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# CASE CLOSED?

## *Diagnosing Idiopathic Hypersomnia Beyond the Usual Suspects*

This educational activity is supported by an educational grant from Alkermes.

# This activity was created in collaboration with the Hypersomnia Foundation


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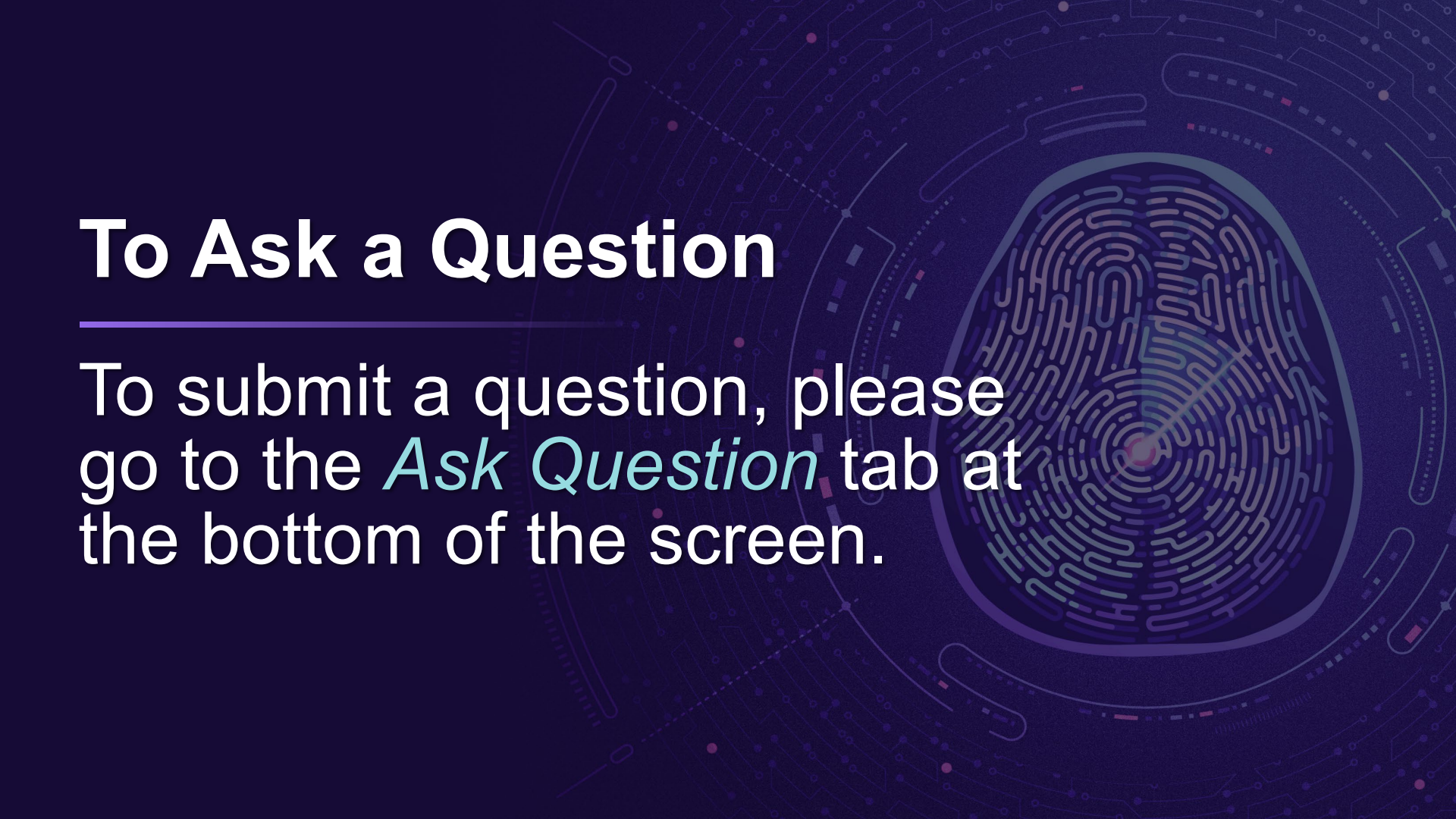

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*All identified conflicts of interest have been mitigated.*

# Disclosures

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*All identified conflicts of interest have been mitigated.*

# LEARNING OBJECTIVES

1. Evaluate the latest efficacy and safety data for current and emerging therapies for patients with IH
2. Integrate appropriate guideline-recommended diagnostic criteria and comprehensive assessments into practice when there is clinical suspicion of IH to improve early and accurate diagnosis
3. Identify the nature of overlapping symptoms of IH and other hypersomnia disorders

# *Idiopathic Hypersomnia Landscape*

*Disease Burden, Diagnostic Framework, Approved Therapy, and Investigational Agents That Could Change the Picture*

# Idiopathic Hypersomnia (IH) Is Too Often Missed or Mislabeled

**> 60%**

of people with IH are initially misdiagnosed

**69%***

experience > 1 year delay to diagnosis

**~20%**

wait ≥ 10 years for an accurate diagnosis

## The Clinical Consequence

IH is commonly misattributed to mood disorders and may be confused with other central disorders of hypersomnolence, especially NT2; insufficient sleep syndrome must also be excluded in the diagnostic workup. Delayed diagnosis prolongs impaired daily functioning, cognitive burden, work/school disruption, and reduced QoL.

*Data from a U.S. patient survey of adults with IH (N = 290); 69% is derived from the 1-2 year, 2-5 year, 5-10 year, and ≥ 10 year categories combined.
IH = idiopathic hypersomnia; NT2 = narcolepsy type 2; QoL = quality of life.

Whalen M, et al. *Sleep*. 2022;45(Suppl 1):A175-A176. Boulanger T, et al. *Sleep Adv*. 2024;5(1):zpae059. Dauvilliers Y, et al. *Sleep Med Rev*. 2022;66:101709. Stevens J, et al. *Nat Sci Sleep*. 2023;15:593-606.

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# Patient Advocate Becky

*Video Clip:*

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Becky Gabany. Interview with CME Outfitters. 2026.

*Current Landscape*

# Approved and Key Emerging IH-Relevant Trials

| Agent | Class/Target | Phase | Current Status |
|---|---|---|---|
| **Low-sodium oxybate** | GABA-B/oxybate | Approved (adult IH) | FDA-approved for IH in adults (Aug 2021); only FDA-approved therapy for adult IH; LCM + real-world studies ongoing |
| **Sodium oxybate ER; once-nightly*** | GABA-B/oxybate | Phase III (IH) | FDA-approved for cataplexy or EDS in adults with narcolepsy (May 2023); phase III in adult IH ongoing |
| **Alixorexton (ALKS 2680)*** | OX2R-selective agonist | Phase II (IH) | VIBRANCE-3 phase II study in adult IH ongoing; estimated primary completion June 2026 |
| **TAK-360*** | OX2R-selective agonist | Phase II (IH) | Recruiting phase II study in adults with IH |
| **Cleminorexton (ORX750 + additional OX2R agonists)*** | OX2R-selective agonist | Phase IIa (NT1/NT2/IH) | CRYSTAL-1 phase IIa includes participants with IH |

*This agent is not currently indicated for the treatment of IH.

GABA-B = gamma-aminobutyric acid type B; LCM = lifecycle management; ER = extended release; EDS = excessive daytime sleepiness; OX2R = orexin 2 receptor; NT1 = narcolepsy type 1.

