

In partnership with



Translating Orexin Science Into Practice: *Psychiatry's Role in Narcolepsy Care*

MasterClass



Supported by an educational grant from Takeda Pharmaceuticals U.S.A., Inc.

Faculty

Craig Chepke, MD, DFAPA

Adjunct Associate Professor of
Psychiatry, Atrium Health

Medical Director, Excel Psychiatric
Associates

Chief Medical Officer, Psych Congress
Huntersville, NC

Logan Schneider, MD

Co-Director, Adjunct Clinical Associate
Professor, Stanford Sleep Center,
Stanford University School of Medicine

Redwood, CA

Jessica Wright, CRNP

Nurse Practitioner, Sleep
Disorders Center of Alabama
Homewood, AL

Faculty Disclosures

- **Craig Chepke, MD, DFAPA:** Advisory Board — AbbVie, Acadia, Alkermes PLC, AxsomeTherapeutics, Biogen, Bristol Myers Squibb, COMPASS Pathways, Corium, Eli Lilly, Idorsia, Intracellular Therapeutics, Jazz, Johnson & Johnson, Lundbeck, Moderna, Neurocrine, Otsuka, Sage, Sumitomo, Takeda, Teva; Consultant — AbbVie, Acadia, Alkermes PLC, Axsome Therapeutics, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Cingulate Therapeutics, Corium, Eli Lilly, Intracellular Therapeutics, Jazz, Johnson & Johnson, Lundbeck, MedinCell, Moderna, Neurocrine, Otsuka, Sage, Sumitomo, Supernus, Teva; Grant/Research Support — Acadia, Axsome Therapeutics, Harmony, Neurocrine, Teva; Speakers Bureau — AbbVie, Acadia, Alkermes PLC, AxsomeTherapeutics, Bristol Myers Squibb, Corium, Intracellular Therapeutics, Jazz, Johnson & Johnson, Lundbeck, Luye, Merck, Neurocrine, Otsuka, Sumitomo, Takeda, Teva
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Learning Objectives



Assess the cognitive, psychiatric, and quality-of-life burden of narcolepsy, including its impact on daily functioning and mental health outcomes



Apply evidence-based screening and diagnostic strategies to distinguish NT1 from psychiatric disorders, medication effects, and other sleep-wake conditions



Explain the role of orexin deficiency in sleep-wake regulation and the pathophysiology of NT1, including its relevance to shared neurobiologic pathways in mental health



Evaluate the mechanism of action, clinical evidence, and safety considerations of emerging orexin receptor 2 agonists for NT1

The Multifaceted Burden of Narcolepsy

Your patient presents with...

Difficulty
concentrating

Memory
impairment

Brain fog

Executive
dysfunction

Declining
school/work
performance

Persistent
fatigue

Mood changes

Irritability



What comes to mind?

Your patient presents with...

Difficulty
concentrating

Cognitive or
Dissociative
Disorder?

Declining
school/work
performance

Persistent
fatigue

ADHD?

Memory
impairment

Anxiety?

Bipolar
Disorder?

Brain fog

Depression?

Mood changes

Irritability

Executive
dysfunction

Burnout?



What comes to mind?

ADHD?



Burnout?

Anxiety?

Cognitive or
Dissociative
Disorder?

Depression?

Bipolar
Disorder?

Difficulty
concentrating

Declining
school/work
performance

Persistent
fatigue

Memory
impairment

Mood changes

Brain fog

Executive
dysfunction

What about *narcolepsy*?

ADHD?



Burnout?

Anxiety?

Cognitive or
Dissociative
Disorder?

Depression?

Bipolar
Disorder?

Difficulty
concentrating

Declining
school/work
performance

Persistent
fatigue

Memory
impairment

Brain fog

Mood changes

Executive
dysfunction

The Burden of Narcolepsy Extends Beyond Excessive Daytime Sleepiness

Cognitive Disturbances



- Attention & concentration impairment
- Executive dysfunction
- Trouble with work or school
- Brain fog/mental fogginess
- Lack of alertness
- Automatic behaviors

Autonomic Disturbances



- Postural orthostatic hypotension syndrome
- Erectile dysfunction
- Syncope
- Nondipping blood pressure and reduced heart rate variability
- Skin temperature abnormalities and night sweats
- Gastric/digestive disturbances
- Abnormal pupillary function



Psychiatric and Emotional Disturbances



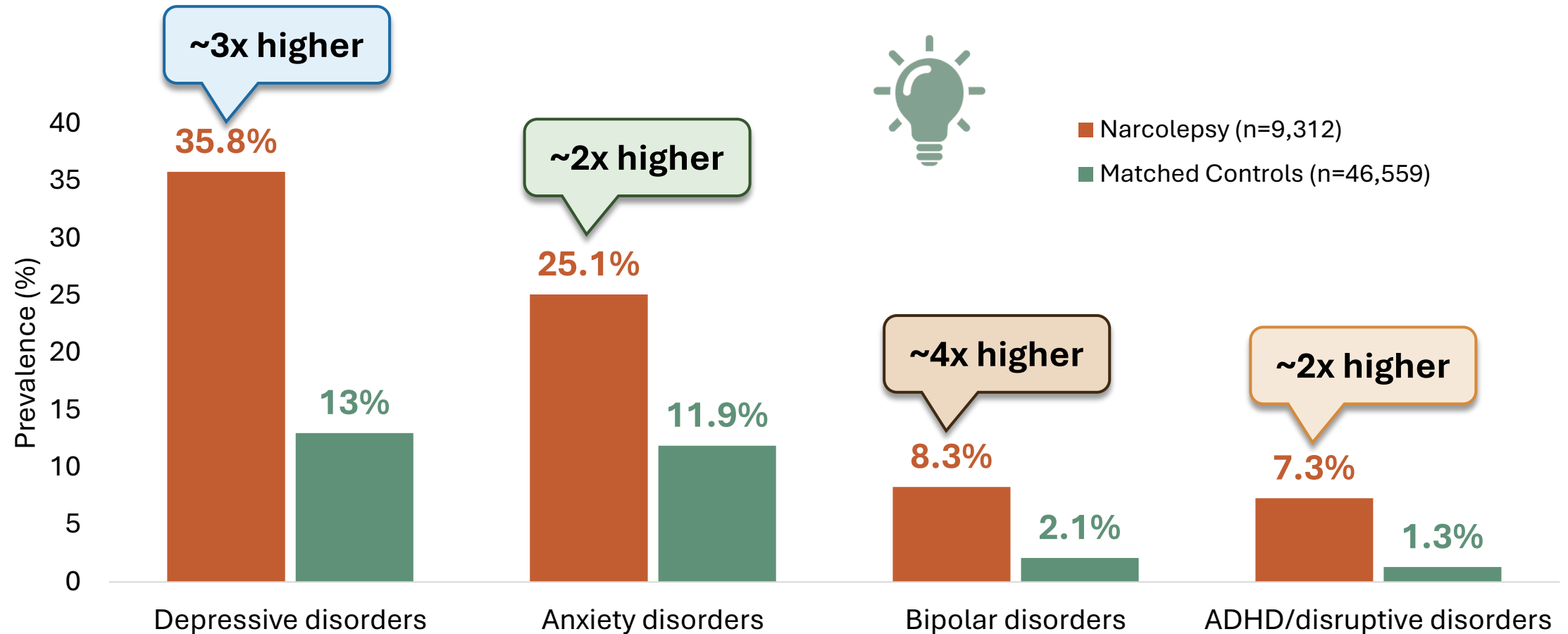
- Depression and anxiety
- Decreased social interaction
- Emotional dysregulation
- Panic, posttraumatic stress disorder
- Reduced self-esteem due to impaired work and school performance
- Strain on social relationships, romantic life, and sexual intimacy
- Changes in mood

Comorbid Medical Conditions



- **Sleep:** obstructive sleep apnea, REM sleep behavior disorder, periodic limb movement disorder, restless legs syndrome, parasomnias
- **Metabolic:** diabetes, obesity, eating disorders
- **Immune-related:** autoimmune diseases, allergies, asthma
- **Cardiovascular:** hypercholesterolemia, hypertension, heart disease
- **Pain:** chronic low back pain, headache/migraine, arthritis, fibromyalgia

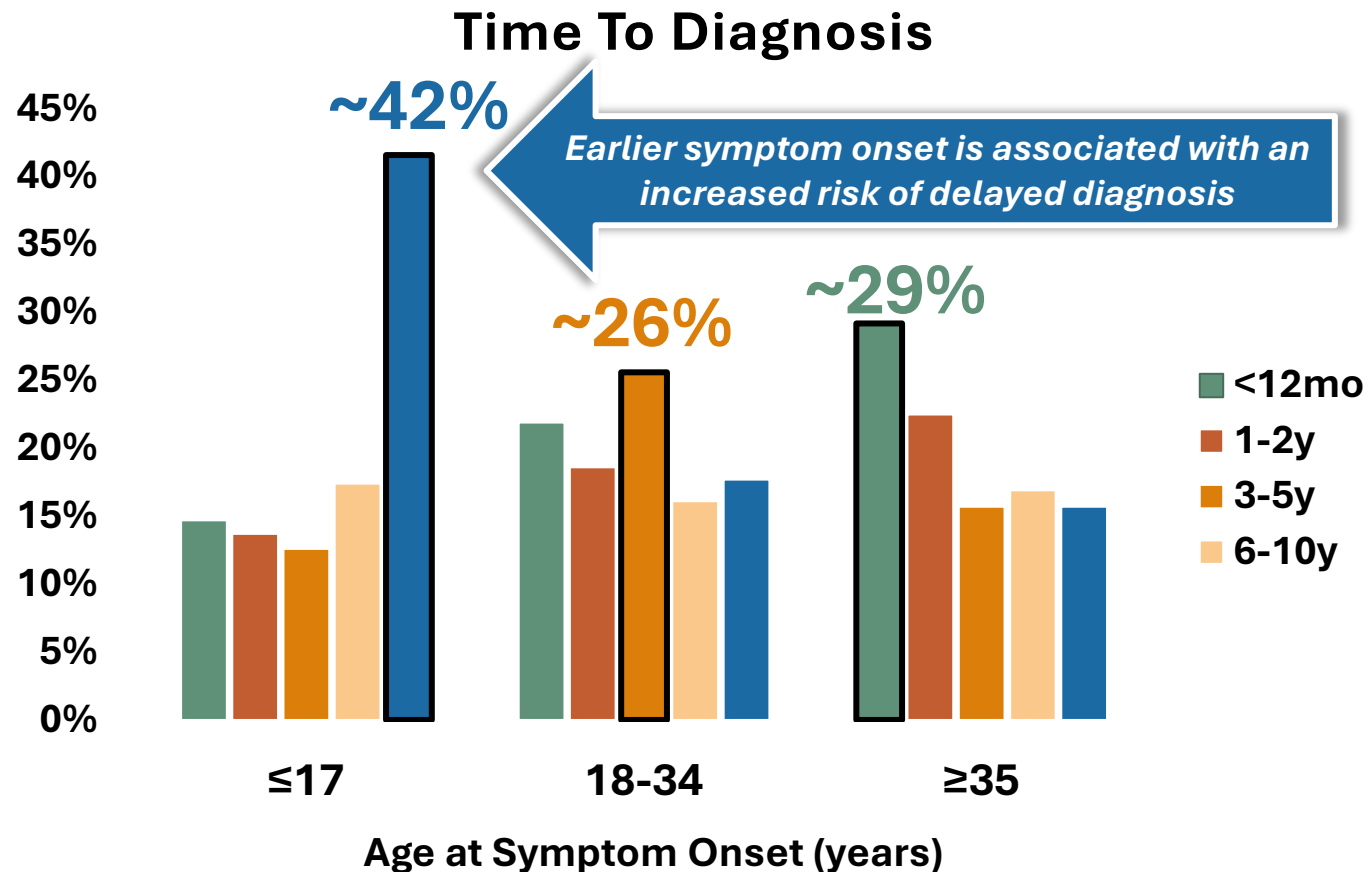
Narcolepsy Is Associated with Higher Prevalence of Psychiatric Disorders



