often more severe in IH compared with NT2



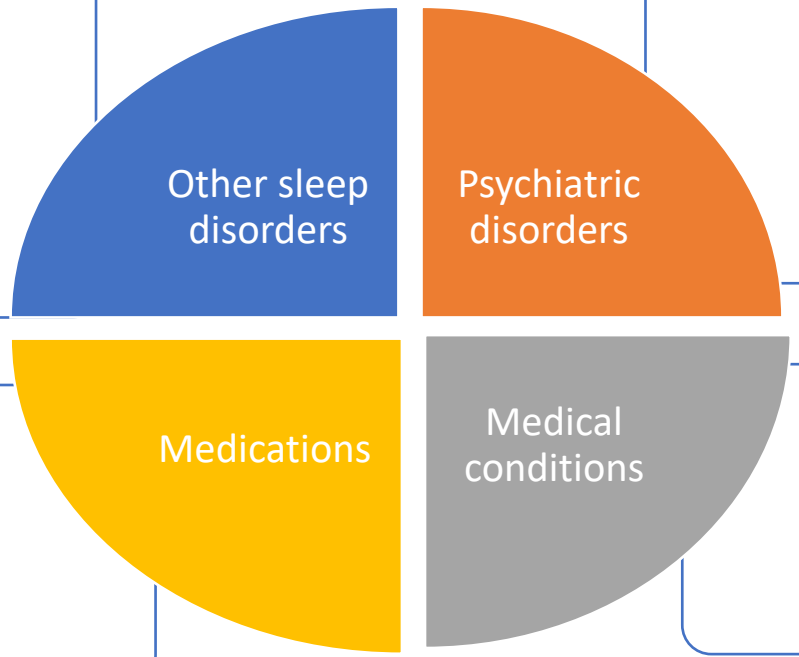
Dauvilliers Y, et al. *Sleep Med Rev*. 2022;66:101709.

Narcolepsy Type 1	Narcolepsy Type 2	Idiopathic Hypersomnia
Criteria A and B must be met	Criteria A-E must be met:	Criteria A-F must be met
A. Daily periods of irrepressible need to sleep for ≥3 months	**A.** Daily periods of irrepressible need to sleep for ≥3 months	**A.** Daily periods of irrepressible need to sleep for ≥3 months
B. Presence of one or both: a. Cataplexy with a mean sleep latency of ≤8 min and ≥2 SOREM on MSLT i. SOREM within 15min of PSG preceding MSLT can be used as one SOREM b. CSF hypocretin-1 concentration is ≤110 pg/mL or 1/3 mean value of normal subjects	**B.** Mean sleep latency of ≤8 min and ≥2 SOREM on MSLT a. SOREM within 15 min of PSG preceding MSLT can be used as one SOREM **C.** Cataplexy is absent **D.** Either CSF hypocretin-1 has not been measured, or levels are >110 pg/mL or > 1/3 mean value of normal subjects **E.** Symptoms of MSLT findings are not better explained by other causes	**B.** MSLT shows <2 SOREM a. SOREM within 15 min of PSG preceding MSLT can be used as one SOREM **C.** Cataplexy is absent **D.** MSLT shows a mean sleep latency ≤8 min, or the total sleep time is ≥660 min on a 24-h PSG (not typically done in the USA) **E.** Insufficient sleep syndrome is ruled out **F.** Symptoms and MSLT findings are not better explained by other causes

AASM. *The International Classification of Sleep Disorders: Diagnostic and Coding Manual*. 3rd ed. 2014

Differential Diagnosis of IH

- Delayed sleep-wake phase disorder
- Obstructive sleep apnea
- Narcolepsy
- Post-Viral Hypersomnia
- Idiopathic Recurrent Stupor
- Ornityl-Carnitine Transferase Deficit



- Mood disorders
- Schizoaffective disorders
- Somatoform disorders
- Depression
- Bipolar Disorder (Rapid Cyclic)
- Seasonal Affective Disorder

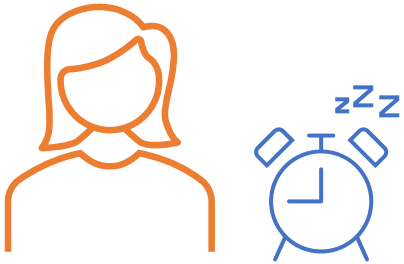
- Sedating medications
- Withdrawal from amphetamines or other stimulants

- Traumatic brain injury
- Chronic fatigue syndrome

There is no specific biomarker for IH. Patients may go undiagnosed for 10 to 15 years after the onset of their initial symptoms of IH

Dauvilliers Y et al. *Sleep Medicine Reviews* 2022: 101709; Lammers GJ. *Sleep Medicine Reviews*. 2020; 52:101306
Trotti LM et al. *Neurotherapeutics* (2021); 18: 20-31; Dauvilliers Y, et al. *Sleep Med Rev*. 2022;66:101709; Masri TJ, et al. *Sleep Med Clin*. 2012;7(2):283-289.

Patient Case - Results of Investigations



ESS: 14

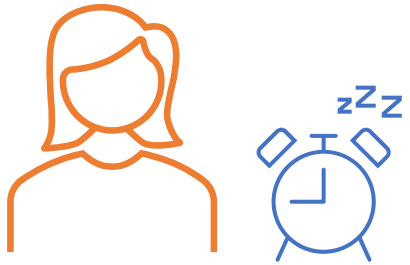
IHSS: 32

PSG: TST 540mins, SE 92%, SL 15 mins, RL 60 mins

AHI 6/hr Lo2Sat 89%

MSLT: MSL: 7 mins 1 SOREMP

ARS #4

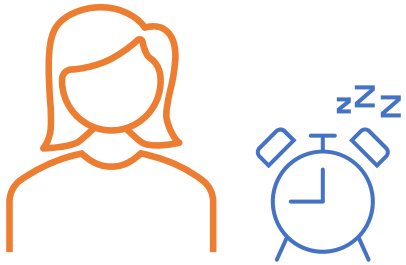


What is your current diagnosis?

1. Delayed sleep phase syndrome
2. Narcolepsy Type 2
3. Idiopathic Hypersomnia
4. Obstructive sleep apnea syndrome
5. Depression

ARS #5

Which do you regard as the best method for investigating Idiopathic Hypersomnia ?

