CMEO
BriefCase

Choosing Treatment: Matching Needs to Therapy

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CME OUTFITTERS

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Learning Objective

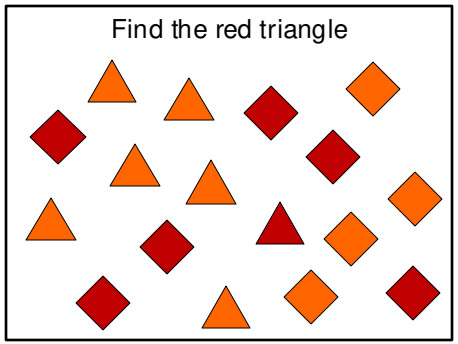
Utilize the latest efficacy and safety data to integrate novel therapies into clinical practice to mitigate the impact of IH.

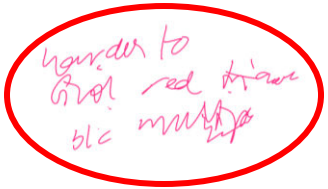
Patient Journey: The Road to Stability

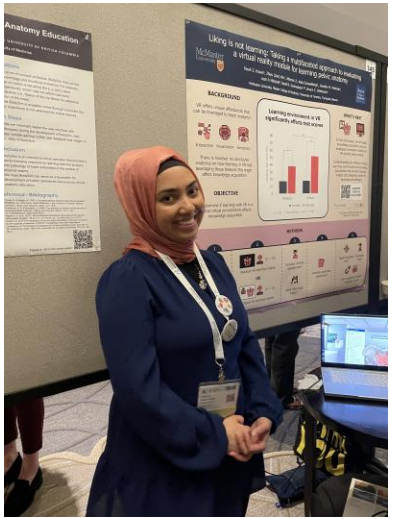
Navigating the disease

Navigating treatment

Symptoms Began → **Living with Symptoms** → **Gaining Stability**







Patient Case: Candice

- 30-year-old Black female presents to clinic after receiving sleep study results
- 24-hour sleep study conducted. Findings:
  - MSLT: 1 sleep-onset REM period
  - Sleep latency: 6 minutes
  - Total sleep time: 702 minutes
- Other diagnoses ruled out, given idiopathic hypersomnia diagnosis
- PMH: Hypertension
- BP = 136/86, BMI = 29
- Medications: hormonal contraception, lisinopril 5 mg
- Patient presents today for treatment initiation
- Expresses desire for simple dosing, something to improve her sleep inertia symptoms (which are significant)

BP = blood pressure; BMI = body mass index; MSLT = multiple sleep latency test; PMH = past medical history; REM = rapid eye movement

Audience Response

Considering Candice's presentation, which might be the most optimal choice of therapy?

A. Modafinil
B. Lower sodium oxybate
C. Pitolisant
D. Sodium oxybate
E. I don't know

Modafinil*

Not indicated for Idiopathic Hypersomnia (IH)

Mechanism of Action

- Weak inhibitor of dopamine reuptake

Idiopathic Hypersomnia Dosing

- 200 - 400 mg/day

Adverse Effects

- Headache, nausea, decreased appetite (< 10%)
- Anxiety, insomnia, dizziness, diarrhea, rhinitis (5 - 10%)

Clinical Considerations

- Can decrease contraceptive effectiveness
- Interactions between cyclosporine, CYP2C19 substrates (e.g., omeprazole, phenytoin, diazepam)
- Use with caution in patients with psychiatric or cardiovascular disease
- Generic oral tablet dosage form

*Modafinil is not FDA-approved for the treatment of IH. PROVIGIL® (modafinil) [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc. Revised 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf. Greenblatt K, et al. Modafinil. StatPearls. 2023. https://www.ncbi.nlm.nih.gov/books/NBK531476/.