All χ^2 significance tests are Bonferroni corrected.
Ruoff CM, et al. J Clin Psychiatry. 2017;78(2):171-176.

Delayed Recognition Creates an Opportunity for Earlier Intervention

Cross-sectional survey of **1,699 adults** with self-reported physician-diagnosed narcolepsy in the US



Why Is Diagnosis Often Delayed?

- Symptoms beginning in childhood may be mistaken for normal sleep needs, poor motivation, or behavioral problems
- Sleepiness, fatigue, and cognitive difficulties overlap across psychiatric and sleep disorders
- Cataplexy may be absent, subtle, or not recognized
- Limited awareness may delay sleep-specialist referral and diagnostic testing

When a patient says, 'I'm tired,' *what could they actually mean?*

**"I'm struggling to
stay awake."**

Hypersomnolence disorder?

Look for unintended naps,
sleep attacks, difficulty
maintaining wakefulness

**"I don't have the
energy or motivation."**

Psychiatric symptoms?

Clarify fatigue, anhedonia,
lack of motivation,
concentration problems

**"I feel sleepy and
slowed down."**

Medication side effects?

Review medication list,
dosing schedule, recent
additions/changes, and
combined sedating effects

**"Everything feels like
it takes more effort."**

Drug-induced Parkinsonism?

Look for bradykinesia,
rigidity, tremor, reduced
facial expression, and gait
changes; review dopamine-
blocking medications and
recent dose changes

Key Learning Points

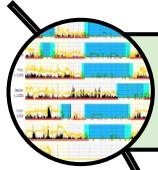


- The burden of narcolepsy extends beyond excessive daytime sleepiness to cognitive, psychiatric, autonomic, and functional impairment
- Psychiatric comorbidities are common, and overlapping symptoms may obscure narcolepsy and delay diagnosis
 - Example: The prevalence of **depressive disorders is approximately 3x higher among patients with narcolepsy** compared to matched controls
- Clarifying what patients mean by “tired” can help distinguish hypersomnolence from psychiatric symptoms, medication effects, and other potential causes

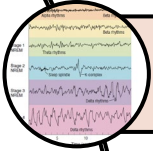
Recognizing Narcolepsy Type 1 in Psychiatric Practice

What does healthy sleep look like?

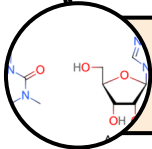
RU_SATED?



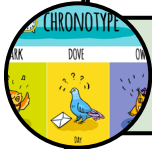
RegUlarity: consistency of bedtime, wake time, and sleep duration



Sleep quality: perceived sleep quality and "objective" sleep quality



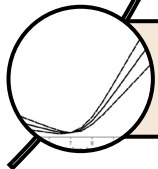
Alertness: normal daytime alertness and/or no countermeasure use



Timing: "normal," diurnal circadian alignment



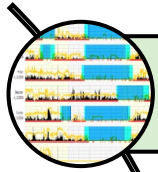
Efficiency: match of sleep opportunity with sleep need



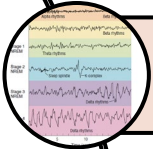
Duration: not too much and not too little...just right

What does *narcolepsy* look like?

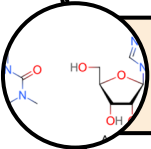
RU_SATED?



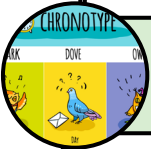
RegUlarity: Normal variability



Sleep quality: Unrefreshing sleep with inertia; insomnia (typically middle), with “weird” phenomena



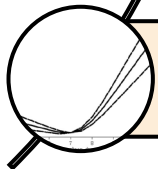
Alertness: Excessive daytime sleepiness & sleep attacks; multiple short, refreshing naps; cataplexy



Timing: Not particularly misaligned



Efficiency: Several nocturnal awakenings, sometimes w/ nightmares or hearing/seeing/sensing things

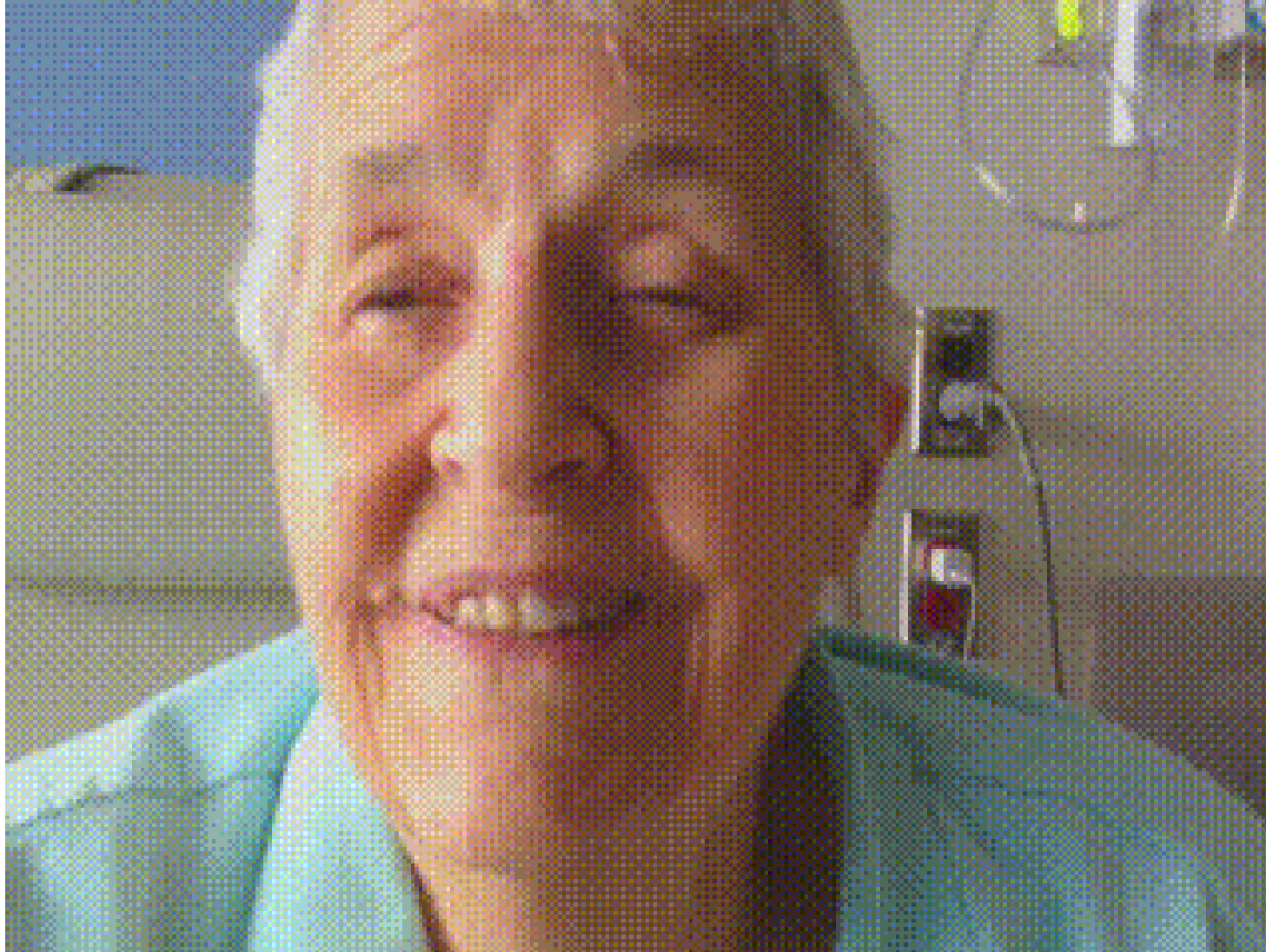


Duration: “Normal” per 24 hours (with naps)...but not consolidated at night

Clear-cut cataplexy



Clear-cut cataplexy



Pre-test Probability: Cataplexy

Do you currently experience, or have you ever experienced episodes of muscle weakness in the legs and/or buckling of your knees when you...