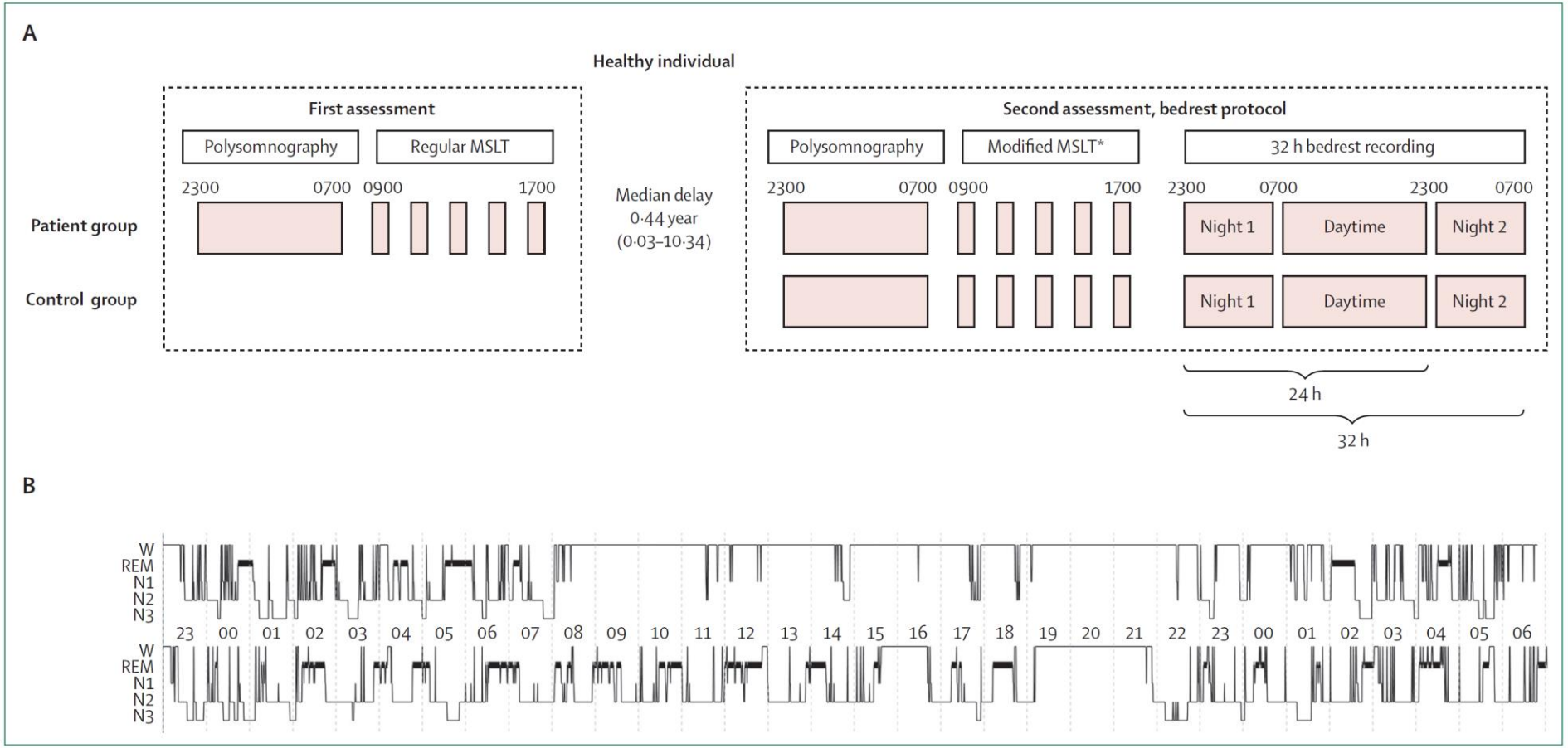


1. Sleep interview
2. Sleep diary
3. Actigraphy
4. Polysomnography and MSLT
5. Continuous 24h PSG recording
6. Continuous 32h PSG recording

Results of Continuous 32-hour PSG recording

TST: 1224 mins (20.4 h/32)

Prolonged first nighttime sleep
Two long naps of more than 1 hour
Normal second nighttime sleep



Pérez-Carbonell L, et al. *The Lancet*. 2022

Current IH Treatment

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Sleep-Wake Disorders Center
Department of Neurology
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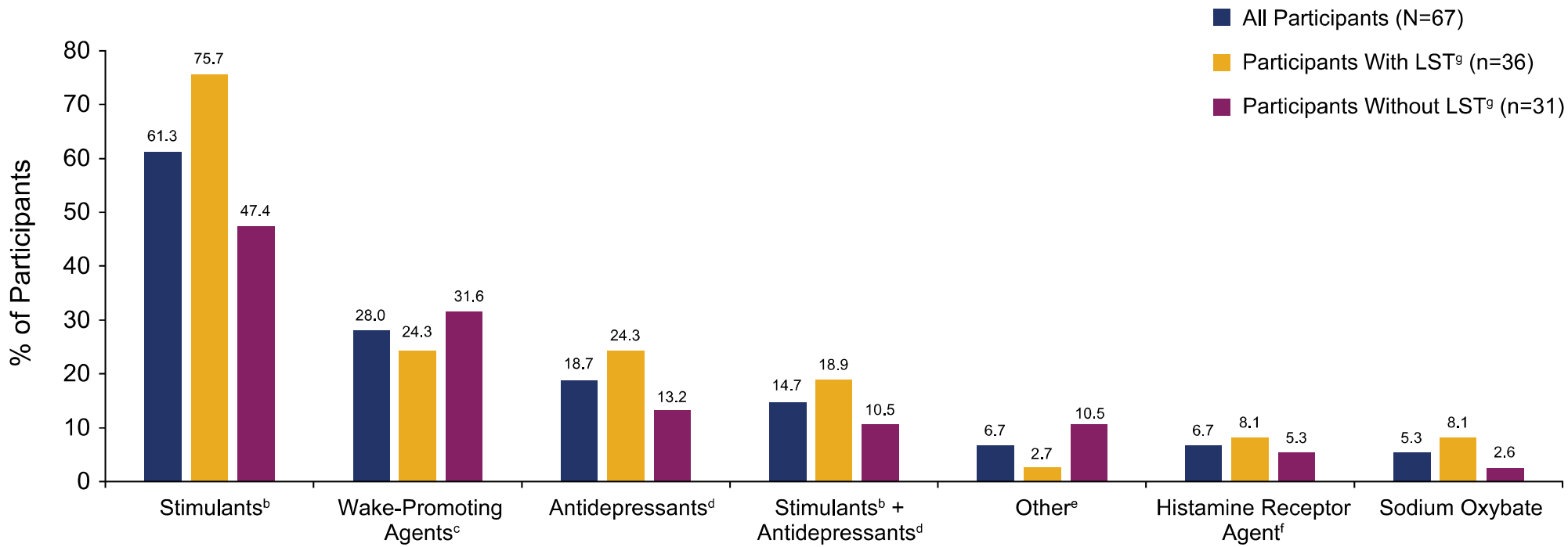
Bronx, NY

According to Hypersomnia Foundation registry data, which of the following is TRUE about alerting medications for IH?

a. They are associated with improvement of symptoms and quality of life
b. The majority of IH patients are satisfied with current treatment
c. The majority of IH patients have satisfactory adherence to current treatments
d. Daily symptoms experienced by most patients despite treatment

Use of Off-Label Medications is Common Among Patients with IH



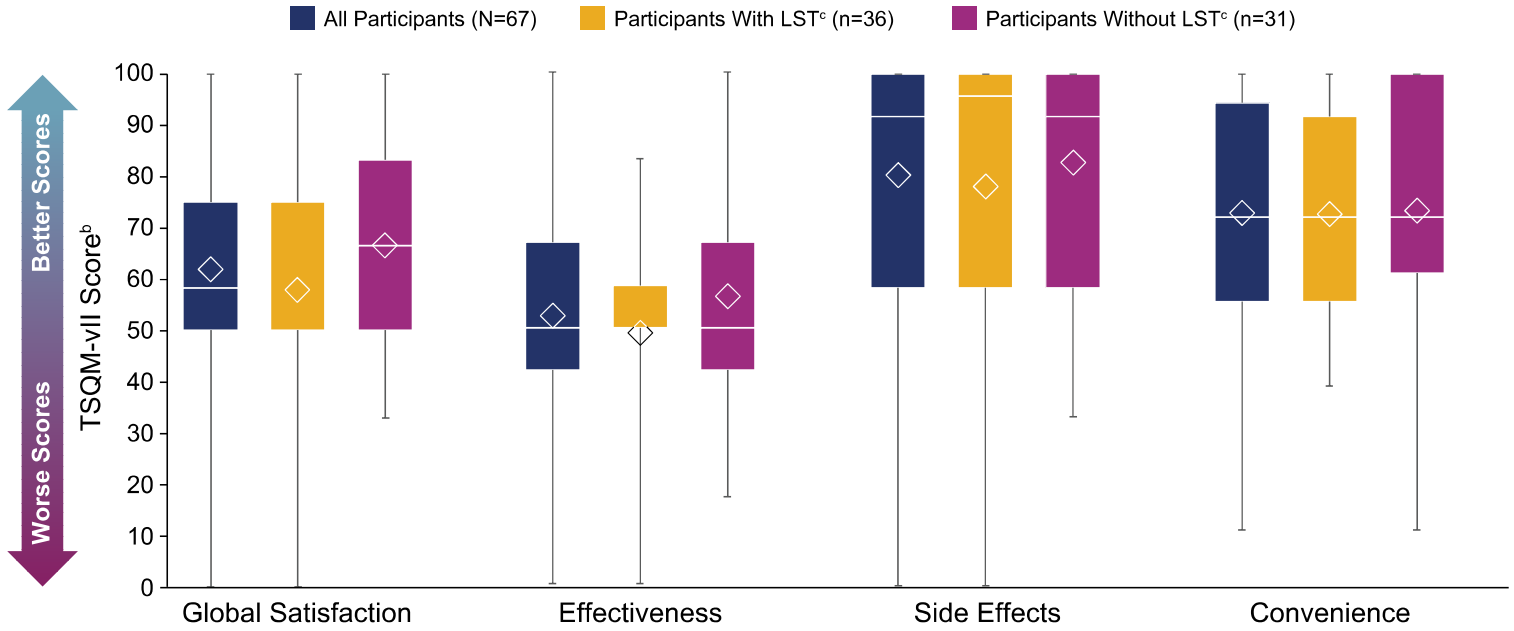
[a]A participant could have taken ≥1 medication; the 8 participants in the full study population who reported no medication use are not included in this analysis. [b]Includes amphetamine and methylphenidate. [c]Includes modafinil and armodafinil. [d]Includes selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors. [e]Includes bupropion HCl, bupropion XL, flumazenil, and levothyroxine. [f]Pitolisant. gLong sleep was defined as ≥11 hours of sleep in a 24-hour period (self-reported).
Abbreviation: LST, long sleep time.