Sodium oxybate [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761061s000lbl.pdf.
Calcium, magnesium, potassium, and sodium oxybates [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212690s011lbl.pdf. ClinicalTrials.gov Identifiers: NCT06812078 and NCT06752668.

*FDA-Approved Therapy*

# Low-Sodium Oxybate: Phase III in Adult IH

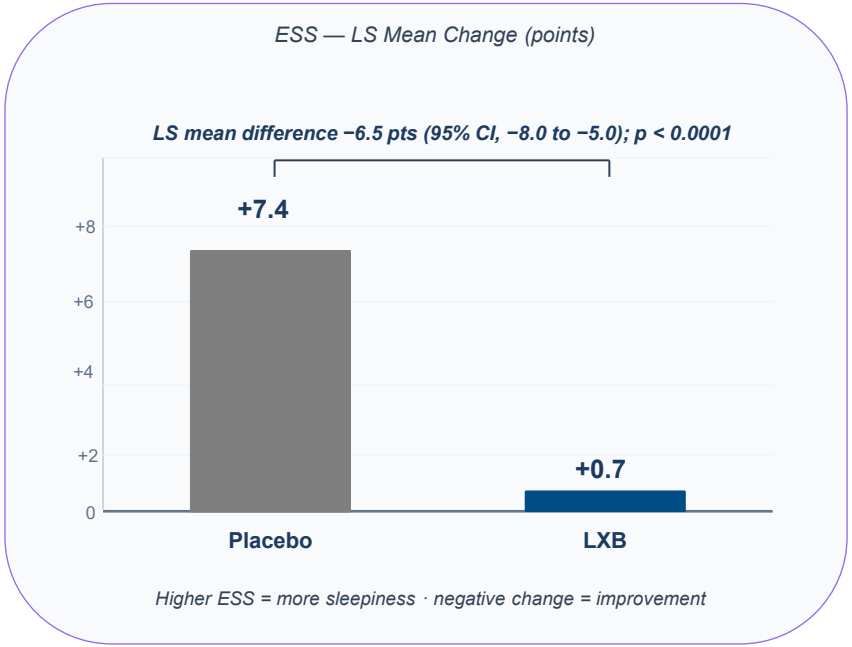
| Parameter | Phase III |
|---|---|
| Design | Phase III, multicenter, placebo-controlled, double-blind randomized-withdrawal study following a 10-14–week open-label titration/optimization period and 2-week stable-dose period |
| Population | Adults age 18-75 with IH meeting ICSD-2 or ICSD-3 criteria; N = 154 enrolled (safety population), N = 115 randomized (modified intention-to-treat population) |
| Primary endpoint | Change in ESS from end of stable-dose period to end of 2-week double-blind randomized withdrawal; ESS worsened on placebo withdrawal but remained stable on low-sodium oxybates (LS mean difference -6.5 points; 95% CI, -8.0 to -5.0; $p < 0.0001$) |
| Key secondaries | Key secondary endpoints PGI-C and IHSS both favored low-sodium oxybates (both $p < 0.0001$) |
| Most common AEs | Nausea (22%), headache (18%), dizziness (12%), anxiety (11%), vomiting (11%) |
| Safety summary | No deaths and no new safety signals in IH relative to the known oxybate profile; boxed warning for CNS depression and abuse/misuse |
| Regulatory outcome | FDA-approved on August 12, 2021 for the treatment of IH in adults; first and only FDA-approved therapy for adult IH |

AE = adverse event; CI = confidence interval; CNS = central nervous system; ESS = Epworth Sleepiness Scale; ICSD-2/3 = International Classification of Sleep Disorders, second/third editions; IHSS = Idiopathic Hypersomnia Severity Scale; LS = least squares; PGI-C = Patient Global Impression of Change; REMS = Risk Evaluation and Mitigation Strategy.

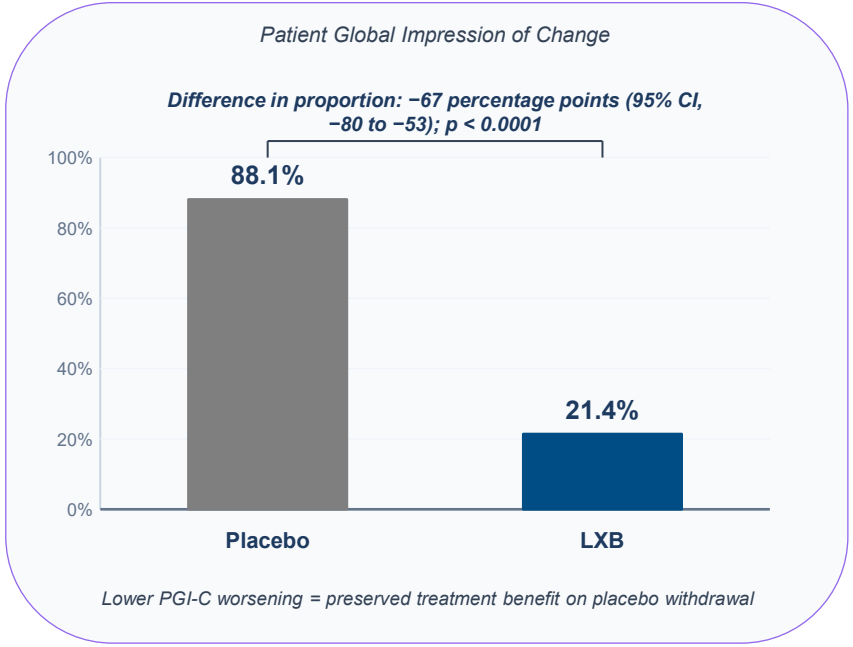
Dauvilliers Y, et al. *Lancet Neurol*. 2022;21(1):53-65. Calcium, magnesium, potassium, and sodium oxybates [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212690s011lbl.pdf.

# Low-Sodium Oxybate: Primary and Secondary Data in Adult IH

**PRIMARY ENDPOINT — ESS CHANGE DURING 2-WEEK RANDOMIZED WITHDRAWAL**




**SECONDARY ENDPOINT — PGI-C — % worsened (minimally, much, or very much worse) at end of withdrawal**

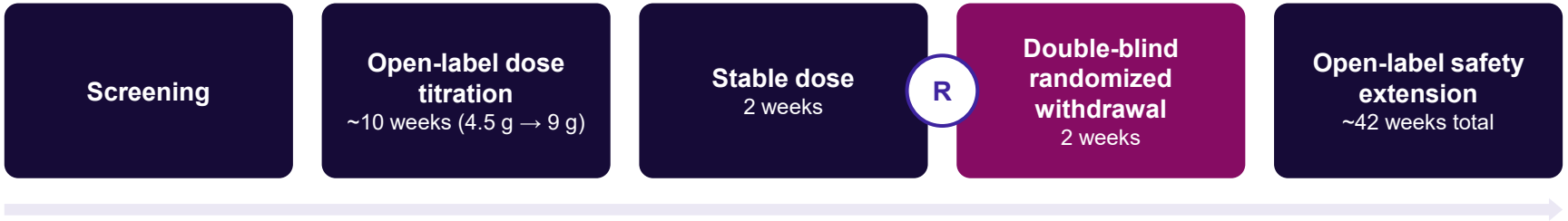



LXB = low-sodium oxybate.

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

# Once-Nightly Sodium Oxybate ER* (REVITALYZ): Study Design at a Glance

**Randomized-withdrawal design:** participants are stabilized on once-nightly oxybate, then randomized to continue active treatment or switch to placebo.