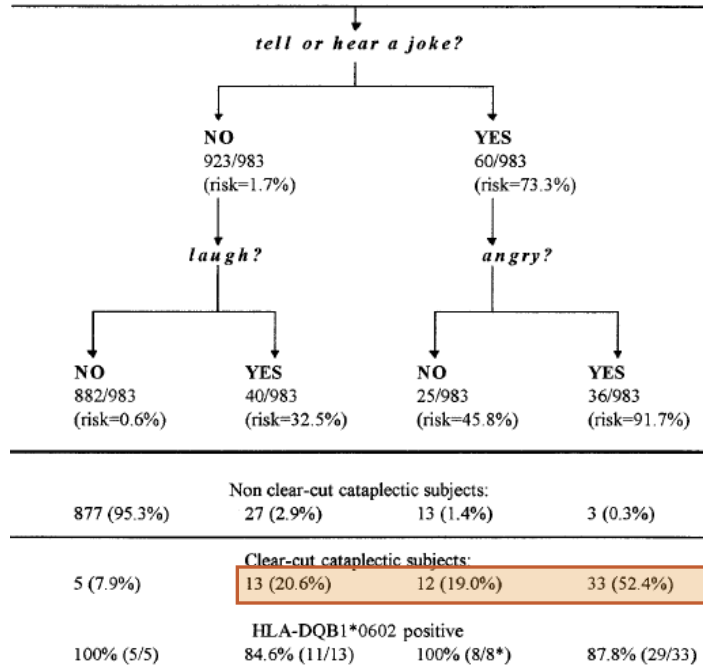
Have you ever experienced a sagging or dropping of your jaw when you...

Have you ever experienced an abrupt dropping of your head and/or shoulders when you...

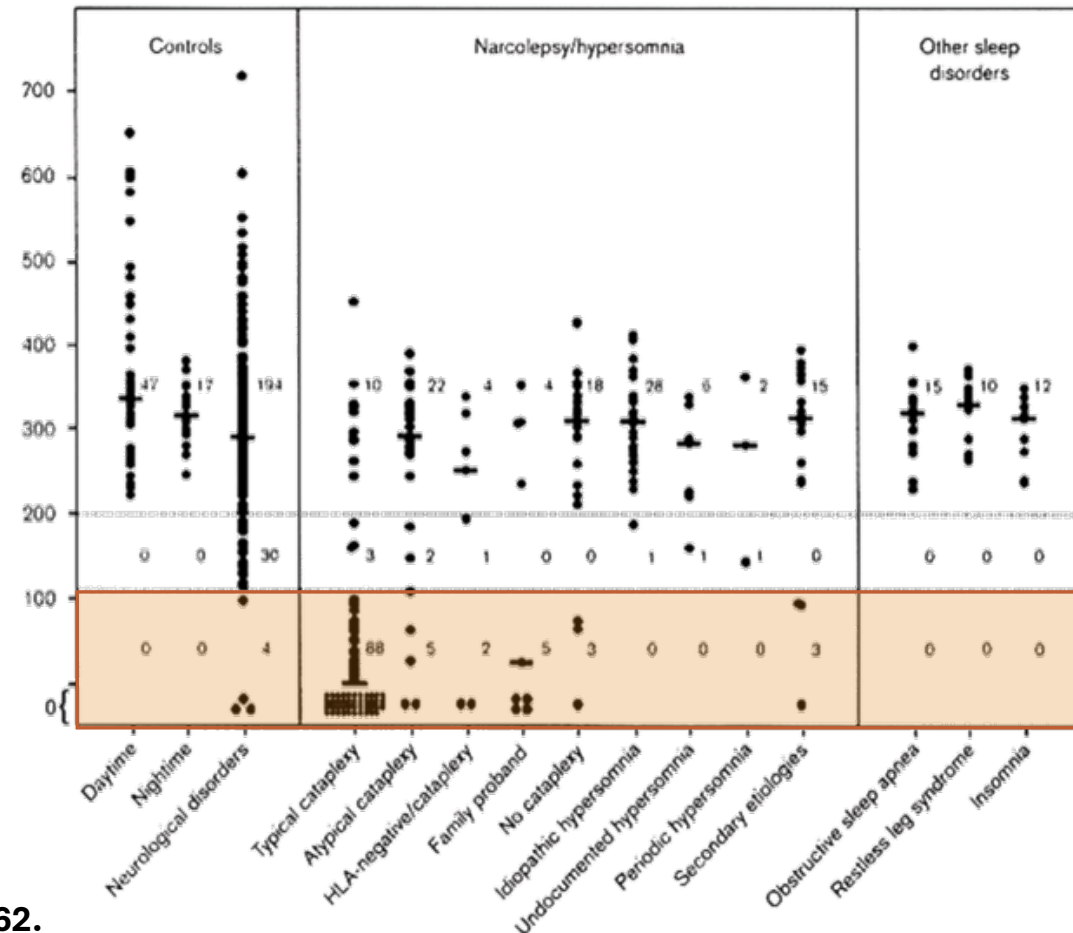
Have you abruptly dropped objects from your hand or felt weakness in your arm when you...

Has your speech ever become slurred when you...

Have you ever fallen to the ground and found yourself unable to move (paralyzed) when you...

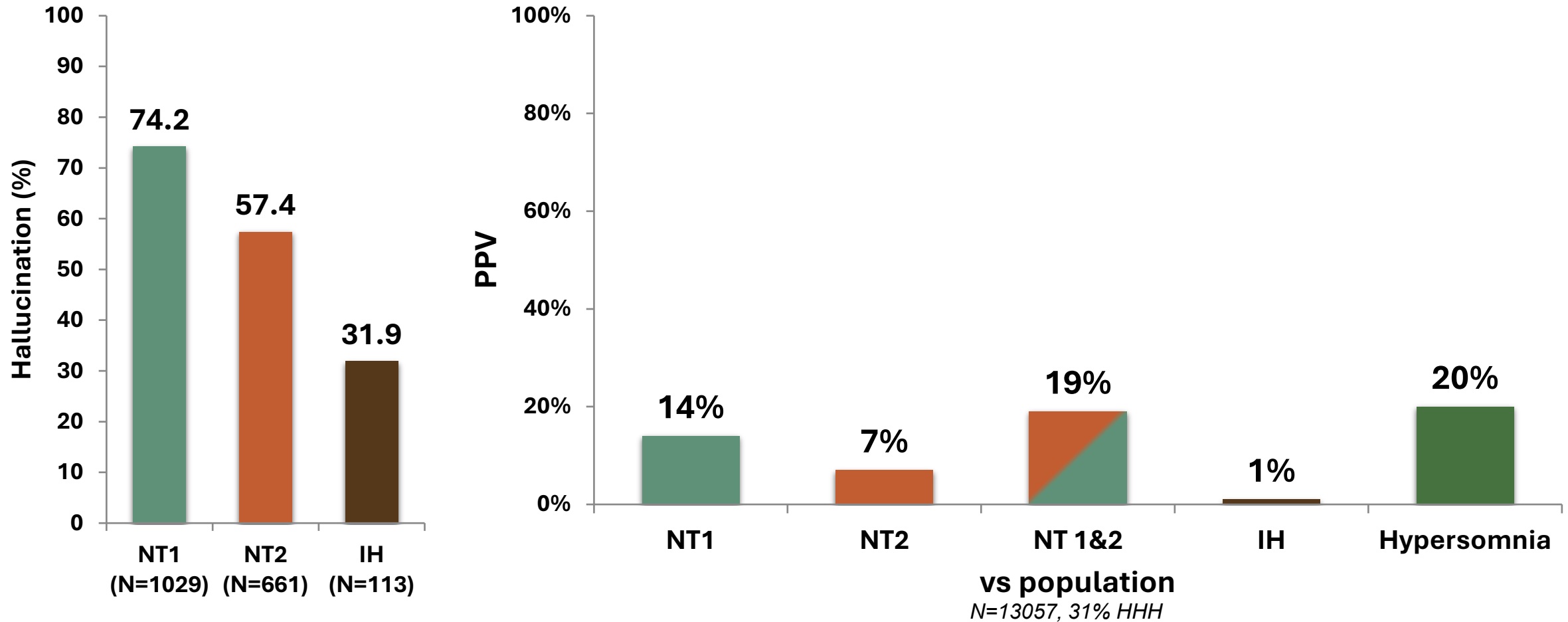


92%



98%

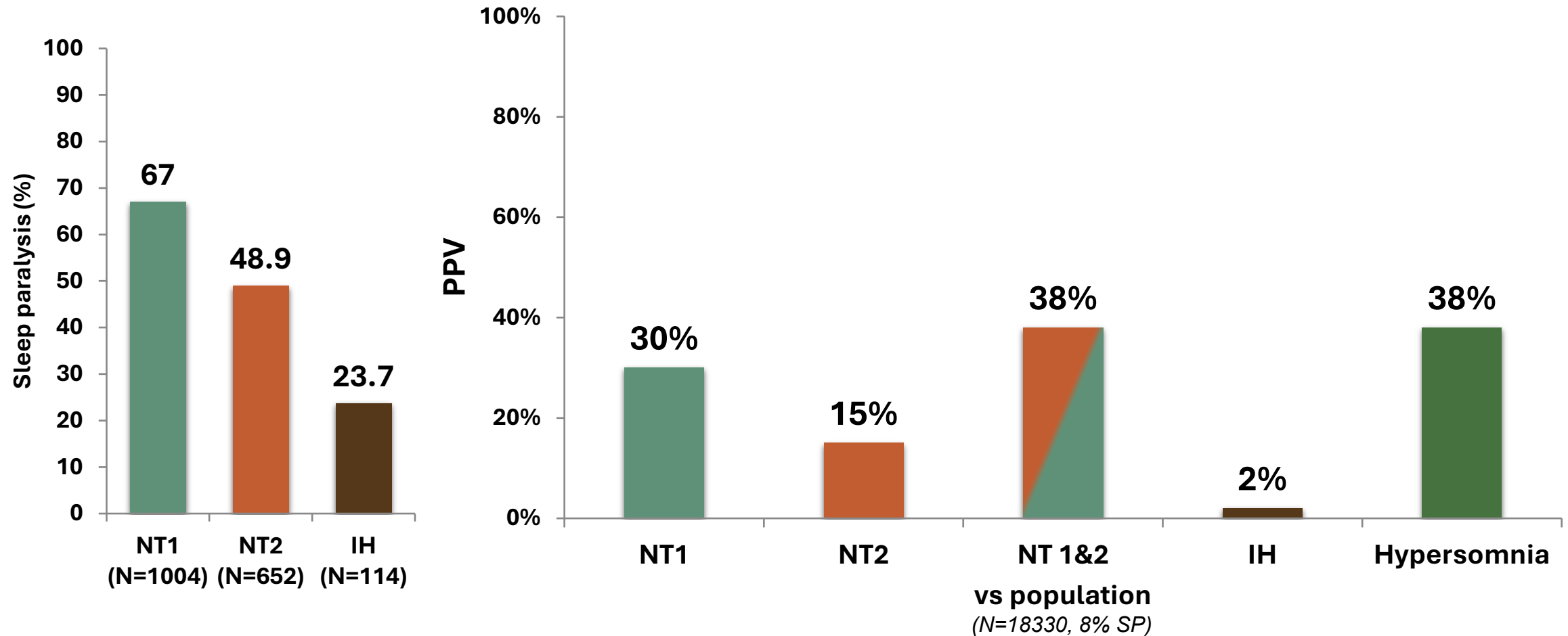
Pre-test Probability: *Hallucinos*



NT1 = narcolepsy type 1, NT2 = narcolepsy type 2, IH = idiopathic hypersomnia, HHH = hypnagogic and hypnopompic hallucinations, PPV = positive predictive value.