Modafinil Clinical Data

- Mayer, et al. 2015
  - 31 patients with IH (without long sleep time)
- Improvement on Epworth Sleep Scale, Clinical Global Impression of Severity

Changes in ESS, sleep latency in MWT and CGI from V2 to V5

	V2 (baseline)	V5 (end of treatment)	Delta (=diff)	*p* (diff)	T-Value	Effect size
ESS						
Placebo	14.00 (13.55, 15.45)	13.00 (10.15, 15.14)	-1.50 (13.80, 0.089)	.023	2.3918	.6376
Modafinil	15.00 (12.57, 16.13)	8.00 (6.42, 11.58)	-6.00 (-7.67, -2.92)			
MWT						
Placebo	13.51 (8.85, 18.89	11.32 (9.42, 21.33)	0.19 (-2.94, 5.96)	NS	1.104	
Modafinil (n = 15)	12.50 (8.70, 18.47)	15.00 (10.88, 26.01)	3.00 (0.11, 9.61)			
CGI						
Placebo	6.00 (5.45, 6.12)	5.50 (4.94, 5.92)	0.00 (-0.84, 0.13)	.0276	-2.3247	.612
Modafinil (n = 16)	6.00 (5.46, 6.16)	5.00 (3.64, 5.24)	-1.00 (-2.26, -031)			

Modafinil is not FDA-approved for the treatment of IH.

Delta (=diff) = differences between baseline [visit (V)2] and 5. Data given as medians and 95% confidence interval (CI).

ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness test; CGI = Clinical Global Impression Scale; NS = not significant

Mayer G, et al. *J Sleep Res*. 2015;24(1):74-81.

Pitolisant*

Not indicated for IH, but findings of phase III INTUNE study expected end 2023

Mechanism of Action

- Histamine-3 (H3) receptor antagonist/inverse agonist

Idiopathic Hypersomnia Dosing

- Phase III dosing same as narcolepsy: titrate to stable dose 17.8 - 35.6 mg once daily

Adverse Effects

- Insomnia, nausea, anxiety (≥ 5%)

Clinical Considerations

- Can decrease contraceptive effectiveness
- Must adjust dosages for strong CYP2D6 inhibitors, strong CYP3A4 inducers
- Increases QT interval
- Oral tablet formulation

*Pitolisant is not FDA-approved for the treatment of IH. WAKIX® (pitolisant) [package insert]. Plymouth Meeting, PA: Harmony Biosciences, LLC. Revised 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211150s000lbl.pdf. Harmony Biosciences, LLC. A Phase 3 Study to Assess the Safety and Efficacy of Pitolisant in Adult Patients With Idiopathic Hypersomnia. ClinicalTrials.gov Identifier: NCT05156047. First Received 2021. Meglio, M. NeurologyLive Website. 2023.

Pitolisant Clinical Data

- Leu-Semescu, et al. 2014
  - 65-treatment refractory IH patients
    - 49 LST, 16 w/o LST
  - Responders – ESS fall of ≥ 3

Patients with IH	Long Sleep Time (LST)	w/o Long Sleep Time	*p*
Maximum Daily Dosage	40 mg (30 - 40)	40 mg (25 - 40)	.99
Time on drug (months)	4 (2 - 14)	7 (2 - 12.5)	.85
ESS at baseline	**17 (14 - 18)**	**17 (16 - 20.5)**	.23
ESS with pitolisant	**14 (12 - 17)**	**16 (13 - 17)**	.34
Responders (%)	37	31	.69

Pitolisant is not FDA-approved for the treatment of IH.
Leu-Semenescu S, et al. *Sleep Med*. 2014;15(6):681-7.

Sodium Oxybate*

Two formulations, twice-nightly and once-nightly

- Neither are indicated for IH, only twice-nightly studied in IH

Mechanism of Action

- Sodium salt of gamma-hydroxybutyrate (GHB), mechanism for IH unknown

Idiopathic Hypersomnia Dosing

- No specific dosing recommendations, but in observational studies, doses were lower than those for narcolepsy

Adverse Effects

- Nausea, dizziness, vomiting, somnolence, enuresis, tremor (≥ 5%)

Clinical Considerations

- Central nervous system (CNS) depressant
- Very high sodium content
- Monitor patients with heart failure, hypertension, impaired renal function
- Twice nightly dosing – must wake up for second dose
- Warning for abuse/misuse

*Sodium oxybate is not FDA-approved for the treatment of IH. XYREM® (sodium oxybate) [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. Revised 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021196s030lbl.pdf. LUMRYZ™ (sodium oxybate) [package insert]. Chesterfield, MO: Avadel CNS Pharmaceuticals, LLC. 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214755Orig1s000lbl.pdf.