- The Real-World Idiopathic Hypersomnia Outcomes Study (ARISE) study showed that stimulants, wake-promoting agents, and antidepressants were the most common medications, taken by 61.3%, 28.0%, and 18.7% of participants, respectively
- Stimulants and antidepressants were taken, respectively, by 75.7% and 24.3% of participants with LST, and 47.4% and 13.2% of patients without LST

LST, long sleep time

Schneider LD, et al. *Nat Sci Sleep*. 2023;15:89-101.

Treatment Satisfaction Among Patients with IH is Low



[a]The 8 participants in the full study population who reported no medication use are not included in this analysis. [b]Scale of 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).26 cLong sleep was defined as ≥11 hours of sleep in a 24-hour period (self-reported). Abbreviations: LST, long sleep time; Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation; TSQM-vII, Treatment Satisfaction Questionnaire for Medication, version II.

- The Real-World Idiopathic Hypersomnia Outcomes Study (ARISE) study showed that treatment effectiveness was scored the lowest out of all TSQM-vII components (mean [SD], 52.4 [18.3])
- The mean (SD) treatment effectiveness scores for participants with and without LST were 49.1 (16.6) and 56.2 (19.7), respectively

EDS, excessive daytime sleepiness

Schneider LD, et al. *Nat Sci Sleep*. 2023;15:89-101.

Suboptimal Treatment Response in IH

	Number (Percent) endorsing symptom at least daily, within the last 30 days	Number (Percent) endorsing symptom at least daily, when symptoms were at their worst	P-Value*
Excessive daytime sleepiness	243 (64.1%)	370 (97.6%)	<0.0001
Long sleep durations	52 (13.7%)	195 (51.5%)	<0.0001
Intentional napping	52 (13.7%)	206 (54.4%)	<0.0001
Unintentional daytime sleep	23 (6.1%)	140 (36.9%)	<0.0001
Requiring multiple alarms to awaken	227 (60.2%)	265 (70.3%)	<0.0001
Having trouble waking up and functioning with normal alertness	228 (61.1%)	301 (80.7%)	<0.0001
Brain fog (being unable to think clearly or concentrate at any time throughout the day)	201 (54.0%)	311 (83.6%)	<0.0001
Difficulty remembering things	189 (51.8%)	262 (71.8%)	<0.0001

Data from the Hypersomnia Foundation Registry

"Despite apparent improvement with medication, daily symptoms of IH still were experienced by a substantial proportion of participants while on treatment"

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

Behavioral and Other Measures are Commonly Used to Manage IH Symptoms

Other Measures Used, n (%)	All Participants N=75	Participants With LST n=37[e]	Participants Without LST n=38[e]
Caffeine	55 (73.3)	27 (73.0)	28 (73.7)
Planned naps	26 (34.7)	17 (45.9)	9 (23.7)
Individual accommodations[b]	24 (32.0)	12 (32.4)	12 (31.6)
Dietary changes[c]	12 (16.0)	8 (21.6)	4 (10.5)
Cognitive behavioral therapy	10 (13.3)	7 (18.9)	3 (7.9)
Melatonin	11 (14.7)	6 (16.2)	5 (13.2)
None	5 (6.7)	2 (5.4)	3 (7.9)
Other[d]	7 (9.3)	2 (5.4)	5 (13.2)

[a]A participant could have used ≥1 other measure. [b]For example, additional time on testing and assignments, delayed morning start time, excused absences related to medication holidays or prolonged sleep durations. [c]For example, maintain a low-carbohydrate diet. [d]Includes the following items: afternoon and evening naps whenever feasible; cardio exercise; consistent sleep schedule and regular physical exercise; exercise; I usually do not start work before 10:00 AM; I wake up to take medication in order to actually get out of bed at a certain time; using a night and morning routine to prepare my body for sleep and wakefulness and keeping a steady sleep schedule. eLong sleep was defined as ≥11 hours of sleep in a 24-hour period (self-reported).
Abbreviation: LST, long sleep time.

- The Real-World Idiopathic Hypersomnia Outcomes Study (ARISE) study showed that 93.3% of participants used other measures to manage their idiopathic hypersomnia symptoms

EDS, excessive daytime sleepiness
Schneider LD, et al. *Nat Sci Sleep*. 2023;15:89-101.

According to current AASM guidelines for the treatment of IH:

- Low-sodium oxybate has a strong recommendation for use
- Modafinil has a strong recommendation for use
- Pitolisant has a strong recommendation for use
- Sodium oxybate has a strong recommendation for use

AASM Practice Parameters for Idiopathic Hypersomnia: (2021)

Agent	Recommendation	Level
• Modafinil	Recommend	Strong
• Sodium Oxybate	Suggest	Conditional
• Pitolisant	Suggest	Conditional
• Clarithromycin	Suggest	Conditional
• Methylphenidate	Suggest	Conditional

Maski K, et al. *Journal of Clinical Sleep Medicine*. 2021; 17.9: 1881-1893

Overview of Pharmacological Trials in IH* Mostly ESS endpoints

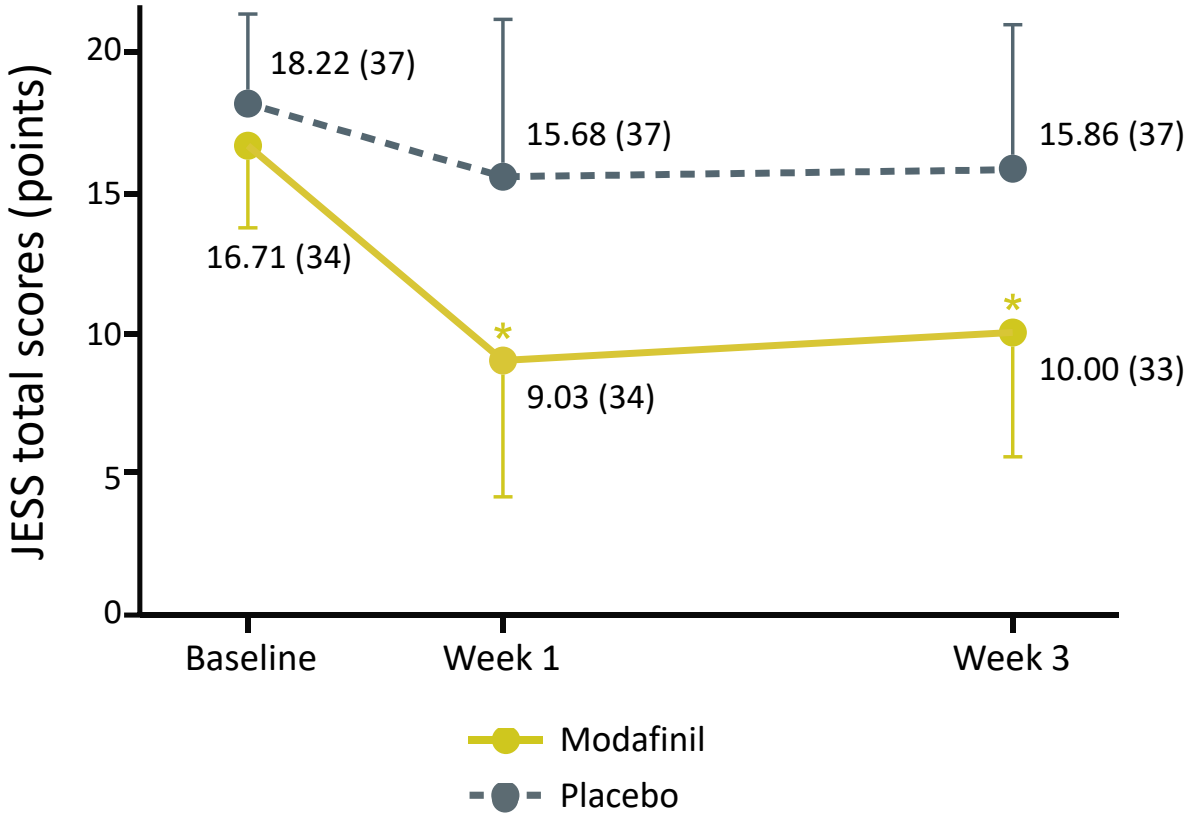
Treatment	Author	Patient population	Conclusion
Modafinil	Mayer et al. 2015	IH without long sleep time (n = 31)	Improvement on ESS: 6.0 points; on CGI: 1.0 point
Methylphenidate	Thakrar et al. 2018	IH (n = 9); NT1 (n = 70), NT2 (n = 47)	Improvement on ESS: 3.1 points
Dextroamphetamine	Ali et al. 2009	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