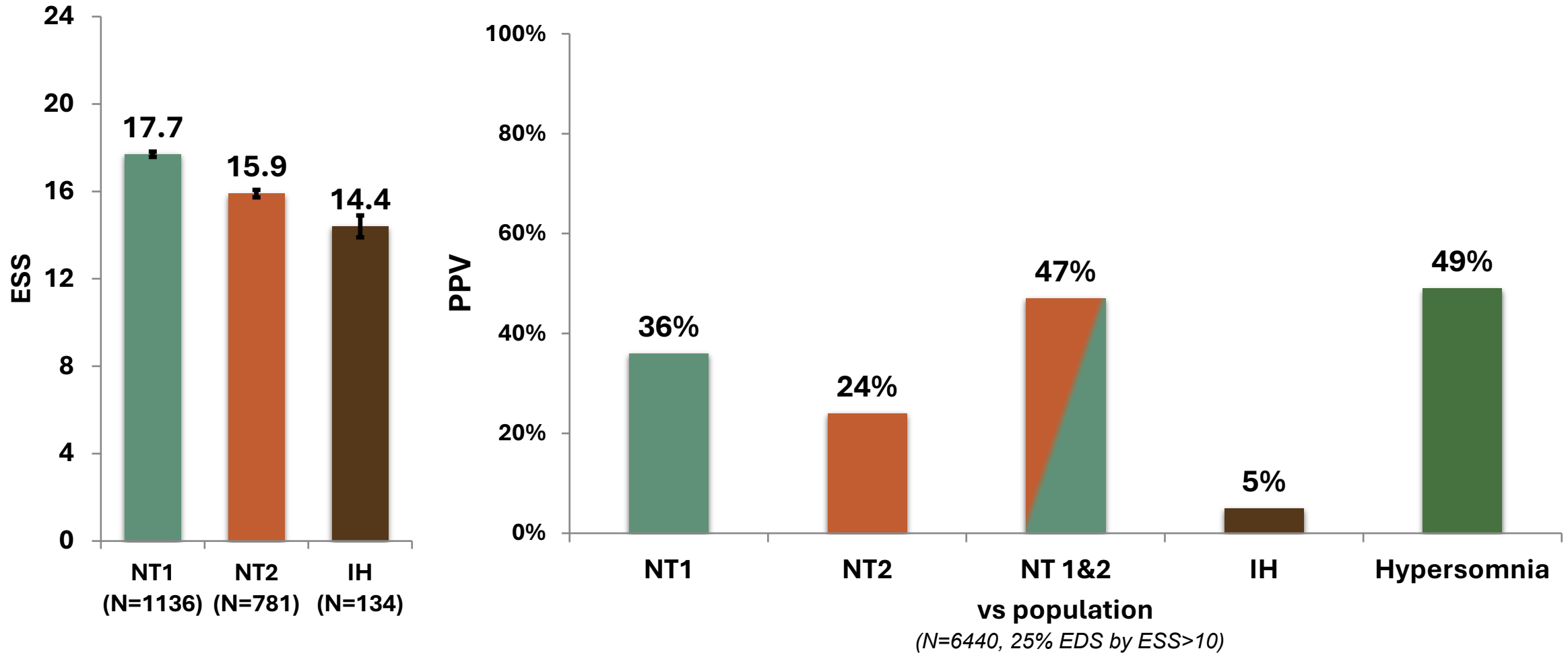
Cheung J, et al. Characterization of the Stanford Narcolepsy Database. *Sleep*. 2016;39(suppl):A246. Abstract 0689; Ohayon MM. *Psychiatry Res*. 2000;97(2-3):153-164

Pre-test Probability: *Sleep Paralysis*



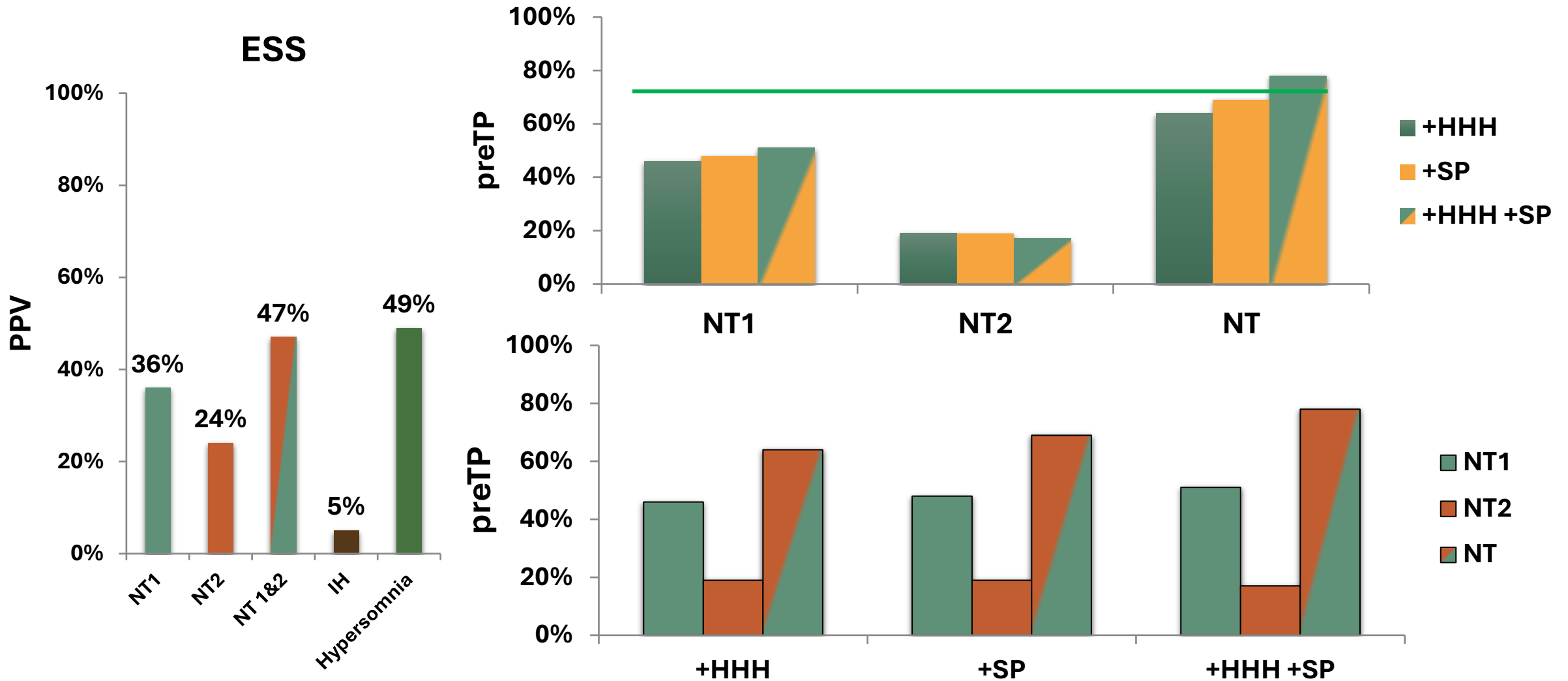
NT1 = narcolepsy type 1, NT2 = narcolepsy type 2, IH = idiopathic hypersomnia, SP = sleep paralysis, PPV = positive predictive value.
Cheung J, et al. Characterization of the Stanford Narcolepsy Database. *Sleep*. 2016;39(suppl):A246. Abstract 0689; Sharpless BA, Barber JP. *Sleep Med Rev*. 2011;15(5):311-315.

Pre-test Probability: *EDS*



NT1 = narcolepsy type 1, NT2 = narcolepsy type 2, IH = idiopathic hypersomnia, EDS = excessive daytime sleepiness, PPV = positive predictive value.
Cheung J, et al. Characterization of the Stanford Narcolepsy Database. *Sleep*. 2016;39(suppl):A246. Abstract 0689; Baldwin CM, et al; Sleep Heart Health Study Group. *Sleep*. 2004;27(2):305-311.

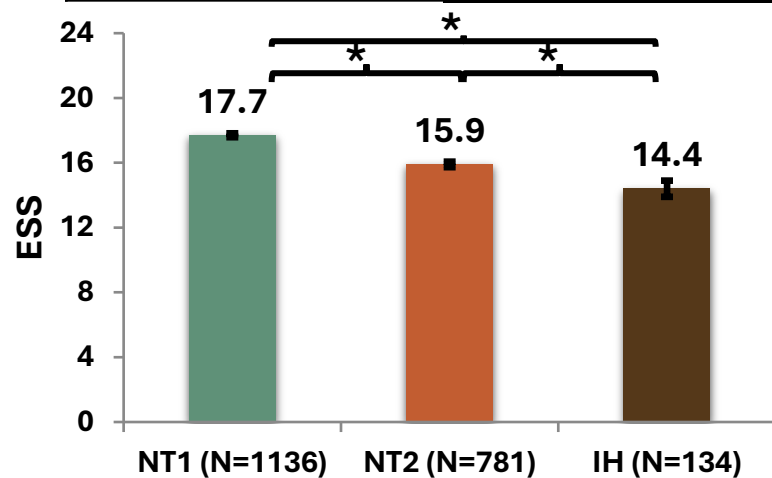
It's because they're sleepy...