Sodium Oxybate Clinical Data

- Leu-Semescu, et al. 2016
  - 41 IH patients vs. 42 narcolepsy type 1
  - 100% of IH patient list severe sleep inertia as reason for treatment, 93% for excessive daytime sleepiness (EDS)

Patients with IH	IH	NT1	*p*
ESS before SXB	15.7 ± 4 [5–24]	17.7 ± 3.7 [8.5–24]	.02
ESS on SXB	13 ± 4.9 [5–23]	13.9 ± 5 [4–24]	.93
Change of ESS	**−3.5 ± 4.5 [−16 to 3]**	**−3.2 ± 4.2 [−17 to 1]**	.25
Good/Very Good Response to SXB	22/34 (65%)	22/46 (48%)	.13
Benefit on Severe Sleep Inertia	24/34 (71%)	3/7 (43%)	.33

Sodium oxybate is not FDA-approved for the treatment of IH. SXB = sodium oxybate.

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

Lower Sodium Oxybate

First treatment indicated for IH in adults

Mechanism of Action

- Calcium, magnesium, potassium, and sodium salts of gamma-hydroxybutyrate (GHB), mechanism for IH unknown

Idiopathic Hypersomnia Dosing

- Twice nightly: 1.5 g divided into two doses and titrated to 9 g total by 1.5 g doses weekly
- Once nightly: 3 g initial dose, titrated to 6 g total by 1.5 g doses weekly

Adverse Effects

- Headache, nausea, dizziness, decreased appetite (≥ 5%)

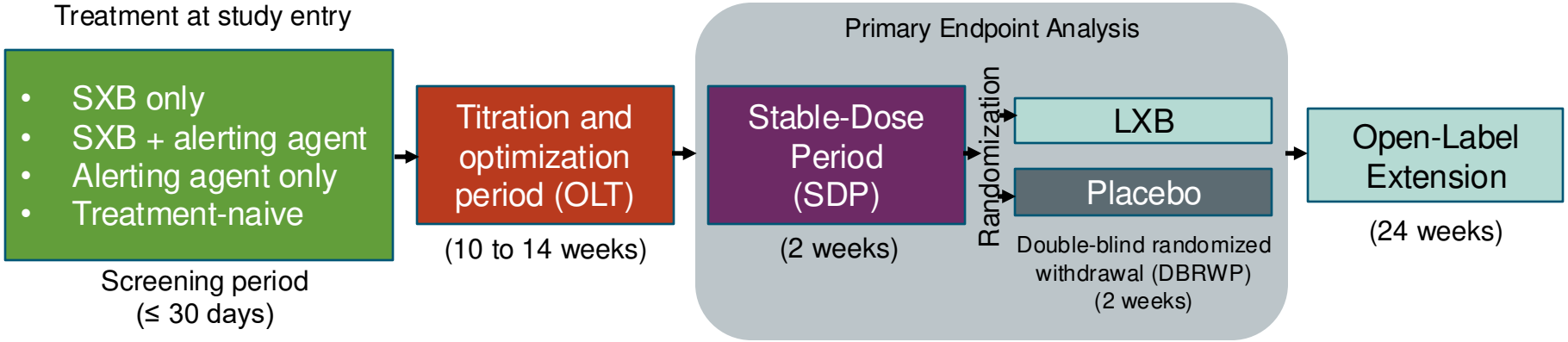
Clinical Considerations

- CNS depressant
- Once nightly dosing option for IH
- 92% less sodium than SXB, no warnings pertaining to cardiovascular (CV) risk
- Warning for abuse/misuse

XYWAV® (calcium, magnesium, potassium, and sodium oxybates) [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. Revised 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212690s000lbl.pdf.