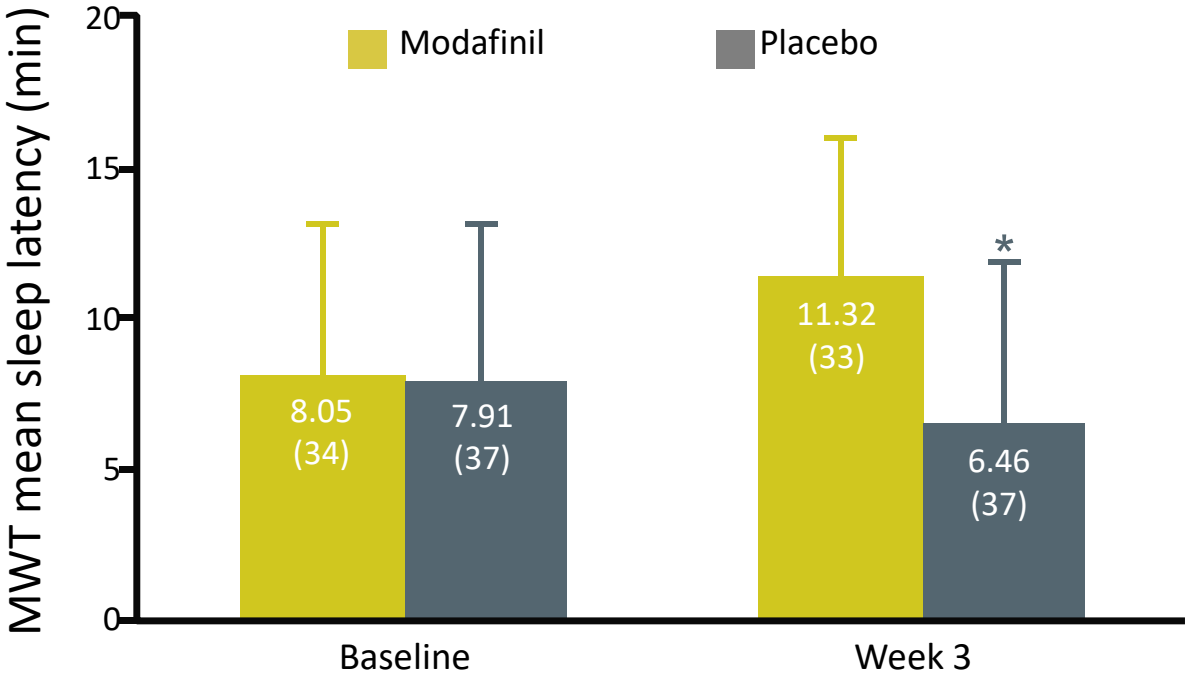
*These agents are not FDA-approved for the treatment of IH.

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

Arnulf I et al. "*Sleep Medicine Reviews* (2023): 101766; 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

Patients with IH	With Long Sleep Time (n=49)	Without Long Sleep Time (n=16)	*p*
Time on pitolisant (months)	4	7	.85
ESS			
Score at baseline	17 (14-18)	17 (16-20.5)	.23
Score with pitolisant	14 (12-17)	16 (13-17)	.34
Responders, % (n)	37 (18)	31 (5)	.69
Treatment stopped, % (n)	67.3 (33)	68.7 (11)	.84
Reasons for stopping			
Lack of efficacy, % (n)	48.5 (16)	63.6 (7)	.6
Adverse effects, % (n)	21.2 (7)	9.1 (1)	.65
Loss of efficacy, % (n)	3 (1)	9.1 (1)	1

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

Treatment of other symptoms in IH

- **Sleep Inertia**
  - Challenge clinically, because patients have difficulty awakening to take medications
  - Alerting medication at night or upon awakening

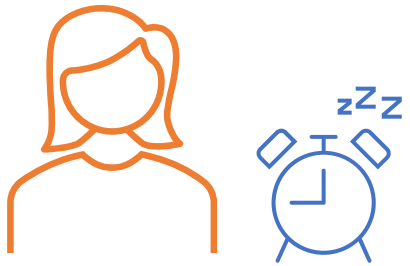
- **Prolonged, unrefreshing daytime or nighttime sleep**
  - Non-pharmacological treatment options : little benefit
    - e.g., naps to alleviate sleepiness are not typically restorative and induce sleep inertia

- **Requirement for specific instruments to assess**
  - Severity of EDS phenotype in IH
  - Sleep inertia
  - Prolonged unrefreshing sleep
  - Treatment responsiveness: IHSS…

- **Regular reassessment : Prognosis – Follow-ups**

Arnulf I et al. "*Sleep Medicine Reviews* (2023): 101766
Dauvilliers Y, et al. *Neurology*. 2019;92(15):e1754-e1762

Hypersomnia Case



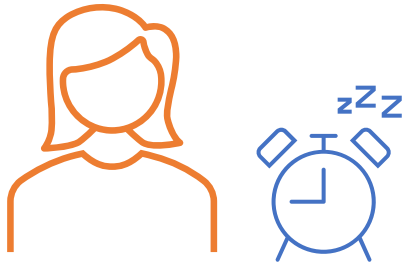
- 26-year-old female
- Weekdays Bedtime: 10pm Out of bed 9am
  - Weekends: BT 2 am OOB 12 noon
- Symptoms: Difficulty awakening, tired confused, disoriented upon awakening

  Sleepy after awakening takes a couple of naps during day.

  Sleep is sound but has vivid dreams and occasional nightmares, dreams in morning naps..

  Mild snoring and morning headaches
- BMI: 31
- On O/Cs
- Mild depression/anxiety on fluoxetine 40mg/day

ARS #6



Ideally which medication would you initiate?

1. Modafinil
2. Pitolisant
3. Methylphenidate
4. Amphetamine
5. Sodium oxybate
6. Low sodium Oxybate

New and Emerging Treatments for IH

Yves Dauvilliers, MD, PhD
Professor of Neurology and Physiology
University of Montpellier
Director, Sleep-Wake Disorders Centre
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Montpellier, France

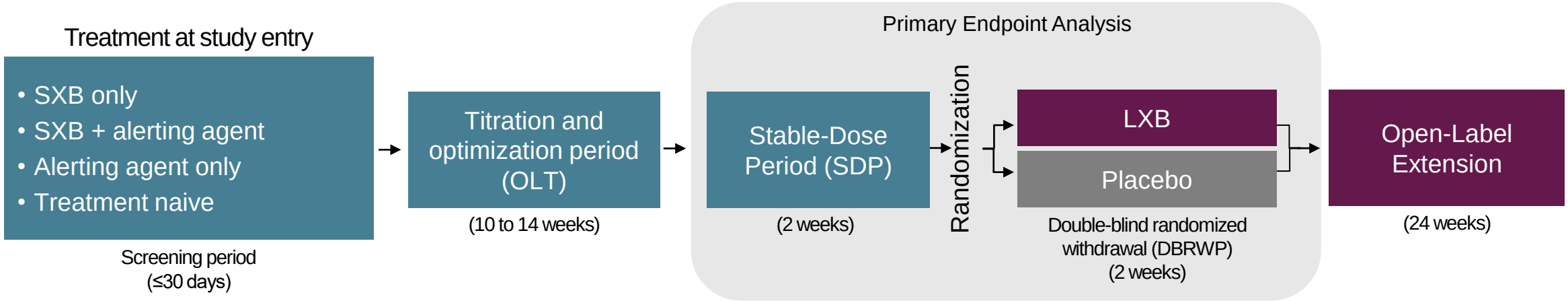
In a phase 3 study leading to its approval in IH, low sodium oxybate:

a. Improved symptoms and quality of life in individuals with and without long sleep time
b. Improved symptoms and quality of life in individuals with long sleep time, but not in those without long sleep time
c. Improved symptoms and quality of life in individuals without long sleep time, but not in those with long sleep time