**PRIMARY ENDPOINT**

Change in ESS total score from end of the stable-dose period to end of the 2-week double-blind randomized withdrawal (assessed ~week 14)

**KEY SECONDARY ENDPOINTS**

PGI-C, IHSS, CGI-C, and FOSQ-10

*This agent is not FDA-approved for the treatment of IH. This agent would be the first new IH dosing paradigm since low-sodium oxybate (2021); registered trial design and endpoints are shown here, with peer-reviewed efficacy/safety results anticipated to follow.
CGI-C = Clinical Global Impression of Change; FOSQ-10 = Functional Outcomes of Sleep Questionnaire.
ClinicalTrials.gov identifier: NCT06525077. BusinessWire. 2026. https://www.businesswire.com/news/home/20260512566395/en/Alkermes-Announces-Positive-Topline-Results-From-REVITALYZ-Phase-3-Study-Evaluating-LUMRYZ-sodium-oxybate-Extended-Release-in-Adults-With-Idiopathic-Hypersomnia#xd_co_f=YzA5MmViNDMtZDQ0NS00MTU0LTk5Y2EtMWFjYmY4MjYyNmU5~.

# Once-Nightly Sodium Oxybate ER* (REVITALYZ): Phase III in Adult IH

| Parameter | Phase III |
|---|---|
| Design | Phase III, multicenter, double-blind, placebo-controlled, randomized-withdrawal study of once-at-bedtime oxybate in adults with IH: ~10-week open-label dose titration (4.5 g up to 9 g) → 2-week stable-dose period → 2-week double-blind randomized withdrawal, followed by an open-label safety extension (~42 weeks total) |
| Population | Approximately 150 adults age 18-75 with IH; total ESS > 11 and average nightly total sleep time > 7 hours at screening; eligible whether initiating oxybate or transitioning from existing oxybate therapy; stable stimulants/alerting agents permitted |
| Primary endpoint | Change in ESS total score (LS mean) from the end of the open-label stable-dose period to the end of the 2-week double-blind randomized withdrawal (assessed at ~week 14)<br>Placebo group showed statistically significant worsening vs participants continuing sodium oxybate ER ($p < 0.0001$) |
| Key secondaries | PGI-C, IHSS, and a measure of functional outcomes of sleep (worsening on placebo vs maintenance on active treatment during randomized withdrawal)<br>Both worsened significantly with placebo vs continued sodium oxybate ER ($p < 0.0001$) |
| Most common AEs | The most common treatment-emergent AEs (occurred in ≥ 10% of participants) were nausea, anxiety, headache, dizziness, and vomiting |
| Safety summary | No new safety signals observed in the IH population. Current approved-product labeling carries a boxed warning for CNS depression and abuse/misuse |
| Regulatory outcome | Once-nightly sodium oxybate ER is FDA-approved (May 2023) for cataplexy or EDS in narcolepsy (age 7+)<br>*This agent is not approved for the treatment of IH. REVITALYZ is designed to support a potential supplemental indication in IH. Enrollment completed Dec 2025; topline results are pending |

DBRW = double-blind randomized withdrawal.

Sodium oxybate [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761061s000lbl.pdf. ClinicalTrials.gov Identifier: NCT06525077. BusinessWire. 2026. https://www.businesswire.com/news/home/20260512566395/en/Alkermes-Announces-Positive-Topline-Results-From-REVITALYZ-Phase-3-Study-Evaluating-LUMRYZ-sodium-oxybate-Extended-Release-in-Adults-With-Idiopathic-Hypersomnia#xd_co_f=YzA5MmViNDMtZDQ0NS00MTU0LTk5Y2EtMWFjYmY4MjYyNmU5~.

*Emerging OX2R Landscape — A Brief Snapshot*

# Active IH Trials

| Agent | Mechanism | Lead Indication | Phase + Lead Study | IH-Relevance Note |
|---|---|---|---|---|
| **Alixorexton (ALKS 2680)** | OX2R-selective agonist | IH | Phase II (Vibrance-3) | Only named OX2R agonist with an active dedicated IH efficacy study; estimated primary completion July 2026; public topline timing not confirmed |
| **TAK-360** | OX2R-selective agonist | IH/NT2 | Phase II (IH; NCT06812078) | Active IH dose-finding study recruiting |
| **ORX750** | OX2R-selective agonist | IH/NT1/NT2 | Phase IIa (CRYSTAL-1) | Includes an IH cohort in an early proof-of-concept crossover study |

Dauvilliers Y, et al. *N Engl J Med*. 2025;392(19):1905-1916. ClinicalTrials.gov Identifiers: NCT06843590, NCT06812078, and NCT06752668.

# Patient Advocate Haley

*Video Clip:*



Haley Wall. Interview with CME Outfitters. 2026.

*Why This Raises The Stakes*

# The Diagnosis Sets the Direction

## The Argument

- IH now has one FDA-approved therapy in adults, with additional mechanisms under investigation that include OX2R agonism and histaminergic wake-promotion. As therapeutic options diversify, **diagnostic mislabeling matters more** because the wrong label can delay both appropriate workup and access to the right treatment pathway.
- The more options exist, the more a misdiagnosis costs the patient: **access to the right mechanism depends on the label.** If a patient is diagnosed with IH rather than narcolepsy, treatment eligibility and future therapeutic options may differ.

Dauvilliers Y, et al. *Lancet Neurol.* 2022;21(1):53-65. Dauvilliers Y, et al. *N Engl J Med*. 2025;392(19):1905-1916. ClinicalTrials.gov Identifiers: NCT06843590, NCT06812078, and NCT06752668.

# *Patient Cases: What Would You Do?*

*Audience, Community/Rural Clinician, KOL, AI, and Faculty Responses to Two Patients with IH*

# PATIENT CASE

## *Elena Brooks*

- 29-year-old graduate student and part-time laboratory technician referred for 12-18 months of persistent daytime sleepiness, difficulty waking, fatigue, and worsening concentration/work/school performance
  - Sleeps 9-10 hours on weeknights, up to 12 hours on weekends, wakes unrefreshed
  - 2-4 sequential alarms to get up; 45-90 min disorientation after waking
  - Reports pervasive mental fog, slowed processing, reduced ability to complete coursework and protocols
  - 1-2 unplanned naps/day, 60-120 min; naps are not restorative and may occasionally worsen alertness
  - 2-3 caffeinated beverages daily with limited benefit
- Targeted history/prior psychiatric framing:
  - Drinks alcohol rarely; no cannabis or illicit substances
  - Not a shift worker
  - Primary care provider prescribed sertraline 50 mg daily; after 10 weeks, no meaningful improvement in daytime sleepiness, sleep inertia, or function
  - Describes symptoms as “still tired when I wake up” and “never fully on”
  - Frustrated that symptoms are framed as stress, burnout, or mood-related
  - Wants a clear diagnostic plan and realistic expectations

# PATIENT CASE

*Elena Brooks*

## Laboratory and Mood Screening

Primary care workup was limited to general lab screening, and no sleep-specific evaluation has yet been performed.

| Assessment | Result | Interpretation |
|---|---|---|
| **CBC** | Within normal limits | *Anemia excluded as driver of fatigue* |
| **TSH** | Within normal limits | *Thyroid dysfunction excluded* |
| **Ferritin** | Within normal limits | *Iron deficiency/RLS association excluded* |
| **Vitamin D (25-OH)** | Within normal limits | *Common reversible fatigue contributor addressed* |
| **PHQ-9** | 8 (mild) | *Depressive symptoms present but not severe; overlaps EDS items* |
| **GAD-7** | 3 (minimal) | *Anxiety unlikely to be primary driver* |



Baseline medical screen does not identify a secondary medical cause of hypersomnolence.
TSH = thyroid-stimulating hormone; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; RLS = restless leg syndrome.