Lower Sodium Oxybate: Phase III Trials

- Study Design
  - Enrolled 154 participants (mean ± SD age, 40 ± 14 years; 68% female; mean ± SD ESS, 16 ± 3.6; mean ± SD IHSS, 32 ± 8; 84% White)
  - Primary efficacy endpoint: change in ESS score from end of SDP to end of DBRWP
  - Key secondary endpoints: change in IHSS total score, proportion of participants with worsening (minimally/much/very much worse) on PGIc
  - Safety assessments included collection of TEAE reports, vital signs, physical examination, electrocardiogram, clinical laboratory tests

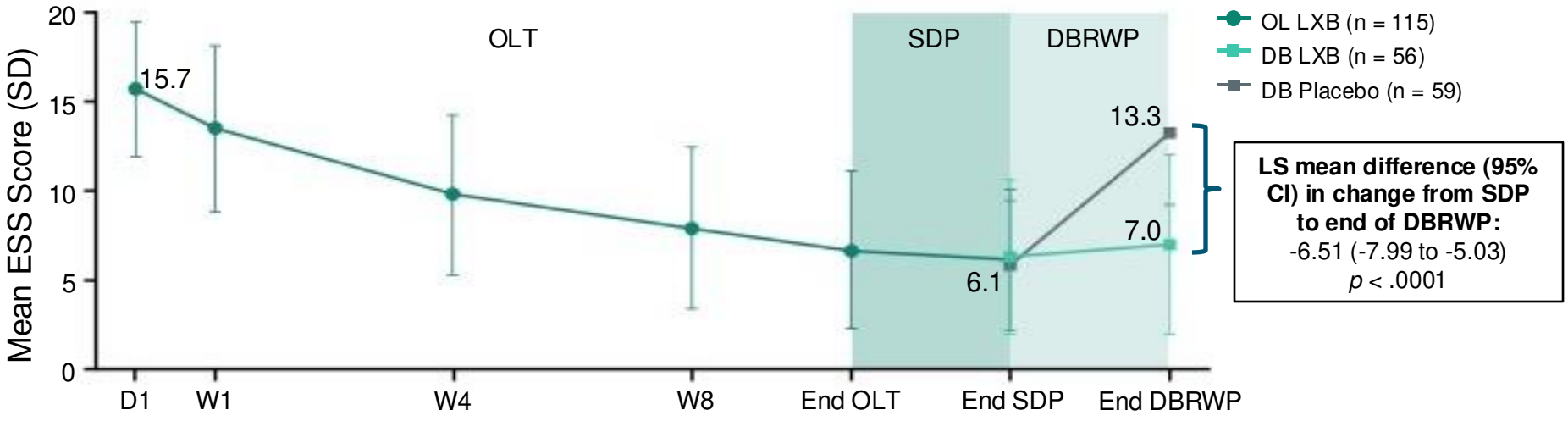


DBRWP = double-blind, randomized withdrawal period; IHSS = Idiopathic Hypersomnia Severity Scale; LXB = lower sodium oxybate; PGIc = Patients' Global Impression of Change; TEAE = treatment-emergent adverse events

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

Lower Sodium Oxybate: Phase III Trials

- Epworth Sleepiness Scale Improvement
  - Worsening in mean ESS score from end of SDP to end of DBRWP with placebo; maintenance of improvement with LXB
  - Subgroup analysis found comparable treatment effects in patients with and without clinician-reported long sleep time



LS = least squares

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

Audience Response

Candice voices specific concerns regarding sleep inertia symptoms. What was found regarding LXB efficacy on sleep inertia in clinical trials?

A. In the double-blind, randomized withdrawal period (DBRWP), VAS-SI scores significantly worsened in patients randomized to placebo compared to those continued on LXB maintenance therapy
B. In the DBRWP, VAS-SI scores numerically worsened in patients randomized to placebo, but this was not significant
C. VAS-SI scores showed no improvement during the study period leading up to the DBRWP
D. I don't know