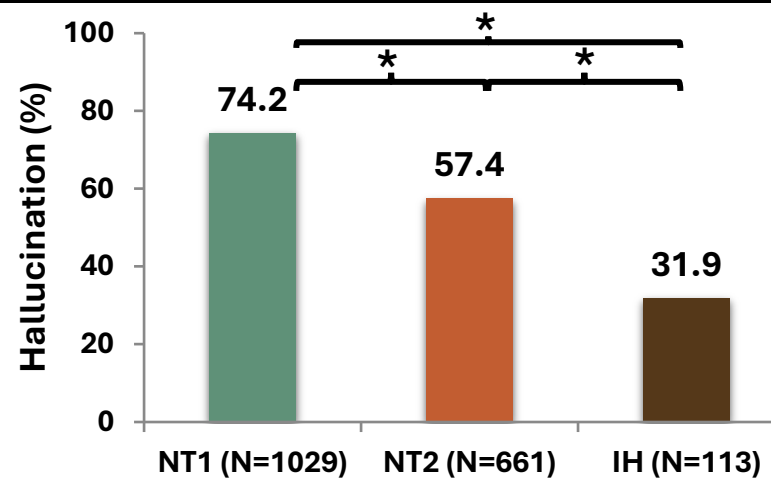
Cheung J, et al. Characterization of the Stanford Narcolepsy Database. *Sleep*. 2016;39(suppl):A246. Abstract 0689; Ohayon MM. *Psychiatry Res*. 2000;97(2-3):153-164; Sharpless BA, Barber JP. *Sleep Med Rev*. 2011;15(5):311-315; Baldwin CM, et al; Sleep Heart Health Study Group. *Sleep*. 2004;27(2):305-311.

In sum: Not-So-Cardinal Symptoms

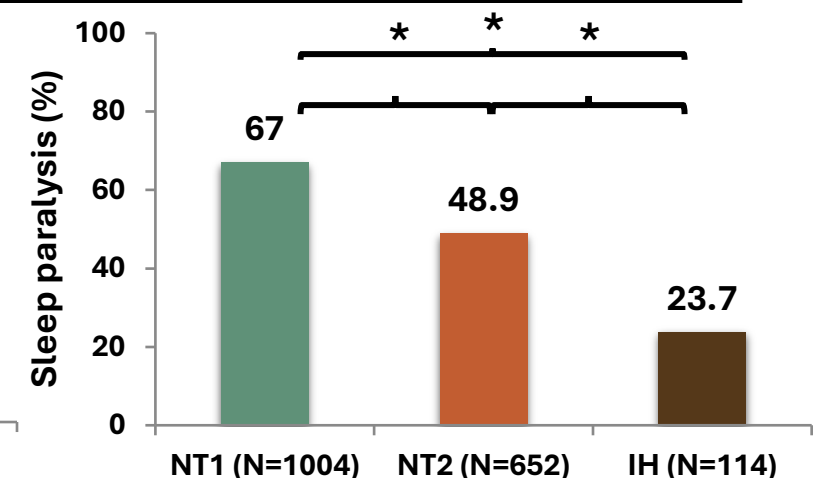
	Narcolepsy type 1	Narcolepsy type 2	Idiopathic hypersomnia	Kleine-Levin syndrome
Excessive daytime sleepiness	Present	Present	Present	Present (recurrent episodes)
Cataplexy	Present (except in rare cases)	Absent	Absent	Absent
Sleep paralysis	Present in 67%	Present in 49%	Present in 24%	Uncommon
Hallucination	Present in 74%	Present in 57%	Present in 32%	Present in 50%
Fragmented nocturnal sleep	Decreased sleep efficiency compared to other hypersomnias	May be common	Not typical	Not typical
Neurocognitive changes	Absent	Absent	Sleep drunkenness associated with automatic behavior and confusion	Present during periods of hypersomnia



* ANOVA between groups $p < 0.001$



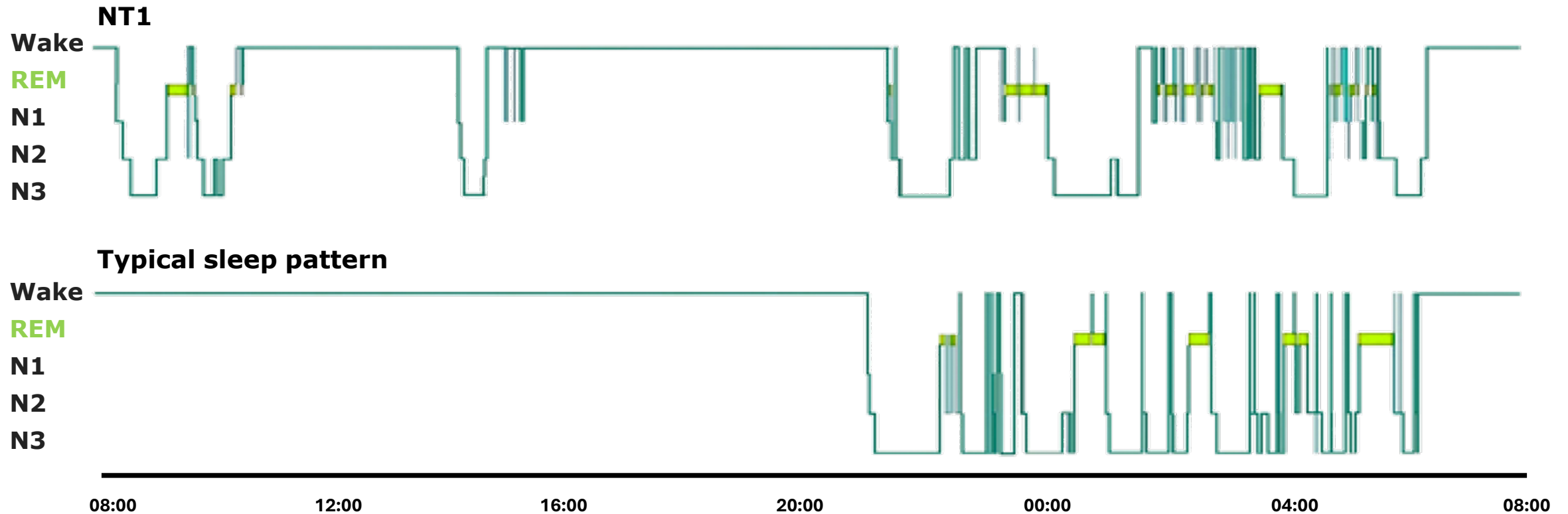
* χ^2 $p < 0.001$



* χ^2 $p < 0.001$

Diagnostic Testing:

Looking for Sleep-Wake Instability

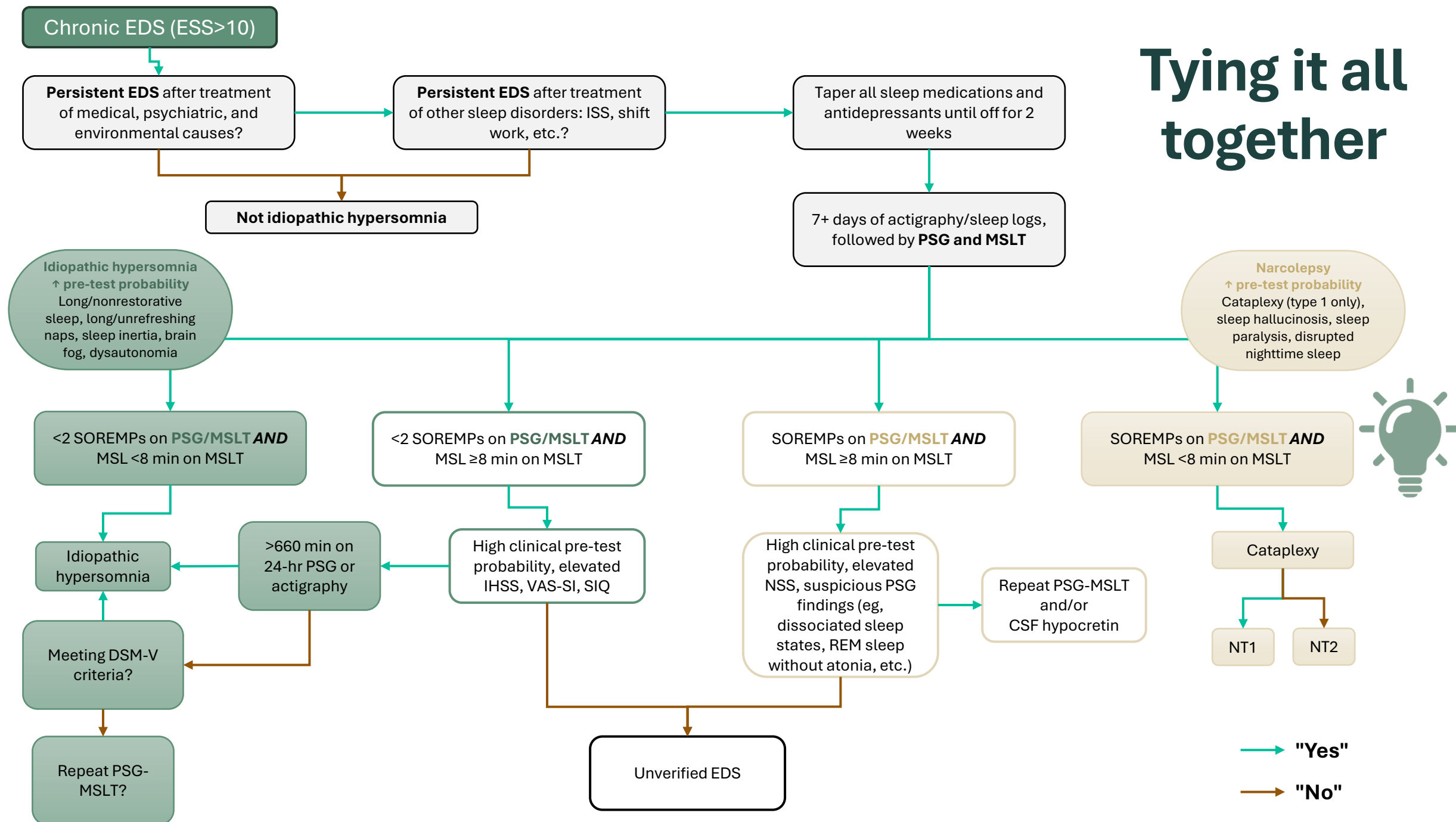


	Narcolepsy Type 1	Narcolepsy Type 2	Idiopathic hypersomnia	Kleine-Levin syndrome
Sleepiness	‡Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.	‡Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.	‡Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.	‡≥2 episodes of excessive sleepiness and sleep duration, each persisting for 2 days to 5 weeks. The patient is normal between episodes.
Cataplexy	‡Present	Absent	Absent	Absent
Additional features			Sleep drunkenness and/or long (>1 hour) unrefreshing naps	‡At least one of the following during an episode: 1. Cognitive dysfunction 2. Altered perception 3. Eating disorder (anorexia or hyperphagia) 4. Disinhibited behavior (e.g. hypersexuality)
MSLT	‡MSL ≤8 min AND ≥2 SOREMPs on an MSLT.	‡MSL ≤8 min AND ≥2 SOREMPs on an MSLT.	‡MSL ≤8 min AND <2 SOREMPs on an MSLT.	N/A
Other measures	‡A SOREMP on the preceding nocturnal PSG	‡A SOREMP on the preceding nocturnal PSG	‡TST ≥660 min by 24-hour PSG OR Actigraphy and sleep log averaged over 7 days	Intra-ictal SPECT shows hypoperfusion of the thalami
CSF hypocretin	‡≤110 pg/mL or <1/3 mean of normal subjects on same assay	‡>110 pg/mL or >1/3 mean of normal subjects on same assay ^s	>110 pg/mL or >1/3 mean of normal subjects on same assay	>110 pg/mL or >1/3 mean of normal subjects on same assay