# PATIENT CASE

*Elena Brooks*

## Medications and Pertinent Clinical Information

| Assessment | Result | Interpretation |
|---|---|---|
| **Sertraline 50 mg daily** | ×10 weeks, no symptomatic benefit | *Adequate trial duration; REM-suppressant (will affect MSLT interpretation)* |
| **Hypnotics/benzodiazepines** | None | *No medication-induced hypersomnolence* |
| **Opioids/cannabinoids** | None | *Excluded* |
| **Stimulants/wake-promoting agents** | None | *Drug-naïve for this indication* |
| **Substance misuse/head trauma** | None reported | *Secondary causes of hypersomnolence unlikely* |
| **Cataplexy history** | None on directed review | *No clear cataplexy identified; diagnostic significance remains unresolved without full reassessment* |

Sertraline duration and dose are adequate - a positive antidepressant response would have been expected by week 6-10 if mood disorder were primary.

# AUDIENCE POLLING

*Which initial assessment approach most appropriately clarifies whether her symptoms reflect IH, a primary mood disorder, or insufficient sleep syndrome?*

A. Administer the ESS, initiate a 2-week sleep diary with actigraphy, and reassess the symptom cluster including prolonged sleep time, severe sleep inertia, unrefreshing naps, and brain fog
B. Administer the IHSS as the primary screening tool
C. Rely on prior PHQ-9 and GAD-7; refer directly for PSG
D. Refer to psychiatry for additional assessment before any sleep-focused evaluation
E. Refer directly for overnight PSG followed by next-day MSLT
F. Reinforce sleep hygiene counseling and reassess in 3 months

*Patient Voice*

# What Patients Need Clinicians to Hear

## This is not just "being tired"

- **65%** reported trouble staying awake or "never feeling fully awake"
- **53%** say that "it is very hard to get out of bed even with alarms"
- **51%** reported brain fog/trouble thinking clearly

## The wrong explanation often comes first

- **42%:** symptoms were commonly attributed to depression/stress/burnout
- **40%** were told to simply get more sleep

## The diagnostic journey is hard to navigate

- **42%:** barriers getting a referral to a sleep specialist
- **30%:** barriers knowing how to describe the symptoms clearly
- **26%:** barriers finding a treatment/management plan that helps

## What patients say would have helped earlier

- **54%:** more targeted questions about waking up, naps, brain fog, and long sleep time
- **47%:** clearer explanations of how IH differs from depression or other conditions
- **39%:** a symptom checklist, diary, or tracking tool

CME Outfitters. *MM-163 Patient Survey*. 2026. N = 57 respondents.

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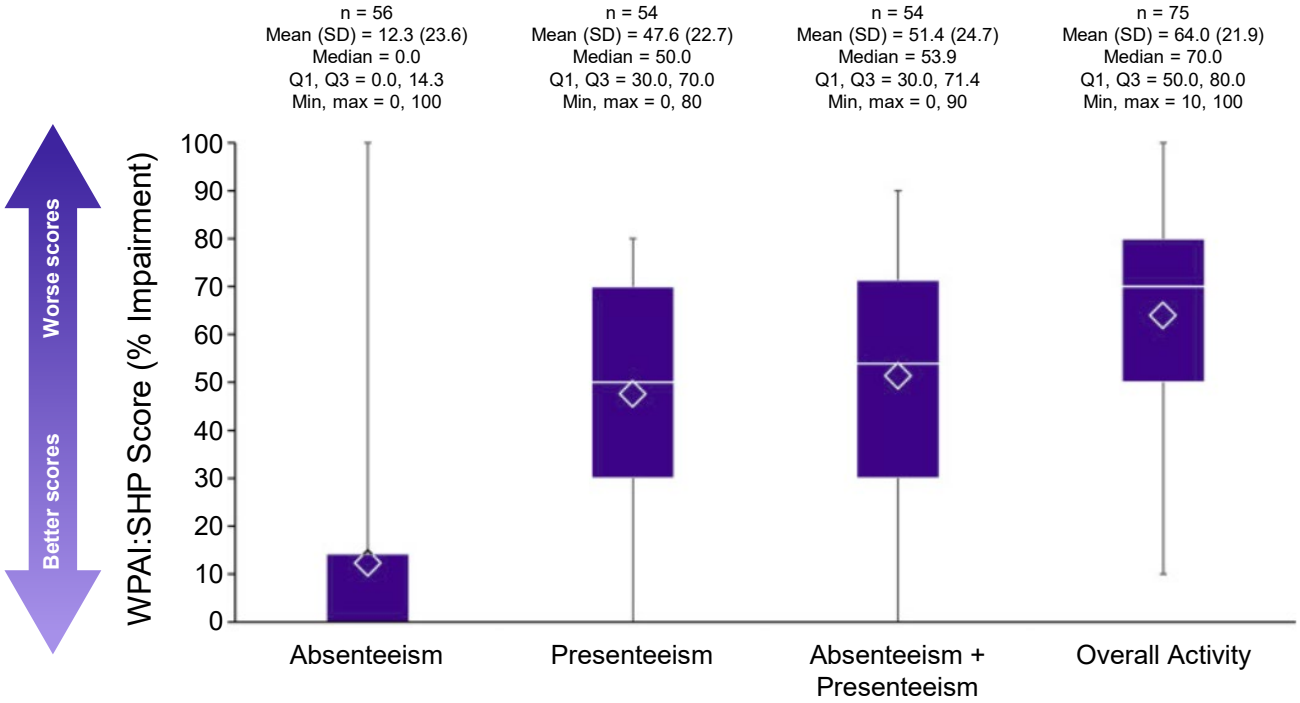
*Disease Burden - Data*

# Functional Impact of IH: ARISE Survey




## Takeaway

IH imposes a **clear, quantifiable burden** on work and daily function, especially presenteeism, overall work-productivity impairment, and nonwork activity impairment.

- Presenteeism: mean 47.6%
- Overall work-productivity impairment: mean 51.4%
- Overall activity impairment: mean 64.0%

These data support **earlier** diagnostic workup and **stronger** documentation of functional impact.

WPAI:SHP scores in all participants. The bottom and top edges of the box indicate the first and third quartiles, 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.

Stevens J, et al. *Nat Sci Sleep.* 2023;15:593-606.

*Disease Burden*

# Core Epidemiology and Patient Burden

| Domain | What the Evidence Shows | Clinical Implication |
|---|---|---|
| **Prevalence** | Diagnosed IH remains rare in U.S. adults: annual prevalence ~10.5-12.1 per 100,000; all-time lookback prevalence 32.7-49.0 per 100,000 in claims data | Rare diagnosis, but likely underrecognized; recognition and diagnostic workup remain the bottleneck |
| **Age of onset** | Typical onset between adolescence and young adulthood (age 15-20); symptoms often chronic and stable | Misattribution to school stress, circadian preference, or mood symptoms may delay correct diagnosis |
| **Diagnostic delay** | 61% reported prior misdiagnosis; 69% reported > 1-year delay in diagnosis; 19% reported ≥ 10 years to diagnosis | Delayed diagnosis prolongs inappropriate labeling and years of untreated disability; years of inappropriate therapy (antidepressants, stimulants) |
| **Functional impact** | ARISE showed substantial work and activity burden: mean absenteeism 12.3%, presenteeism 47.6%, overall work productivity impairment 51.4%, and daily activity impairment 64.0% | Measurable occupational and academic cost; strengthens case for expedited workup |
| **Symptom profile** | Core burdensome symptoms extend beyond EDS and include severe sleep inertia/sleep drunkenness, long sleep duration or nonrestorative sleep, prolonged unrefreshing naps, and daytime cognitive dysfunction/brain fog | ESS alone is insufficient; pair ESS with IHSS, sleep diary/actigraphy, and a structured symptom history to distinguish IH from depression, insufficient sleep syndrome, and NT2 |

Markt SC, et al. *Sleep Adv*. 2026;7(1):zpag011. Zhang Z, et al. *J Sleep Res*. 2025;35(2):e70170. Whalen M, et al. *Sleep*. 2022;45(Suppl 1):A175-A176. Stevens J, et al. *Nat Sci Sleep*. 2023;15:593-606. Boulanger T, et al. *Sleep Adv*. 2024;5(1):zpae059. Dauvilliers Y, et al. *Neurology*. 2019;92(15):e1754-e1762.