Lower-sodium oxybate (LXB): The First FDA Approved Treatment for IH

154 adult patients with IH with and without long sleep time

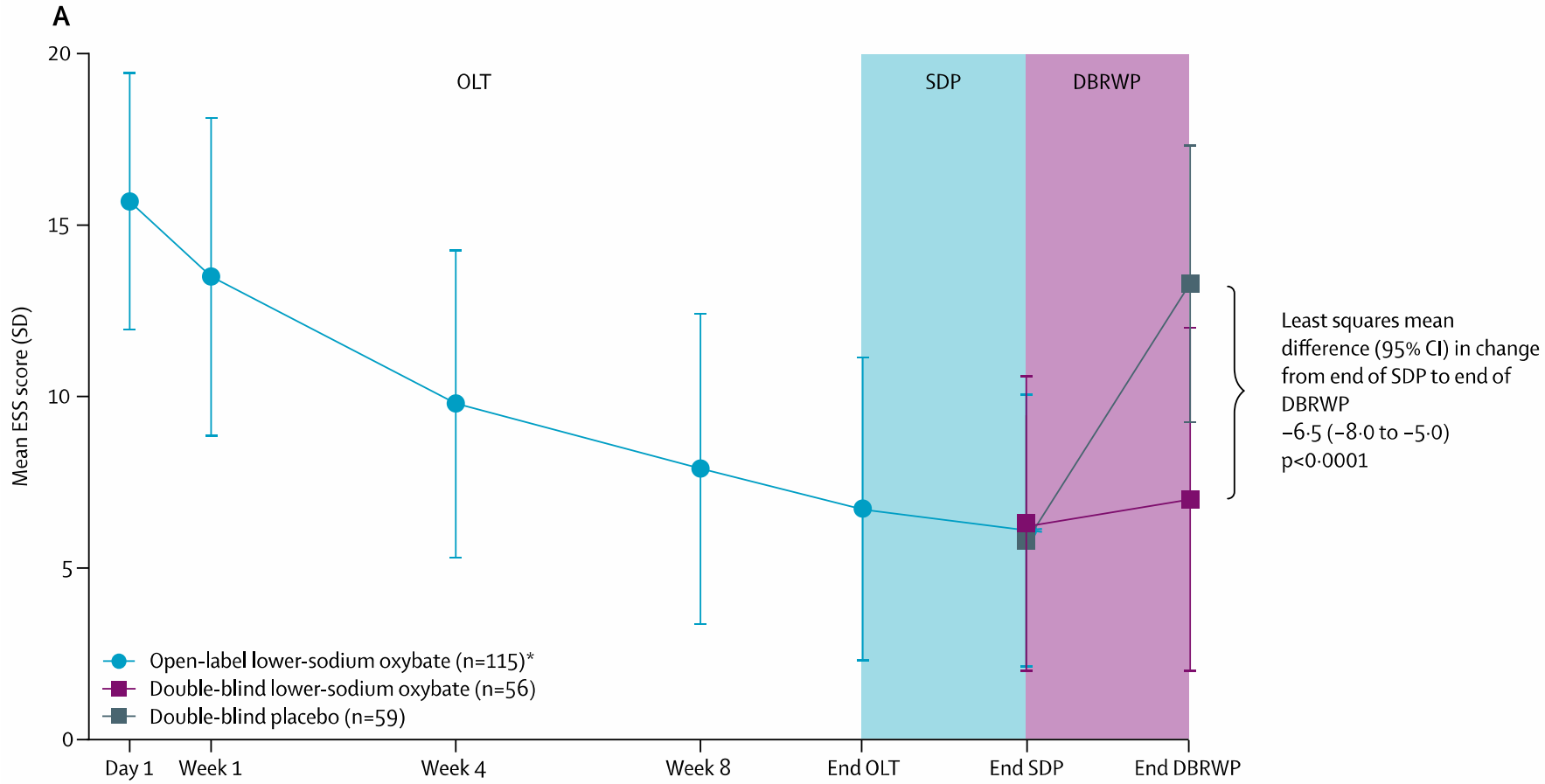
included and 115 randomized with either PCB or LXB



- Primary efficacy endpoint: change in ESS score from end of SDP to end of DBRWP
- Key secondary endpoints: from end of SDP to end of DBRWP
  - Proportion of participants with worsening (minimally/much/very much) on PGIc
  - Change in IHSS total score
- Safety assessments included collection of TEAEs, vital signs, physical examination, electrocardiogram, clinical laboratory tests, and the Columbia-Suicide Severity Rating Scale

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

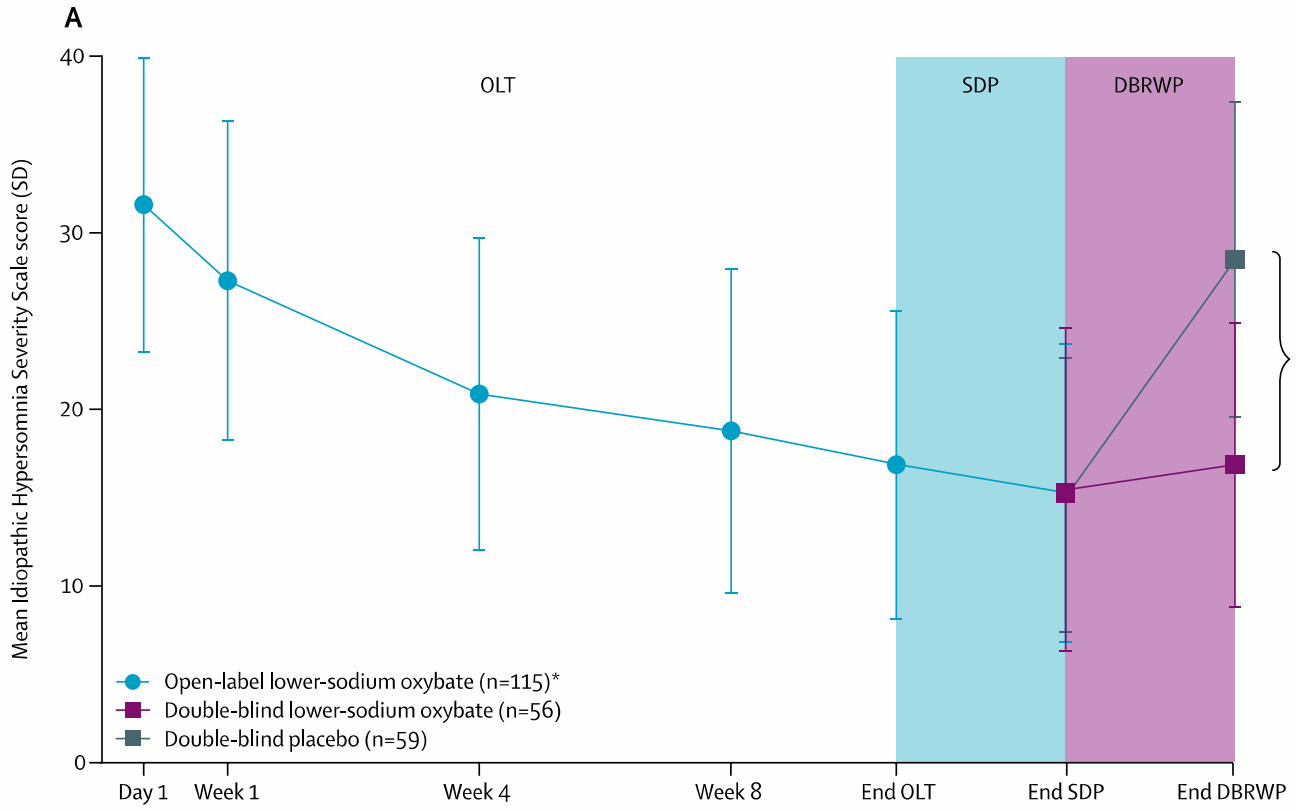
LXB Treatment Resulted in a Clinically Meaningful Improvement in IH Symptoms Based on the ESS Scores