‡keys to the diagnosis of the disorder

CSF = cerebrospinal fluid; MSL = mean sleep latency; MSLT = Multiple Sleep Latency Test; PSG = polysomnography; REM = rapid eye movement; SOREMP = sleep-onset REM period; TST = total sleep time.

Tying it all together



A simpler algorithm



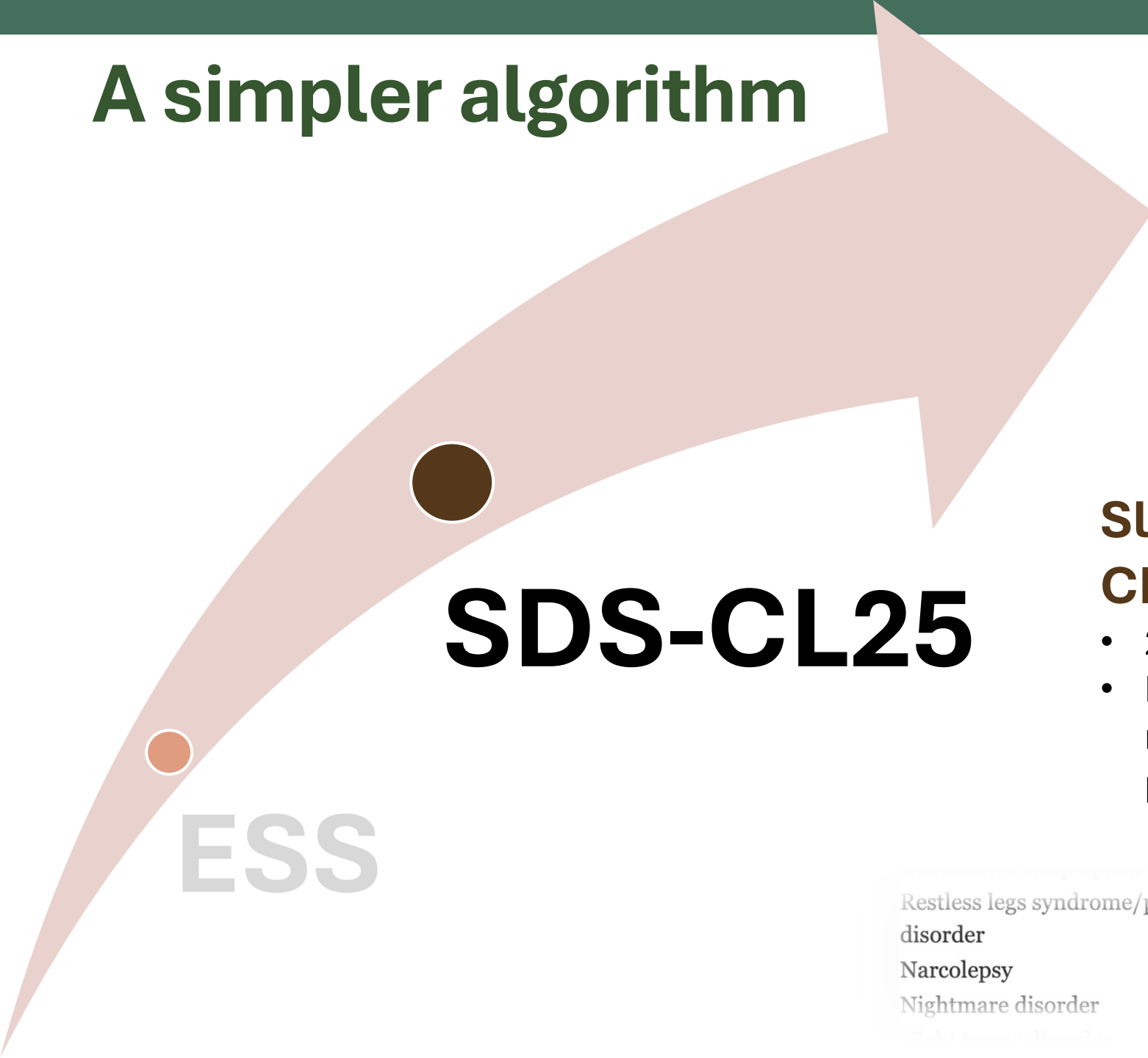
ESS

Epworth Sleepiness Scale

The “vital sign of sleep”

- 8-self-reported questions: 0 → 24
- >10 excessively sleepy

A simpler algorithm



SDS-CL25

Sleep Disorders Symptom Checklist-25

- 25 self-report questions (most Likert)
- Has an algorithmic interpretation of responses to help identify a host of possible sleep disorders

ESS

Restless legs syndrome/periodic limb movement disorder

Narcolepsy

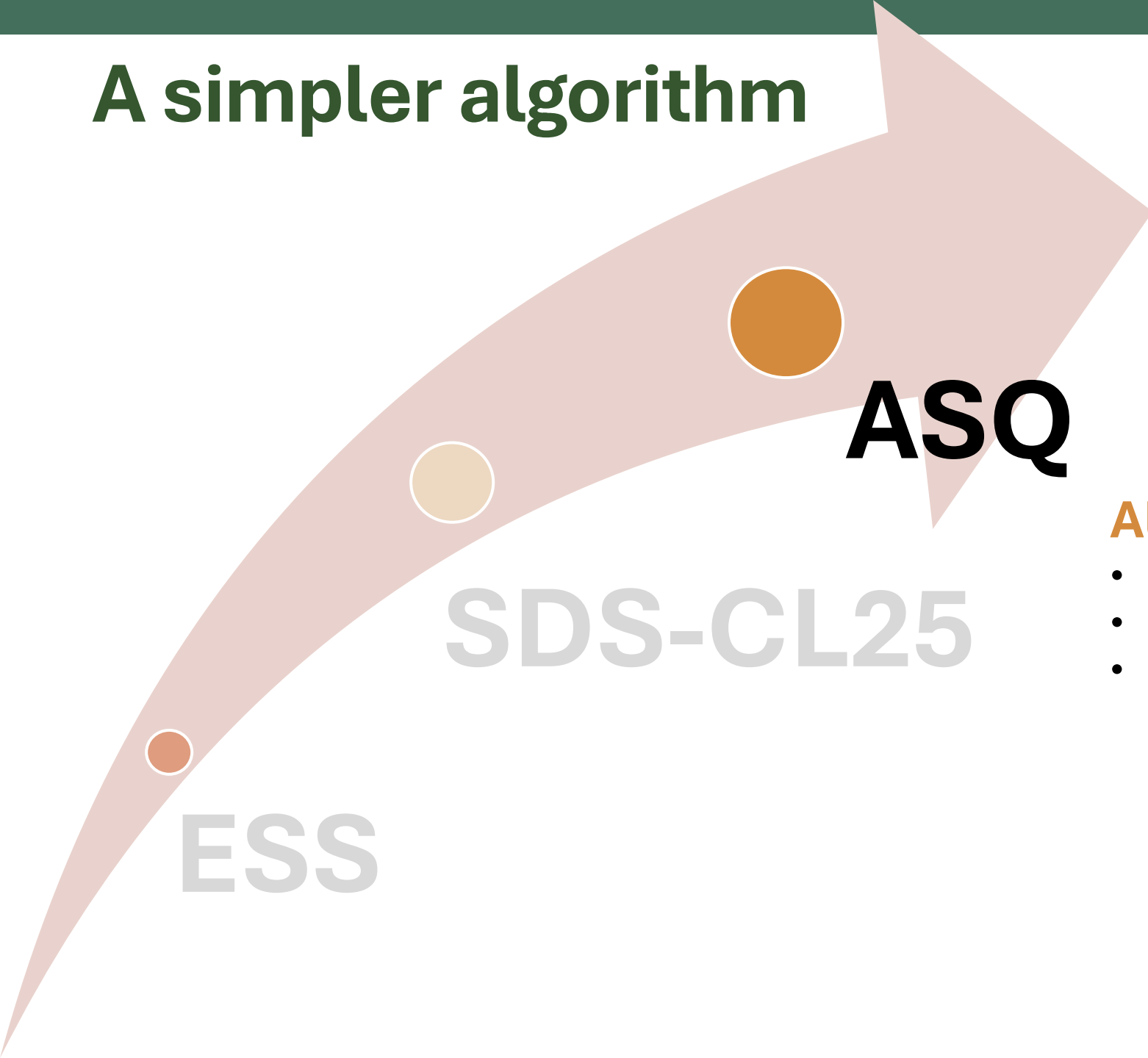
Nightmare disorder

$Q15 - Q17 + (Q6 \text{ or } Q9 \text{ or } Q25)$

$Q18 - Q20 + Q9 \text{ (also } Q6 \text{ or } Q25)$

$Q21 + Q25$

A simpler algorithm



ASQ

Alliance Sleep Questionnaire

- <https://mysleep.stanford.edu/>
- Multiple validated scales integrated
- Branching logic to minimize burden...but still runs about 15-30 minutes



Key Learning Points

- Start with sleep health: RuSATED?
- If sleepiness is truly "excessive," suss out the NT1 pentad:
 - **C**ataplexy
 - **H**allucinosi*s*
 - **E**DS
 - **S**leep paralysis
 - **S**leep disruption
- Evidence REM dysregulation and/or hypocretin deficiency

Cataplexy plus an MSLT showing ≤ 8 -minute sleep latency and ≥ 2 SOREMPs supports narcolepsy type 1.