# Foundational Framework

*ICSD-3-TR Criteria for Idiopathic Hypersomnia*

## All of the following must be present:*

- Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months
- Cataplexy is absent
- MSLT shows < 2 SOREMPs, or no SOREMPs if REM latency on the preceding PSG is ≤ 15 minutes
- Presence of at least one:
  - (1) MSLT ≤ 8 min; or
  - (2) total 24-hour sleep time ≥ 660 min (typically 12-14h) on 24hr performed after correction of chronic sleep deprivation, or actigraphy with sleep diary/log averaged over ≥ 7 days of unrestricted sleep
- Insufficient sleep syndrome ruled out, ideally with sleep diary ± actigraphy when clinically needed and/or documented lack of improvement after adequate sleep extension
- Hypersomnolence/MSLT findings are not better explained by another sleep disorder, circadian rhythm sleep-wake disorder, medical disorder, mental disorder medication/substance use or withdrawal

*Criteria A-F must be met; criterion D requires at least 1 of the 2 objective findings above.
ICSD-3-TR = International Classification of Sleep Disorders, Third Edition, Text Revision; MSLT = Multiple Sleep Latency Test; SOREMP = sleep-onset rapid eye movement period; REM = rapid eye movement; PSG = polysomnography.

American Academy of Sleep Medicine [AASM]. 2023. https://aasm.org/clinical-resources/international-classification-sleep-disorders/. Krahn LE, et al. *J Clin Sleep Med*. 2021;17(12):2489-2498. Dauvilliers Y, et al. *Sleep Med Rev*. 2022;66:101709.

# EXPERT FACULTY

*Live Discussion*

## Decision Point

*Patient Case: Elena Brooks*

# COMMUNITY/RURAL KOL

*Audio Recording: Case 1 Elena*

**E** Refer directly for overnight PSG followed by next-day MSLT

- Enough information that any of the other options would be delaying what needs to take place – the sleep study
- Depression does not make sense given her PHQ-9 is 3
- Never seen or heard of a patient with overwhelming hypersomnia with no depression symptoms otherwise
- Symptoms tend to convey a classic sleep disorder
- Use screening scales to rule out depression or other mood disorders during that initial patient visit
- Insufficient sleep syndrome unlikely as patient is getting excessive yet unrestful sleep



CME Outfitters. *MM-163 Healthcare Provider Survey*. 2026.

# COMMUNITY/RURAL KOL

*Audio Recording: Case 1 Elena*

**A** Administer the ESS, initiate a 2-week sleep diary with actigraphy, and reassess the symptom cluster including prolonged sleep time, severe sleep inertia, unrefreshing naps, and brain fog

- Reflex with daytime sleepiness is to think OSA first, but no evidence
- Presence of long sleep that does not refresh, morning sleep inertia, unrefreshing naps, and cognitive fog; none of which is consistent with OSA
- Diary and actigraphy indicates whether or not it is insufficient sleep
- IHSS not something reached for in primary care
- Mood scores only mildly elevated
- Repeat referral to psychiatry would be a mistake
- Want sleep document before PSG and MSLT



OSA = obstructive sleep apnea.

CME Outfitters. *MM-163 Healthcare Provider Survey*. 2026.

# COMMUNITY/RURAL KOL

*Audio Recording: Case 1 Elena*

**A** Administer the ESS, initiate a 2-week sleep diary with actigraphy, and reassess the symptom cluster including prolonged sleep time, severe sleep inertia, unrefreshing naps, and brain fog

- ESS and sleep diary is what is currently done in office
- Determine if she is getting enough sleep prior to sending for hours of testing
- Symptoms are not consistent with OSA
- Since she already failed an antidepressant trial, would not repeat
- Going straight to sleep study should be preceded by prep first



CME Outfitters. *MM-163 Healthcare Provider Survey*. 2026.

# Additional Community KOL Responses for Case 1 Elena

| | | |
|---|---|---|
| RESPONDENT 1 | B | Administer the IHSS as the primary screening tool |
| RESPONDENT 2 | A | Administer the ESS, initiate a 2-week sleep diary with actigraphy, and reassess the symptom cluster including prolonged sleep time, severe sleep inertia, unrefreshing naps, and brain fog |
| RESPONDENT 3 | A | Administer the ESS, initiate a 2-week sleep diary with actigraphy, and reassess the symptom cluster including prolonged sleep time, severe sleep inertia, unrefreshing naps, and brain fog |



CME Outfitters. *MM-163 Healthcare Provider Survey*. 2026.

# KOL: Kiran Maski, MD, MPH

*Video Recording: Case 1 Elena*

**A** Administer the ESS, initiate a 2-week sleep diary with actigraphy, and reassess the symptom cluster including prolonged sleep time, severe sleep inertia, unrefreshing naps, and brain fog

# KOL: Yves Dauvilliers, MD, PhD

*Video Recording: Case 1 Elena*

**B** Administer the IHSS as the primary screening tool

# KOL: John Carter, MD

*Video Recording: Case 1 Elena*

**A** Administer the ESS, initiate a 2-week sleep diary with actigraphy, and reassess the symptom cluster including prolonged sleep time, severe sleep inertia, unrefreshing naps, and brain fog



Dr. John Carter. Interview with CME Outfitters. 2026.

# AI: ChatGPT 5.2

## *User-Fed Response: Case 1 Elena*

**New chat** → Here's the case's subjective, objective, and plan/multiple choice question. Based on the information provided, which answer choice would you choose and what is your brief rationale for your chosen answer and unchosen options?

**A** Administer the ESS, initiate a 2-week sleep diary with actigraphy, and reassess the symptom cluster including prolonged sleep time, severe sleep inertia, unrefreshing naps, and brain fog

**Rationale:** This patient's history is highly suggestive of IH. However, a diagnosis of IH requires documentation that: 1) she is obtaining adequate sleep; 2) symptoms are not due to chronic sleep deprivation; and 3) another sleep disorder is not responsible.

### Rule outs

**IHSS:** is not the preferred initial screening tool
**PHQ-9 and GAD-7:** evaluate mood and anxiety symptoms, not hypersomnolence disorders
**Refer to psychiatry:** her symptoms are dominated by sleep, not mood
**Overnight PSG and next-day MSLT:** should occur after documenting sleep; REM-suppressing meds should be discontinued before MSLT
**Sleep hygiene counseling:** no evidence poor sleep hygiene is causative

# Patient Advocate Caitlin

*Video Clip*

CASEWISE™ by CME OUTFITTERS

Caitlin Dilley. Interview with CME Outfitters. 2026.

# Patient Advocate Haley

*Video Clip:*



Haley Wall. Interview with CME Outfitters. 2026.