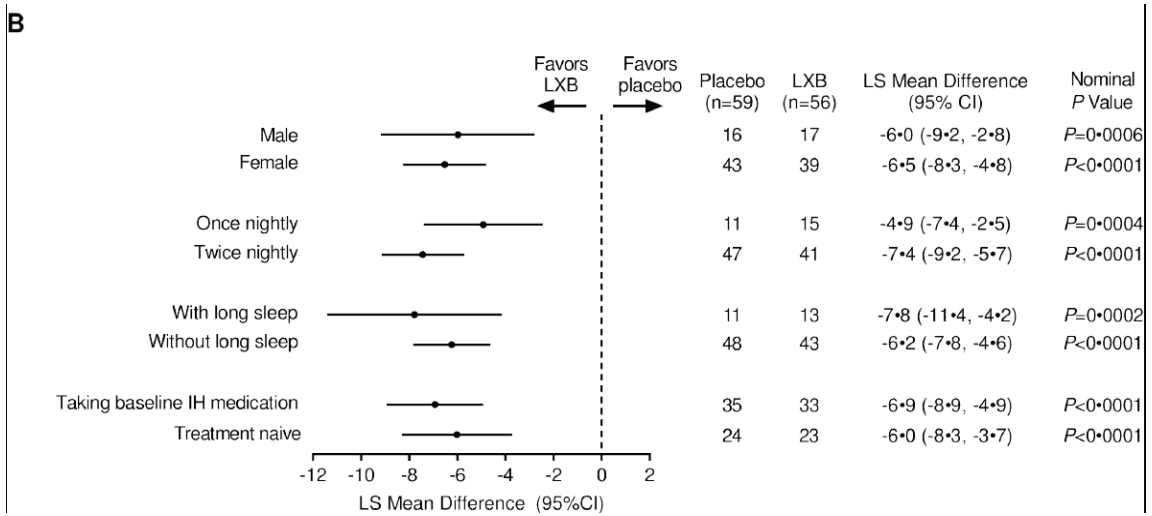
- ESS scores decreased (indicating improvement) with LXB treatment during the OLT, and the decrease was maintained during the SDP

DBRWP, doubleblind, randomised withdrawal period;OLT, open label titration; SDP, stabledose period
Dauvilliers Y, et al. Lancet Neurol. 2022;21(1):53-65.

LXB Treatment Resulted in a Clinically Meaningful Improvement in IH Symptoms Based on the IHSS Scores

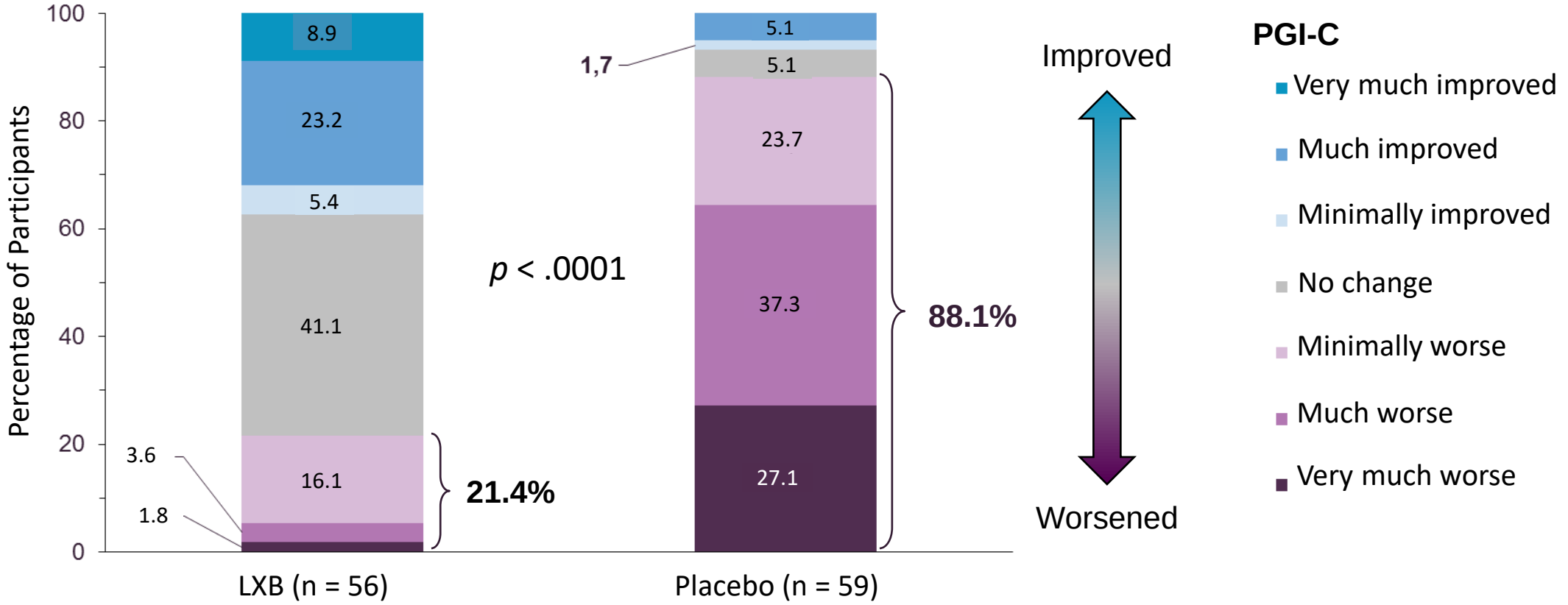


Estimated median difference (95% CI) in change from end of SDP to end of DBRWP
−12·0 (−15·0 to −8·0)
p<0·0001



DBRWP, doubleblind, randomised withdrawal period;OLT, open label titration; SDP, stabledose period
Dauvilliers Y, et al. Lancet Neurol. 2022;21(1):53-65.

LXB Treatment Resulted in a Clinically Meaningful Improvement in IH Symptoms Based on Patient Global Impression of Change (PGIc)