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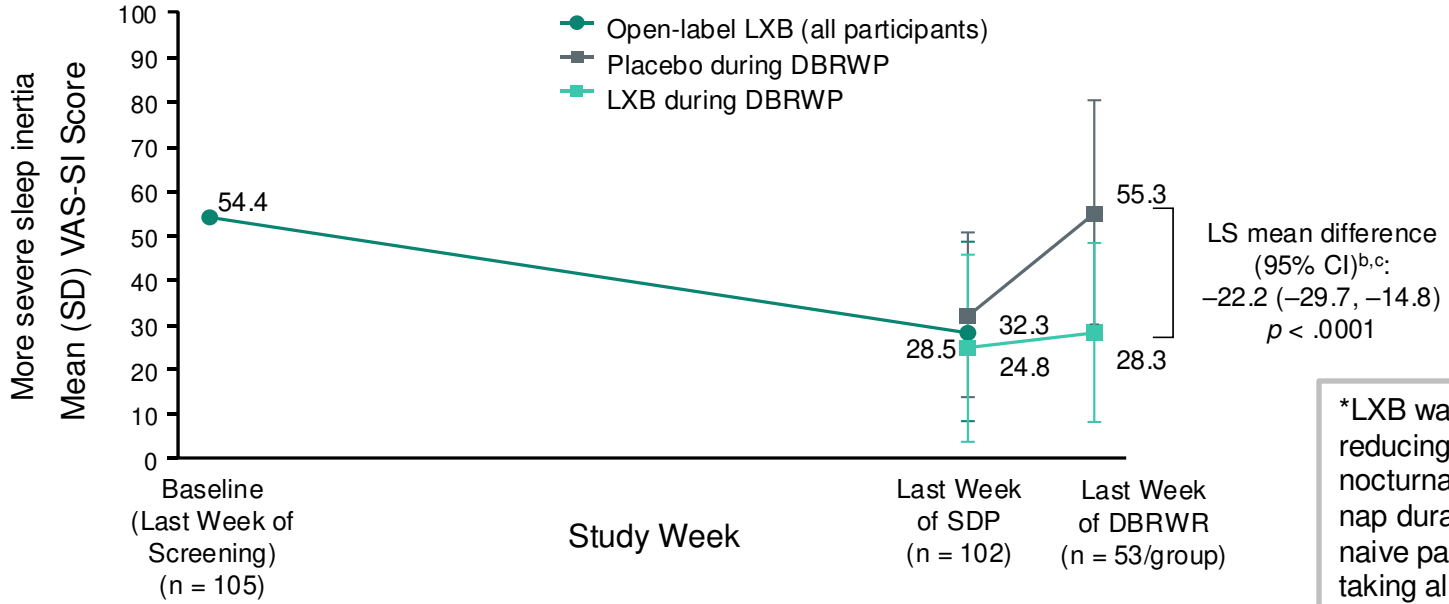
Effect of LXB on Sleep Inertia

- Sleep Inertia
  - Exploratory endpoint: Visual Analogue Scale-Sleep Inertia (VAS-SI)
  - Self-reported retrospective measure of difficulty awakening each morning
    - Range from 0 (very easy) to 100 (very difficult)
  - Sleep inertia improved with LXB treatment, with significant differences between LV+XB and placebo after DBRWP



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

[b] Difference in change from end of SDP to end of DBRWP. [c] LXB, n = 49; placebo, n = 51.

Bogan RK, et al. *Sleep*. 2021;44(Suppl 2):A192.

Patient Case: Candice

- 30-year-old Black female presents to clinic after receiving sleep study results, diagnosed with idiopathic hypersomnia

What are the clinical considerations for determining treatment?

From the patient perspective, what can your physician do to help you succeed with your treatment?

What are our next steps?

SMART Goals

- Identify FDA-approved novel treatments for idiopathic hypersomnia
- Customize pharmacological treatments for idiopathic hypersomnia based on patient characteristics, dosing and dosage forms, efficacy and safety data, and other clinical considerations
- Utilize the most recent clinical trials data from recently FDA-approved treatments in treatment decisions for patients diagnosed with idiopathic hypersomnia
- Include patients and their unique perspectives in shared decision-making conversations for optimized patient treatment success and patient satisfaction

Specific, Measurable, Attainable, Relevant, Timely

Series on Idiopathic Hypersomnia

CME BriefCase 2

Recognizing IH: The Patient Journey to Diagnosis

CME BriefCase 3

Diagnostic Tools: A Process of Exclusion

www.CMEOutfitters.com/sleep-disorders-hub/

Sleep Disorders Education Hub

A robust hub of patient education and resources for your patients to learn more about idiopathic hypersomnia

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