Treatment Landscape

US and European Recommendations For Pharmacologic Management of Adult Narcolepsy

Medication Class	Target Symptoms	AASM Grade*	European Grade*	Primary Clinical Consideration
Modafinil/Armodafinil	EDS	STRONG†	STRONG	CYP3A4 inducer; reduces oral contraceptive efficacy.
Pitolisant	EDS, Cataplexy	STRONG‡	STRONG	Non-scheduled; dose-dependent QTc monitoring required.
Solriamfetol	EDS	STRONG	STRONG	Avoid in severe cardiovascular disease; dose adjustments in renal impairment.
Oxybates	EDS, Cataplexy	STRONG	STRONG	Central nervous system depressant; strict REMS program distribution.
Traditional Stimulants	EDS	CONDITIONAL	WEAK	Second-line due to cardiovascular risks, tolerance, and abuse potential.
Antidepressants (SNRIs)	Cataplexy (off-label)	INSUFFICIENT EVIDENCE	STRONG	Rapid withdrawal can trigger status cataplecticus.

*indicates strength of recommendation (not quality of evidence) †CONDITIONAL for armodafinil ‡WEAK for cataplexy

EDS = excessive daytime sleepiness, CYP = cytochrome P450, REMS = risk evaluation and mitigation strategy, QTc = corrected QT interval.

Maski K, et al. *J Clin Sleep Med*. 2021;17(9):1881-1893; Bassetti CLA, et al. *Eur J Neurol*. 2021;28(9):2815-2830.

Common Narcolepsy Symptom-Management Approach

EDS Predominant (NT2 / Mild NT1)

FIRST-LINE MONOTHERAPY

- **Modafinil/Armodafinil** (DAT inhibitor)
- **Solriamfetol** (DNRI; robust wakefulness)
- **Pitolisant** (H3 antagonist/inverse agonist)



REFRACTORY / ADD-ON ESCALATION

- Combine dual wake-promoting mechanisms
- Add nightly oxybate for fragmented sleep
- Consider classical stimulant (methylphenidate)

EDS + Cataplexy (NT1)

FIRST-LINE MULTI-SYMPTOM COVERAGE

- **Oxybate Formulations (SXB, LXB, ON-SXB):** Single-agent control for EDS + Cataplexy (+ DNS)
- **Pitolisant:** Dual control for EDS + mild/moderate Cataplexy



TARGETED COMBINATION OPTIMIZATION

- Add daytime wake-agent (Solriamfetol/Modafinil) to Oxybate
- Add SNRI (Venlafaxine) if cataplexy persists

Key Takeaways

- Current standard of care is symptomatic management:
 - Excessive daytime sleepiness (EDS)
 - Cataplexy
- Lay a foundation, then "spot-treat" residual symptoms

Shared Neurobiology: Orexin as the Nexus

Orexin Promotes Motivational Activation Synergistically Across Monoaminergic Systems



Arousal Systems:

Each monoamine system can promote wakefulness, **but acts synergistically**

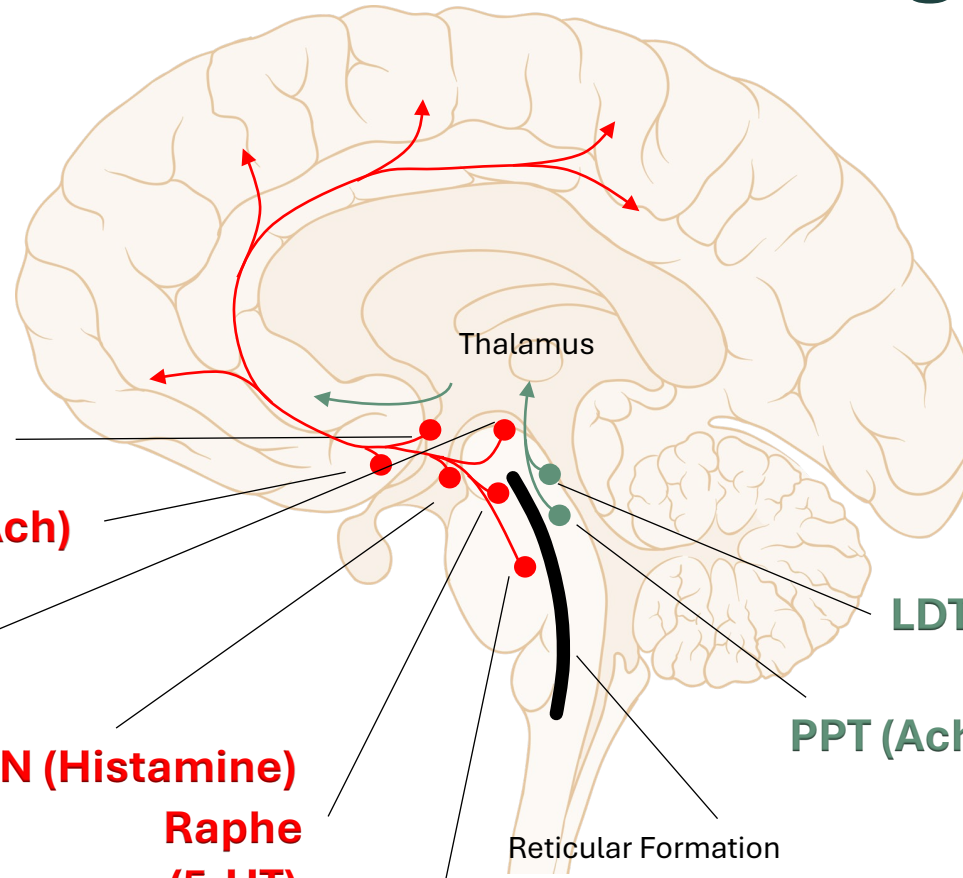
LH/PeF
(orexin; ORX)

BF (ACh)

vPAG (DA)

TMN (Histamine)
Raphe
(5-HT)

LC
(NE)



NOT an On/Off Switch:

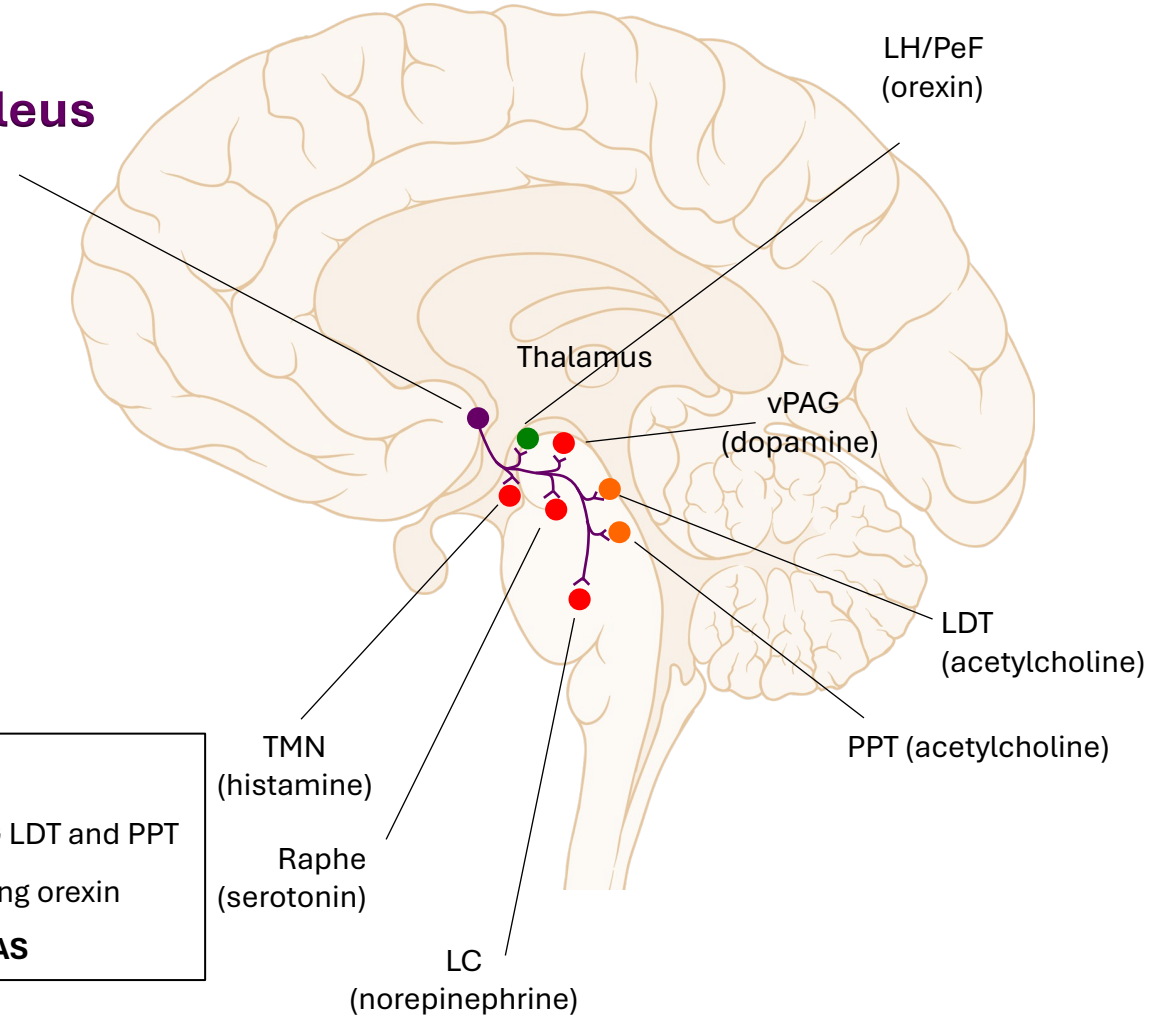
Systems active in wakefulness but not solely for arousal

LH = lateral hypothalamus; PeF = perifornical area; ORX = orexin; BF = basal forebrain; ACh = acetylcholine; vPAG = ventral periaqueductal grey; DA = dopamine; TMN = tuberomammillary nucleus; 5-HT = serotonin; LC = locus coeruleus; NE = norepinephrine; PPT = pedunculopontine nucleus; LDT = laterodorsal tegmental nucleus.