# Patient Advocate Becky

*Video Clip:*

CASEWISE™ by CME OUTFITTERS

Becky Gabany. Interview with CME Outfitters. 2026.

# Case Perspective Summary

## *Case 1 Elena*

| Most Appropriate Assessment Approach | Community/Rural | KOLs | AI |
|---|---|---|---|
| Administer the ESS, initiate a 2-week sleep diary with actigraphy, and reassess the symptom cluster including prolonged sleep time, severe sleep inertia, unrefreshing naps, and brain fog | 4 | 2 | 1 |
| Administer the IHSS as the primary screening tool | 1 | 1 | — |
| Rely on prior PHQ-9 and GAD-7; refer directly for PSG | — | — | — |
| Refer to psychiatry for additional assessment before any sleep-focused evaluation | — | — | — |
| Refer directly for overnight PSG followed by next-day MSLT | 1 | — | — |
| Reinforce sleep hygiene counseling and reassess in 3 months | — | — | — |



CME Outfitters. *MM-163 Healthcare Provider Survey*. 2026.

# FACULTY DISCUSSION

*What have we learned from Elena's case?*

- **Diagnostic delay has real costs:** functional decline and QoL loss while the workup stalls
- **Red flags hide in plain sight:** long sleep, sleep inertia, and unrefreshing naps were reframed as stress or mood
- **Ask about sleep, then dig deeper:** quantify sleep duration, wake difficulty, nap quality, and sleep inertia
- **A mild PHQ-9 is not the diagnosis:** overlapping EDS may inflate it, and a failed antidepressant trial can argue against mood as primary
- **No single test stands alone:** pair ESS and IHSS with a sleep diary/actigraphy and PSG → MSLT for a full clinical picture
- **Check confounders before testing:** REM suppressants can distort MSLT



Lammers GJ, et al. *Sleep Med Rev.* 2020;52:101306. Fronczek R, et al. *Sleep*. 2020;43(8):zsaa044. Krahn LE, et al. *J Clin Sleep Med.* 2021;17(12):2489-2498. Dauvilliers Y, et al. *Sleep Med Rev.* 2022;66:101709. AASM. 2023. https://aasm.org/clinical-resources/international-classification-sleep-disorders/.

*Putting It Together — Diagnostic Pathway*

# A Practical Diagnostic Algorithm for Suspected IH

**1. Recognize**
Chronic EDS ≥ 3 months despite adequate sleep; long sleep time, severe sleep inertia, unrefreshing naps

**2. Characterize and screen**
Symptom history + ESS and IHSS; screen mood (PHQ-9); reconcile medications/substances

**3. Exclude mimics**
Insufficient sleep (1-2–wk diary ± actigraphy, sleep extension), OSA, medication/substance, circadian, medical/psychiatric

**4. Objective testing**
Overnight PSG, then next-day MSLT after ≥ 7 days unrestricted sleep; taper REM suppressants first

## Reaching the Diagnosis (ICSD-3-TR)

**IH confirmed when all are met:**

- MSLT mean sleep latency ≤ 8 min and/or 24 h total sleep time ≥ 660 min
- Fewer than 2 SOREMPs; or no SOREMPs, if the REM latency on the preceding overnight sleep study (PSG) was ≤ 15 min
- Cataplexy absent
- Not better explained by another disorder, medication/substance, or insufficient sleep

## Branch points

- ≥ 2 SOREMPs → evaluate for narcolepsy
- Symptoms resolve with adequate sleep → insufficient sleep syndrome
- Explained by OSA, medication, circadian, or psychiatric cause → treat that condition and reassess

TST = total sleep time.

Sateia MJ. *Chest*. 2014;146(5):1387-1394. Boulanger T, et al. *Sleep Adv*. 2024;5(1):zpae059. Dauvilliers Y, et al. *Neurology*. 2019;92(15):e1754-e1762. Dauvilliers Y, et al. *Sleep Med Rev*. 2022;66:101709.

*Faculty Discussion — Validated Measures*

# IHSS and ESS: What Each Scale Measures

| Attribute | Epworth Sleepiness Scale (ESS) | Idiopathic Hypersomnia Severity Scale (IHSS) |
|---|---|---|
| **What it measures** | Subjective propensity to doze in 8 everyday situations – a single sleepiness dimension; does not capture sleep inertia or long sleep time | Severity, frequency, and functional impact of the 3 core IH symptoms: EDS/naps, prolonged unrefreshing night and day sleep, and sleep inertia |
| **Items and score range** | 8 items; total score 0-24 | 14 items; total score 0-50 |
| **Interpretation/cut-offs** | > 10 suggests excessive daytime sleepiness (not diagnosis-specific) | ≥ 22 discriminates untreated IH from controls (sensitivity 91%, specificity 94%); severity: mild 0-12, moderate 13-25, severe 26-38, very severe 39-50 |
| **Disease specificity** | Generic across sleep disorders; cannot distinguish IH from OSA, narcolepsy, or insufficient sleep | Developed and validated specifically for IH |
| **Treatment responsiveness** | Responsive to change in sleepiness; used as a primary endpoint in IH trials | Responsive to treatment; used as a key secondary endpoint in IH trials |
| **Best use in practice** | Quick screen and tracking of overall sleepiness | Characterize the full IH symptom burden and monitor response – use alongside, not instead of, the ESS |

AI tool Claude Opus 4.8 was utilized to assist in content development and graphic layout. Reviewed by Siddharth Mohan.

Johns MW. *Sleep*. 1991;14(6):540-545. Dauvilliers Y, et al. *Neurology*. 2019;92(15):e1754-e1762. Rassu AL, et al. *J Clin Sleep Med.* 2022;18(2):617-629.

*Faculty Discussion — Differential Diagnosis*

# Differentiating IH From Depression and Mood Disorders

| Clinical Feature | Idiopathic Hypersomnia | Depression/Mood Disorder |
|---|---|---|
| **Predominant complaint** | Irrepressible daily sleepiness with long, unrefreshing sleep; sleepiness is the primary, persistent disturbance | Low mood/anhedonia is primary; hypersomnolence is one of several symptoms and tends to fluctuate with mood |
| **Daytime naps** | Often long (1-4 h) and characteristically unrefreshing | Frequently short or absent; daytime lying down may reflect low drive rather than true sleep propensity |
| **Sleep inertia and long sleep time** | Severe sleep inertia (sleep drunkenness) and long sleep time are hallmark features | Less prominent; early morning awakening or insomnia is common |
| **Objective testing (PSG/MSLT)** | Long total sleep time; MSLT mean sleep latency ≤ 8 min in many (not all) patients, with < 2 SOREMPs | MSLT often shows normal or long sleep latency; objective sleepiness frequently not confirmed |
| **Response to antidepressants** | EDS, sleep inertia, and long sleep time persist despite an adequate antidepressant trial | Hypersomnolence typically improves as mood improves with adequate treatment |
| **Overlap to remember** | Depressive symptoms are common in IH (up to ~two-thirds screen positive on PHQ-9); comorbidity is not causation | PHQ-9 sleep/energy items overlap with EDS and can inflate scores; screen for an underlying sleep disorder |

AI tool Claude Opus 4.8 was utilized to assist in content development and graphic layout. Reviewed by Siddharth Mohan.
Dauvilliers Y, et al. *Sleep Med Rev*. 2022;66:101709. Plante DT. *Sleep Med Rev*. 2017;31:48-57. Lammers GJ, et al. *Sleep Med Rev*. 2020;52:101306. AASM. 2023. https://aasm.org/clinical-resources/international-classification-sleep-disorders/.