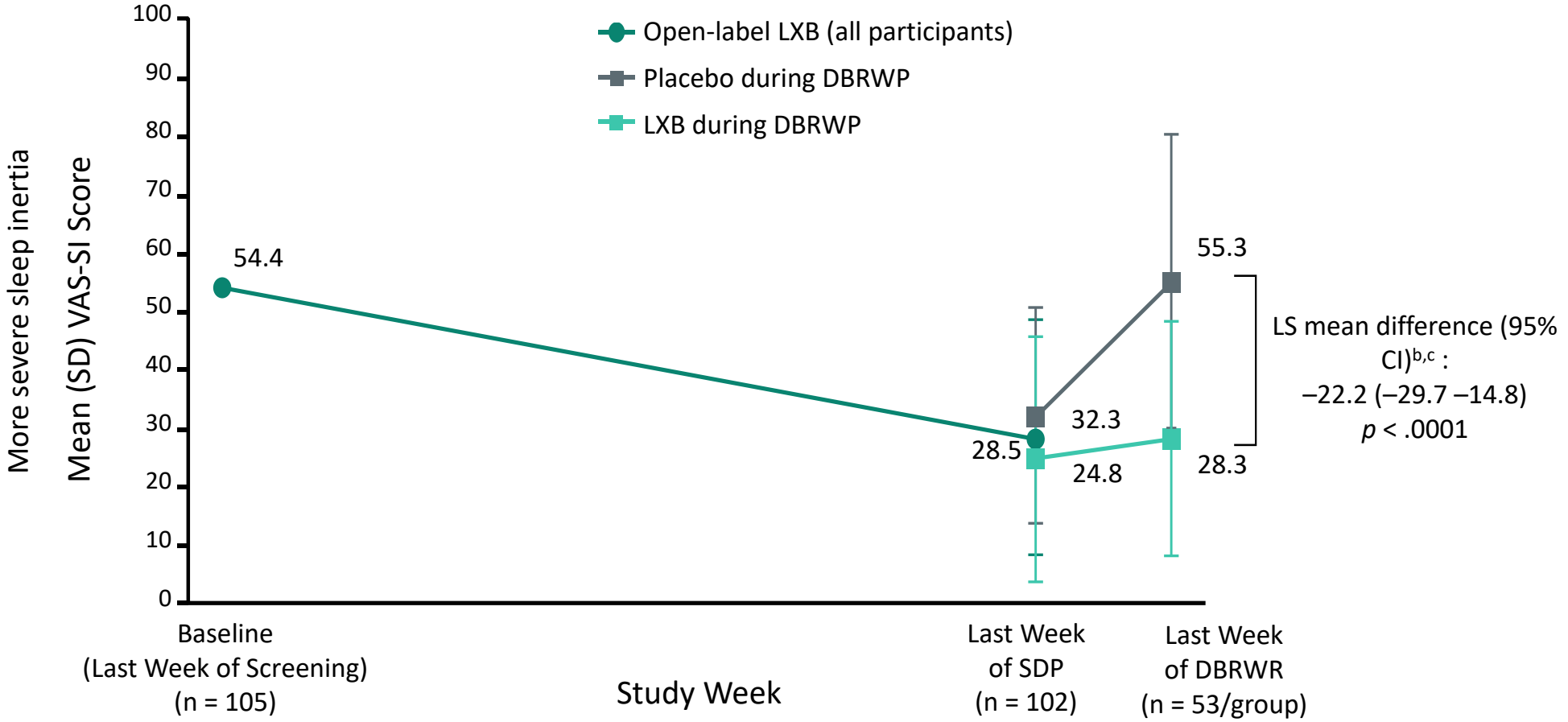


At the end of DBRWP, significant worsening in PGI-C ratings was observed in participants randomized to placebo vs. LXB (88.1% vs. 21.4% rated minimally/much/very much worse)

DBRWP, doubleblind, randomised withdrawal period;OLT, open label titration; SDP, stabledose period

Dauvilliers Y, et al. Nat Sci Sleep. 2022;14:531-546; 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.

Bogan R, et al. *Sleep*. 2021: A192

LXB Adverse Events

TEAEs Across All Study Periods in ≥5% of Total Participants, by Treatment at Study Entry[a]

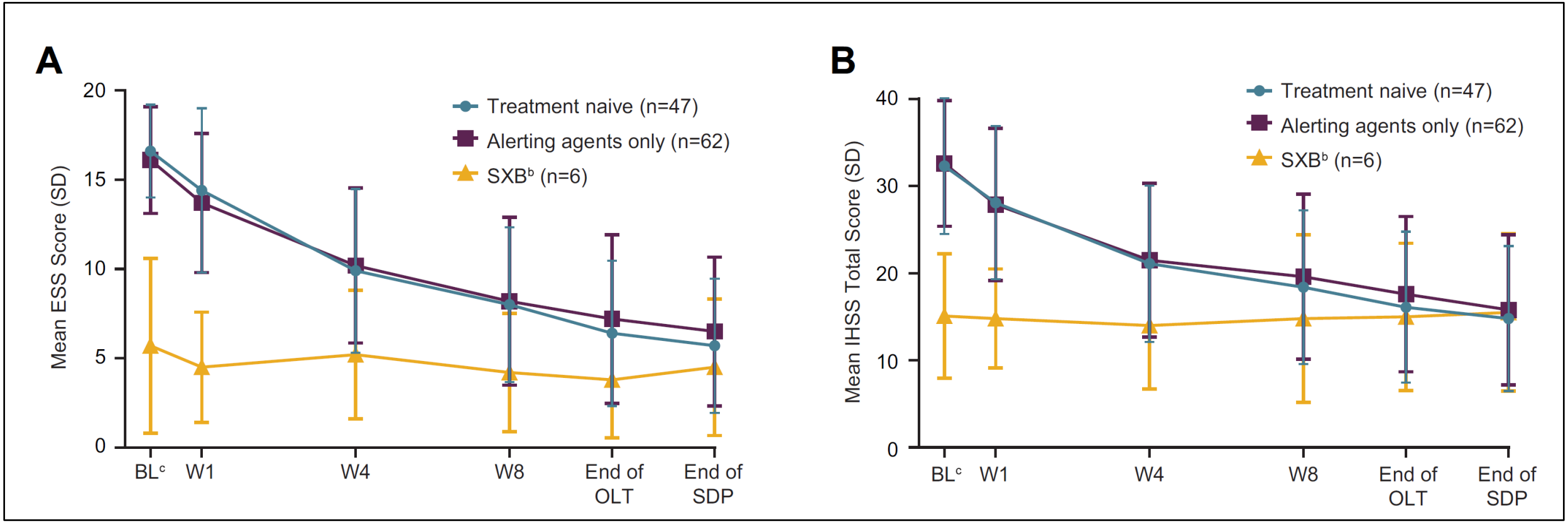
		Treatment at Study Entry	
TEAE, n (%)	Safety Population Total N=154	Baseline IH Medication[b] (n=88)	Treatment Naive[c] (n=66)
Participants with ≥1 TEAE	**123 (79.9)**	73 (83.0)	50 (75.8)
Nausea	33 (21.4)	20 (22.7)	13 (19.7)
Headache	25 (16.2)	15 (17.0)	10 (15.2)
Dizziness	18 (11.7)	8 (9.1)	10 (15.2)
Anxiety	16 (10.4)	9 (10.2)	7 (10.6)
Vomiting	16 (10.4)	13 (14.8)	3 (4.5)
Decreased appetite	14 (9.1)	7 (8.0)	7 (10.6)
Diarrhea	12 (7.8)	9 (10.2)	3 (4.5)
Upper respiratory tract infection	12 (7.8)	7 (8.0)	5 (7.6)
Urinary tract infection	12 (7.8)	6 (6.8)	6 (9.1)
Insomnia	11 (7.1)	9 (10.2)	2 (3.0)
Dry mouth	10 (6.5)	8 (9.1)	2 (3.0)
Nasopharyngitis	10 (6.5)	5 (5.7)	5 (7.6)
Fatigue	9 (5.8)	6 (6.8)	3 (4.5)
Night sweats	8 (5.2)	6 (6.8)	2 (3.0)
Tremor	8 (5.2)	8 (9.1)	0 (0.0)

- All TEAEs are as of the interim data cutoff on 7/2/2020
- At interim, 32 completed OLE, 9 discontinued OLE, and 65 remained in OLE

TEAE, treatment-emergent adverse event.
[a]Excludes placebo data.
[b]Includes participants who were taking SXB and/or an alerting agent at study entry.
[c]Includes participants not taking SXB or an alerting agent at study entry.

DBRWP, doubleblind, randomised withdrawal period;OLT, open label titration; SDP, stabledose period
Dauvilliers Y, et al. Nat Sci Sleep. 2022;14:531-546; Dauvilliers Y, et al. Lancet Neurol. 2022;21(1):53-65.

LXB: Open-Label Titration Period



- Improvement in ESS and IHSS
- Improvement in quality of life and functional measures

BL: baseline; ESS: Epworth Sleepiness Scale; IHSS: Idiopathic Hypersomnia Severity Scale; mITT: modified intent-to-treat; OLT: open-label titration and optimization period; SDP: stable-dose period; SXB: sodium oxybate

Thorpy MJ, et al. *Nature and Science of Sleep*. 2022: 1901-1917

Agents Under Investigation

New Forms of Sodium Oxybate
- Once a night formulation
- Non-cation oxybate

Modafinil Augmentation
- Modafinil/Flecainide (THN102)