# AUDIENCE POLLING REVISITED

*Now, what would you do next?*

A. Administer the ESS, initiate a 2-week sleep diary with actigraphy, and reassess the symptom cluster including prolonged sleep time, severe sleep inertia, unrefreshing naps, and brain fog

B. Administer the IHSS as the primary screening tool

C. Rely on prior PHQ-9 and GAD-7; refer directly for PSG

D. Refer to psychiatry for additional assessment before any sleep-focused evaluation

E. Refer directly for overnight PSG followed by next-day MSLT

F. Reinforce sleep hygiene counseling and reassess in 3 months

# PATIENT CASE

## *Daniel Mercer*

- 37-year-old man, software engineer, is referred for reevaluation after a prior assessment for presumptive OSA
  - Symptoms have persisted for 5-6 years with progressive functional impact
  - Describes “never feeling fully awake” with mental fog, difficulty sustaining attention at work
  - Sleeps ≥ 8 hours on weeknights and often 10-11 hours on weekends, still wakes unrefreshed
  - 45-90 min of poor wakefulness despite multiple alarms
  - Daytime naps 30-90 min on 3-4 days/week, minimal restorative benefit
  - Symptoms interfering with work performance and daily functioning
  - Wants to understand what evaluation is needed to clarify diagnosis
- Prior workup/targeted history:
  - Prior HSAT did not show OSA
  - Presents believing narcolepsy is likely after reading about it online
  - No clear cataplexy
  - No muscle weakness with laughter, surprise, or strong emotion
  - No head drops, jaw sag, or knee buckling
  - No paralysis on awakening
  - No consistent hypnagogic hallucinations
  - Occasional vivid dreams; no dream enactment
  - Main symptom pattern remains long sleep time, severe morning sleep inertia, persistent fogginess, and nonrestorative naps



HSAT = home sleep apnea test.

# PATIENT CASE

*Daniel Mercer*

## Sleep-Specific Assessments and Mood Screening

| Assessment | Result | Interpretation |
|---|---|---|
| **Medication status** | No current stimulant, wake-promoting agent, or antidepressant use | *Current symptom burden is not being actively modified by alerting or antidepressant therapy* |
| **PHQ-9** | 6 (mild) | *Mild depressive symptoms present; does not independently explain the full hypersomnolence picture* |
| **GAD-7** | 4 (minimal) | *Anxiety unlikely to be primary driver* |
| **ESS** | 18/24 | *Severe excessive daytime sleepiness* |
| **HSAT** | Negative for OSA | *Prior OSA screen unrevealing; does not establish the cause of hypersomnolence* |
| **Swiss Narcolepsy Scale/directed cataplexy inventory** | Negative for cataplexy | *No clear cataplexy signal on screening; clinical significance remains unresolved without full sleep-focused reassessment* |



Prior test timing: HSAT > 3 years earlier; narcolepsy screening, PSG, and MSLT ~2 years earlier.

# AUDIENCE POLLING

*What is the most appropriate next diagnostic step?*

A. Proceed directly to overnight PSG followed by next-day MSLT

B. Obtain a 2-week sleep diary and actigraphy and reassess while formal testing is pending

C. Obtain a detailed current symptom history, document adequate sleep with a 2-week sleep diary and actigraphy, and perform an overnight PSG followed by next-day MSLT

D. Administer the ESS and a validated hypersomnia questionnaire and manage based on score

# EXPERT FACULTY

*Live Discussion*

## Decision Point

*Patient Case: Daniel Mercer*

# COMMUNITY/RURAL KOL

*Audio Recording: Case 2 Daniel*

**A** Proceed directly to overnight PSG followed by next-day MSLT

- Patient has a significant ongoing history of:
  - Hypersomnolence
  - Unrestful sleep
  - ESS is very high
- Functional impairment due to his symptoms is evident
- No or minimal evidence of medical- or substance-related issues contributing to symptoms

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# COMMUNITY/RURAL KOL

*Audio Recording: Case 2 Daniel*

**C** Obtain a detailed current symptom history, document adequate sleep with a 2-week sleep diary and actigraphy, and perform an overnight PSG followed by next-day MSLT

- Severe ESS, negative HSAT, no cataplexy
- Symptoms not consistent with narcolepsy
- Positive for long sleep, severe inertia, unrefreshing naps, and brain fog, which is more consistent with IH than narcolepsy
- Immediate PSG and MSLT skips documenting adequate sleep
- Diary and actigraphy alone insufficient, need objective tests
- Questionnaires cannot distinguish narcolepsy from IH
- Teaching point: negative HSAT does not rule out sleep disorder



CME Outfitters. *MM-163 Healthcare Provider Survey*. 2026.

# COMMUNITY/RURAL KOL

*Audio Recording: Case 2 Daniel*

**C** Obtain a detailed current symptom history, document adequate sleep with a 2-week sleep diary and actigraphy, and perform an overnight PSG followed by next-day MSLT

- Negative HSAT yet still sleepy
- Full, proper workup is needed
- Confirm if history indicates adequate sleep first, then PSG and MSLT
- Score on questionnaire alone insufficient for diagnosis
- Skipping sleep documentation would undercut testing



CME Outfitters. *MM-163 Healthcare Provider Survey*. 2026.

# Additional Community KOL Responses for Case 2

| | | |
|---|---|---|
| RESPONDENT 1 | C | Obtain a detailed current symptom history, document adequate sleep with a 2-week sleep diary and actigraphy, and perform an overnight PSG followed by next-day MSLT |
| RESPONDENT 2 | C | Obtain a detailed current symptom history, document adequate sleep with a 2-week sleep diary and actigraphy, and perform an overnight PSG followed by next-day MSLT |
| RESPONDENT 3 | C | Obtain a detailed current symptom history, document adequate sleep with a 2-week sleep diary and actigraphy, and perform an overnight PSG followed by next-day MSLT |



CME Outfitters. *MM-163 Healthcare Provider Survey*. 2026.

# KOL: Kiran Maski, MD, MPH

*Video Recording: Case 2 Daniel*

**C** Obtain a detailed current symptom history, document adequate sleep with a 2-week sleep diary and actigraphy, and perform an overnight PSG followed by next-day MSLT



Dr. Kiran Maski. Interview with CME Outfitters. 2026.

# KOL: Yves Dauvilliers, MD, PhD

*Video Recording: Case 2 Daniel*

**C** Obtain a detailed current symptom history, document adequate sleep with a 2-week sleep diary and actigraphy, and perform an overnight PSG followed by next-day MSLT

# KOL: John Carter, MD

*Video Recording: Case 2 Daniel*

**C** Obtain a detailed current symptom history, document adequate sleep with a 2-week sleep diary and actigraphy, and perform an overnight PSG followed by next-day MSLT



Dr. John Carter. Interview with CME Outfitters. 2026.

# AI: ChatGPT 5.2

## *User-Fed Response: Case 2 Daniel*

**New chat** → Here's the case's subjective, objective, and plan/multiple choice question. Based on the information provided, which answer choice would you choose and what is your brief rationale for your chosen answer and unchosen options?

**C** Obtain a detailed current symptom history, document adequate sleep with a 2-week sleep diary and actigraphy, and perform an overnight PSG followed by next-day MSLT

**Rationale:** Daniel's history strongly suggests IH, clues including long sleep duration, severe sleep inertia, unrefreshing naps, brain fog, severe sleep per ESS, no cataplexy, and negative HSAT for OSA

### Rule outs

**Overnight PSG + next-day MSLT:** current guidelines recommend documenting sleep adequacy beforehand
**Two-week diary and actigraphy:** ESS score, functional impairment, and negative OSA warrant definitive sleep testing
**Administer ESS and hypersomnia questionnaire:** questionnaires do not diagnose IH; they quantify symptoms, measure severity, and track treatment response



OpenAI. Generated by ChatGPT, model 5.2. Used 2026.

# Case Perspective Summary

## *Case 2 Daniel*

| Most Appropriate Assessment Approach | Community/Rural | KOLs | AI |
|---|---|---|---|
| Proceed directly to overnight PSG followed by next-day MSLT | 1 | — | — |
| Obtain a 2-week sleep diary and actigraphy and reassess while formal testing is pending | — | — | — |
| Obtain a detailed current symptom history, document adequate sleep with a 2-week sleep diary and actigraphy, and perform an overnight PSG followed by next-day MSLT | 5 | 3 | 1 |
| Administer the ESS and a validated hypersomnia questionnaire and manage based on score | — | — | — |



CME Outfitters. *MM-163 Healthcare Provider Survey*. 2026.

# FACULTY DISCUSSION

*What have we learned from Daniel's case?*

- **A prior label can anchor and mislead:** a negative HSAT neither excludes OSA nor explains his sleepiness
- **Delay compounds impairment:** 5-6 years "never fully awake" before anyone reopened the workup
- **ESS is necessary but not sufficient:** ESS 18/24 confirms severe EDS but is nonspecific – it cannot separate IH from OSA, narcolepsy, or insufficient sleep; pair it with the IHSS and a full symptom history
- **IH vs NT2:** lookalikes need objective separation
- **Depression overlap and ruling out insufficient sleep:** PHQ-9 of 6 is mild and does not explain the full picture
- **Diagnosis is the gateway to treatment:** 5-6 years of progressive impairment shows the cost of delay



Lammers GJ, et al. *Sleep Med Rev.* 2020;52:101306. Fronczek R, et al. *Sleep*. 2020;43(8):zsaa044. Krahn LE, et al. *J Clin Sleep Med.* 2021;17(12):2489-2498. Dauvilliers Y, et al. *Sleep Med Rev.* 2022;66:101709. AASM. 2023. https://aasm.org/clinical-resources/international-classification-sleep-disorders/.

*Faculty Discussion — Differential Diagnosis*

# Differentiating IH From OSA, Insufficient Sleep, and Medication-Related Causes

| Mimic or Cause | Distinguishing Features vs IH | How to Confirm or Exclude |
|---|---|---|
| **OSA** | Snoring, witnessed apneas, obesity; nonrestorative sleep with EDS but usually without severe sleep inertia or long sleep time; may coexist with IH | Overnight PSG (AHI). Treat OSA first; persistent EDS with normal sleep duration after adequate therapy warrants workup for a central disorder of hypersomnolence |
| **Insufficient sleep syndrome** | Chronic curtailed sleep with marked weekend/vacation "catch-up"; symptoms resolve with adequate sleep – an explicit ICSD-3-TR exclusion for IH | 1-2–week sleep diary ± actigraphy documenting habitual short sleep; reassess after a structured sleep-extension trial |
| **Medication- or substance-related** | Sedating agents (antihistamines, benzodiazepines, opioids, some antidepressants/antipsychotics), alcohol, or withdrawal can cause or worsen hypersomnolence | Reconcile medications and substances; REM suppressants (e.g., antidepressants) can confound the MSLT; therefore, taper appropriately before testing when feasible |
| **Diagnostic principle** | IH is a diagnosis of exclusion; these causes must be ruled out before it is made | Layer symptom history + sleep diary/actigraphy + overnight PSG with next-day MSLT; revisit prior labels when symptoms don't fit |

AI tool Claude Opus 4.8 was utilized to assist in content development and graphic layout. Reviewed by Siddharth Mohan.
AHI = apnea-hypopnea index.
AASM. 2023. https://aasm.org/clinical-resources/international-classification-sleep-disorders/. Lammers GJ, et al. *Sleep Med Rev.* 2020;52:101306. Dauvilliers Y, et al. *Sleep Med Rev.* 2022;66:101709. Krahn LE, et al. *J Clin Sleep Med*. 2021;17(12):2489-2498.

# AUDIENCE POLLING REVISITED

*Now, what would you do next?*

A. Proceed directly to overnight PSG followed by next-day MSLT

B. Obtain a 2-week sleep diary and actigraphy and reassess while formal testing is pending

C. Obtain a detailed current symptom history, document adequate sleep with a 2-week sleep diary and actigraphy, and perform an overnight PSG followed by next-day MSLT

D. Administer the ESS and a validated hypersomnia questionnaire and manage based on score

# Patient Advocate Haley

*Video Clip:*



Haley Wall. Interview with CME Outfitters. 2026.

# Patient Advocate Caitlin

*Video Clip*



Caitlin Dilley. Interview with CME Outfitters. 2026.

# Case Closed

*Turning Complexity Into Clarity in IH Care*

**IH care demands earlier recognition, accurate diagnosis, and readiness for an evolving treatment landscape.**

## Diagnostic delays impose a measurable and preventable burden

Overlapping symptoms with mood disorders and other sleep conditions drive diagnostic delays; raising clinical suspicion early is the first step

## ICSD-3-TR criteria are a starting point, not a finish line

A layered approach combining objective testing, validated scales, and a thorough symptom history is necessary to reach an accurate diagnosis

## The correct label unlocks the correct treatment pathway

A misdiagnosis of depression or NT2 delays access to it and to emerging therapies

## An expanding pipeline makes getting the diagnosis right more consequential than ever

With new therapeutic options emerging, accurate diagnosis matters more than ever; the right label connects patients to the right treatment at the right time


# Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- **Improve** clinician confidence in differentiating IH from depression/mood disorders, NT2, OSA, and insufficient sleep syndrome when evaluating chronic EDS
- **Increase** the proportion of patients with suspected IH who receive a guideline-concordant workup; i.e., structured symptom history, validated scales (ESS and IHSS), sleep diary/actigraphy, and overnight PSG followed by next-day MSLT
- **Increase** the use of validated patient-reported measures, such as the IHSS and ESS, to characterize sleep inertia, long sleep time, and unrefreshing naps at diagnosis and to track treatment response over time
- **Reduce** diagnostic delay by reassessing ≥ 15% more patients carrying a presumptive depression or NT2 label for an underlying central disorder of hypersomnolence when symptoms persist despite treatment

# QUESTIONS & ANSWERS

Thank you for joining us.
Don’t forget to collect your credit.

# Additional Resources

Visit www.cmeoutfitters.com for clinical information and certified educational activities

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*Visit the*

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https://www.cmeoutfitters.com/practice/sleep-disorders-hub/

# This activity was created in collaboration with the Hypersomnia Foundation


To learn more and access additional resources, scan the QR code

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   *(MOC credit can be claimed even if a question goes unanswered or an incorrect response is entered)*
2. Complete the post-test and evaluation at the conclusion of the webcast
3. Enter your **ABIM ID number** and **DOB** (MM/DD) on the evaluation, so credit can be submitted to ABIM

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- Complete the post-test and activity evaluation at the link provided
- Over the next 3 months, actively work to incorporate improvements from this presentation into your clinical practice
- In approximately 3 months, complete the follow-up survey from CME Outfitters

CME for MIPS IMPROVEMENT ACTIVITY

CMEO will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity.™

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# CASE CLOSED?

## *Diagnosing Idiopathic Hypersomnia Beyond the Usual Suspects*

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