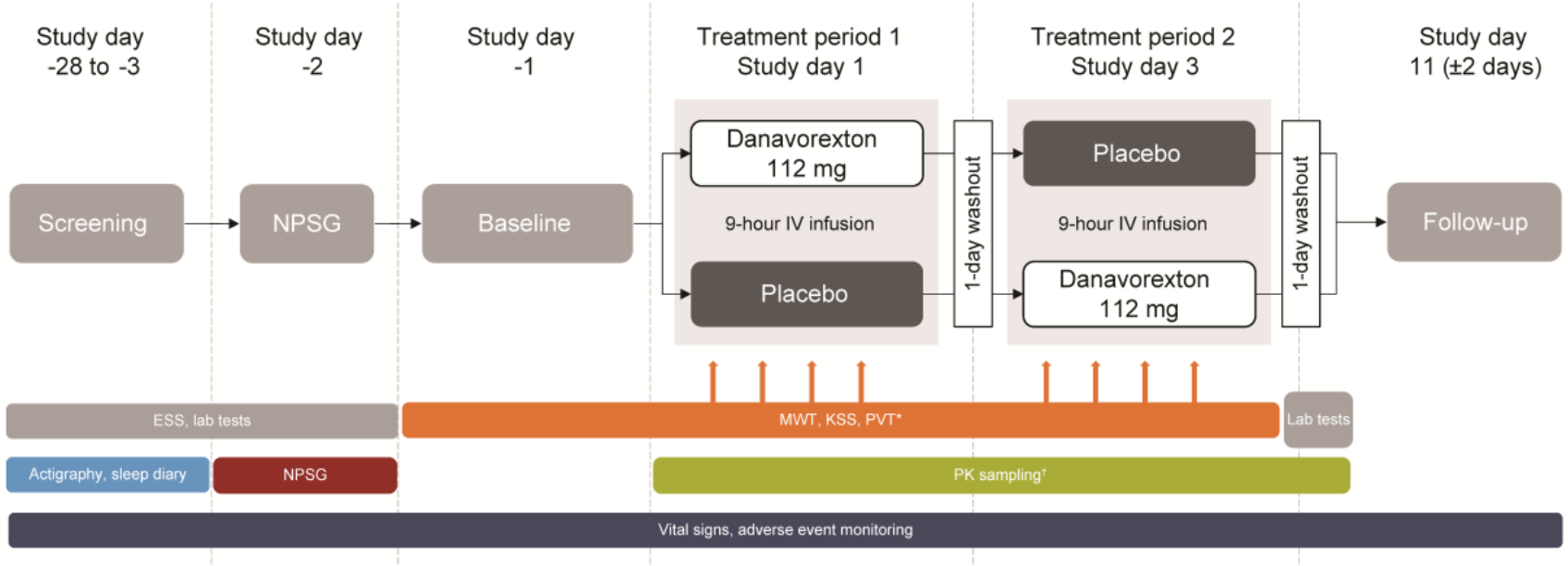
GABA-A Antagonists
- Clarithromycin
- Flumazenil
- Pentetrazon (BTD-101)

Norepinephrine Reuptake Inhibitors (NERIs)
- Reboxetine

H3R Inverse Agonists
- Samilisant
- Pitolisant

Orexin Agonists
- TAK-681
- Mazindol (not sure orexin agonists, and no planned study)
- Danavorexton (TAK-925)
- JZP-441

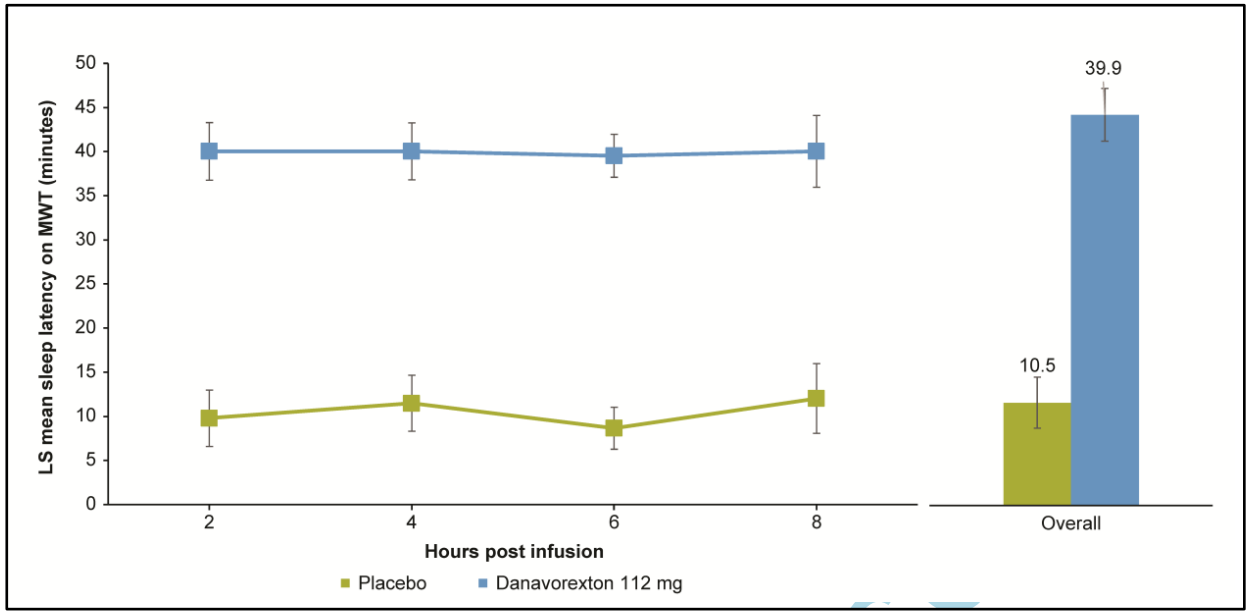
Danavorexton (TAK-925) Activity was Evaluated in Patients with IH in Phase 1b Study

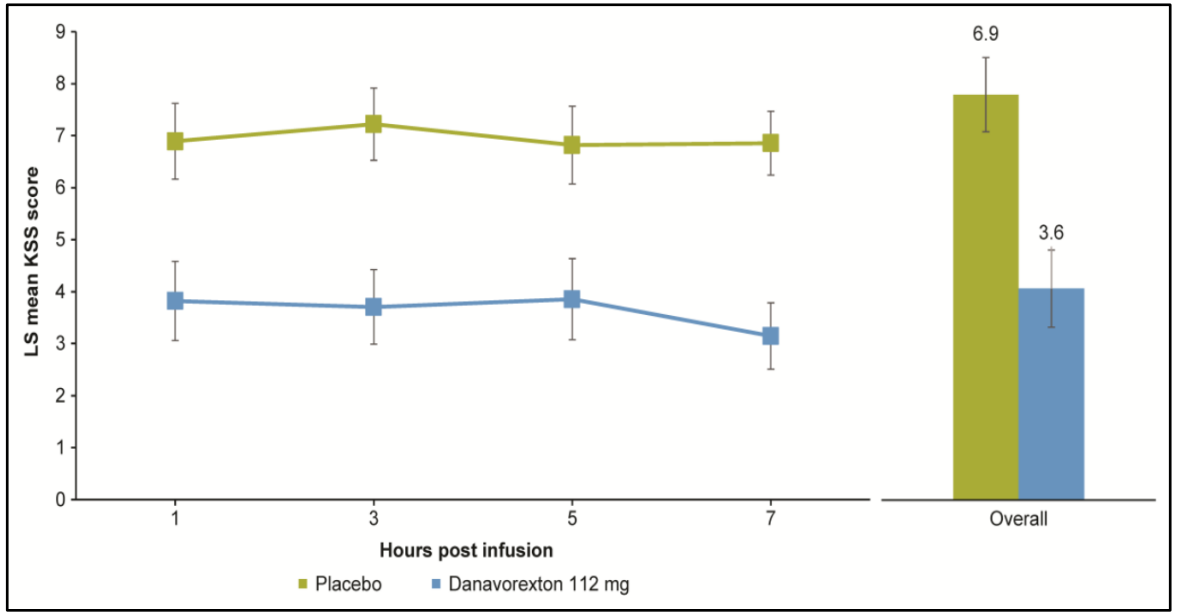


- The phase 1b, randomized, placebo-controlled, crossover study aimed to evaluate the safety, pharmacokinetics, and pharmacodynamics of danavorexton
- Pharmacodynamic endpoints included the maintenance of wakefulness test (MWT), the Karolinska Sleepiness Scale (KSS), and the psychomotor vigilance task (PVT)

Yin J, et al. *Nat Commun*. 2022;13(1):2902. Published 2022 May 25; Mignot E, et al. *Sleep*. 2023.

Danavorexton (TAK-925) Improved Mean Sleep Latency & Reduced Subjective Sleeping





- Danavorexton treatment increased sleep latency values compared with placebo
- Average sleep latency values were 10.5 and 39.9 minutes for placebo and danavorexton, respectively.

- Danavorexton treatment lowered KSS scores compared with placebo at all timepoints
- Danavorexton treatment resulted in significant improvements in sustained attention/vigilance,

Yin J, et al. *Nat Commun*. 2022;13(1):2902. Published 2022 May 25; Mignot E, et al. *Sleep*. 2023.

Concluding Remarks & Takeaways

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