VLPO Inhibits Ascending Arousal System

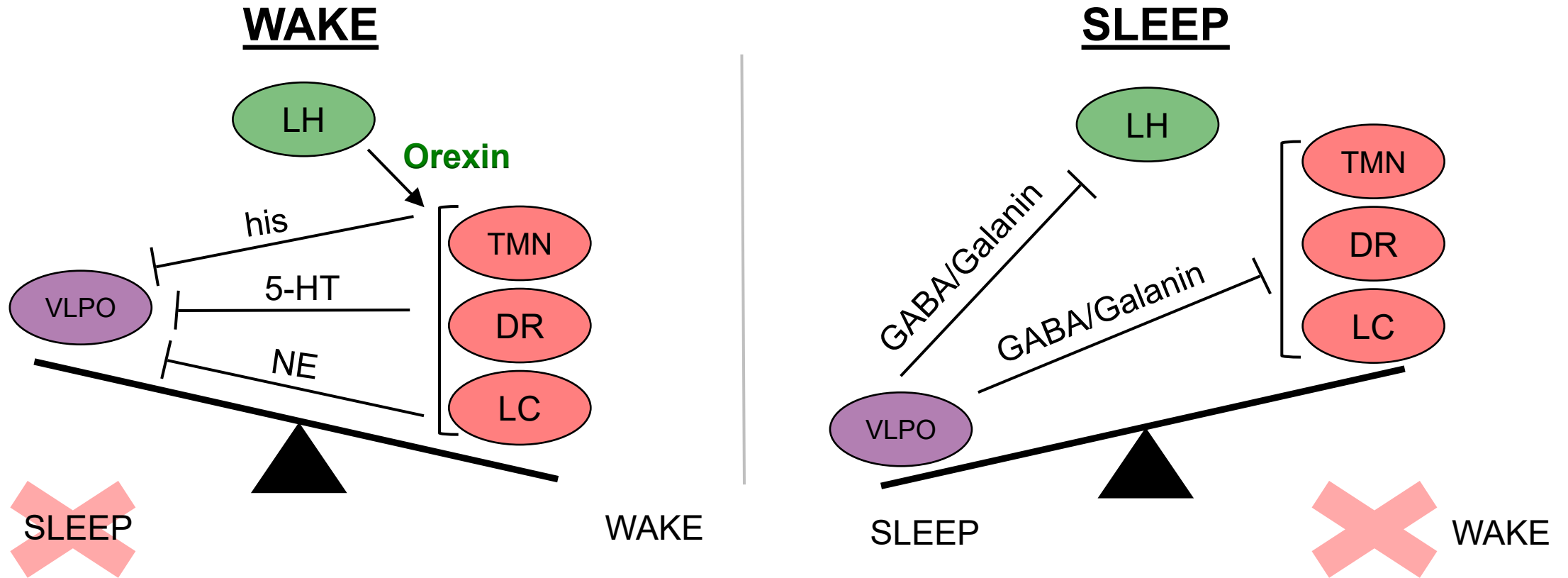
Ventrolateral Preoptic Nucleus (VLPO)

- GABA (majority) and galanin
 - Projections to TMN, Raphe, LC, vPAG, LDT and PPT
 - Innervates LH/PeF neurons containing orexin
- ***Promotes sleep via inhibition of AAS**



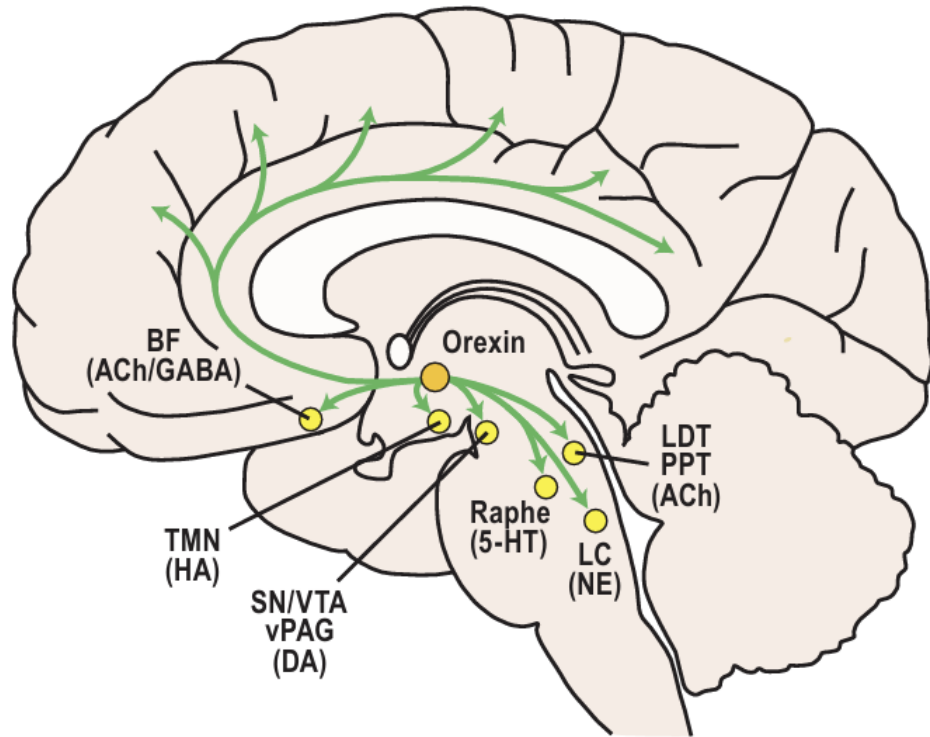
VLPO = ventrolateral preoptic nucleus; GABA = gamma-aminobutyric acid; AAS = ascending arousal system.

Flip-Flop Switch Model



Model allows for rapid vigilance state transitions
Orexin neurons serve as the “finger on the switch” to maintain state

Orexin Interaction with Other Monoamines and Neurotransmitters



Key Concept:
Orexins promote motivational activation, especially in high-relevance states (need, threat, reward) → organizing diverse, adaptive responses

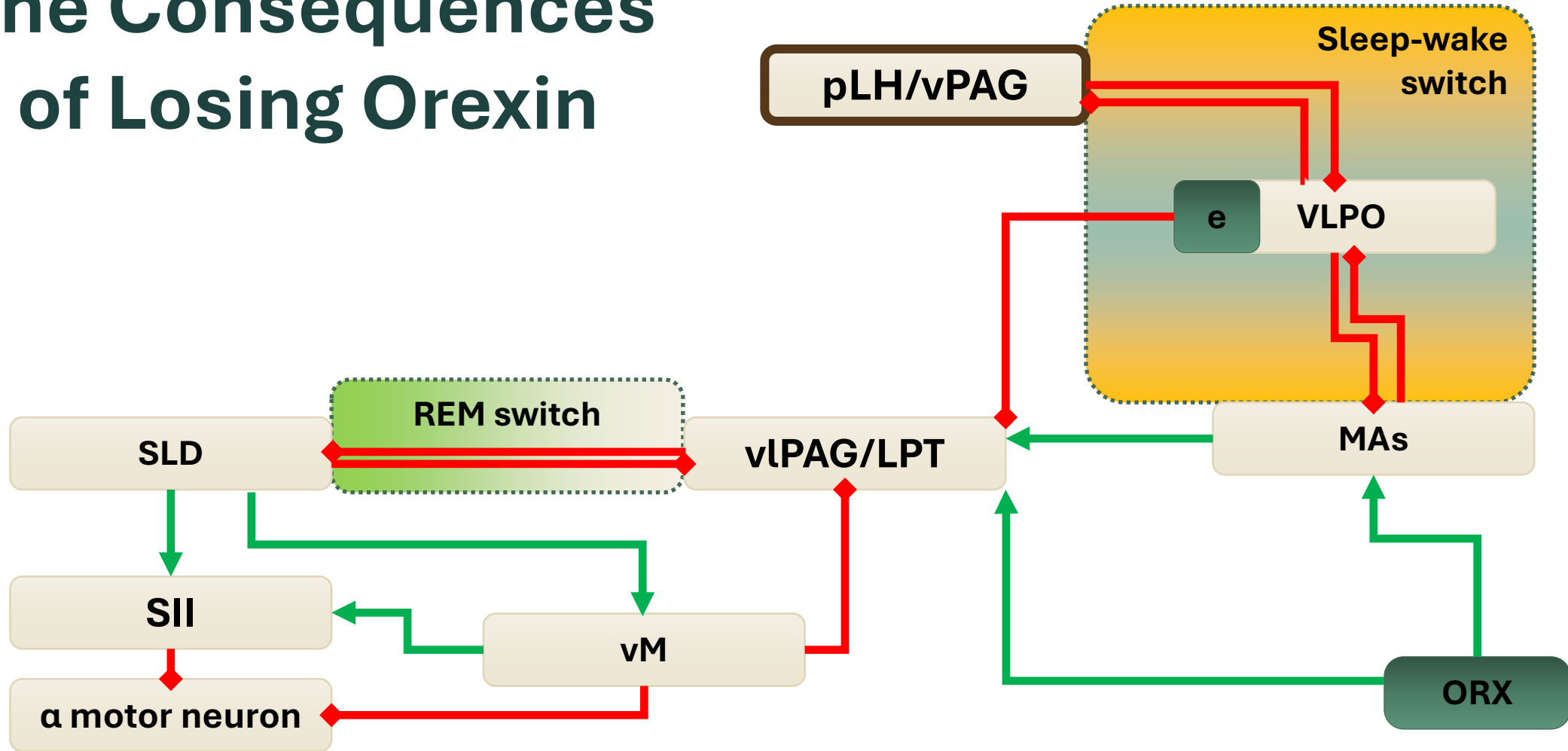
- Arousal Systems: **Each monoamine system can promote wakefulness, but acts synergistically**
- Not an On/Off Switch: Systems active in wakefulness but not solely for arousal

HA = histamine.

Mahler SV, et al. *Nat Neurosci.* 2014;17(10):1298-1303; España, R. A., & Scammell, T. E. (2011). *Sleep*, 34(7), 845–858.

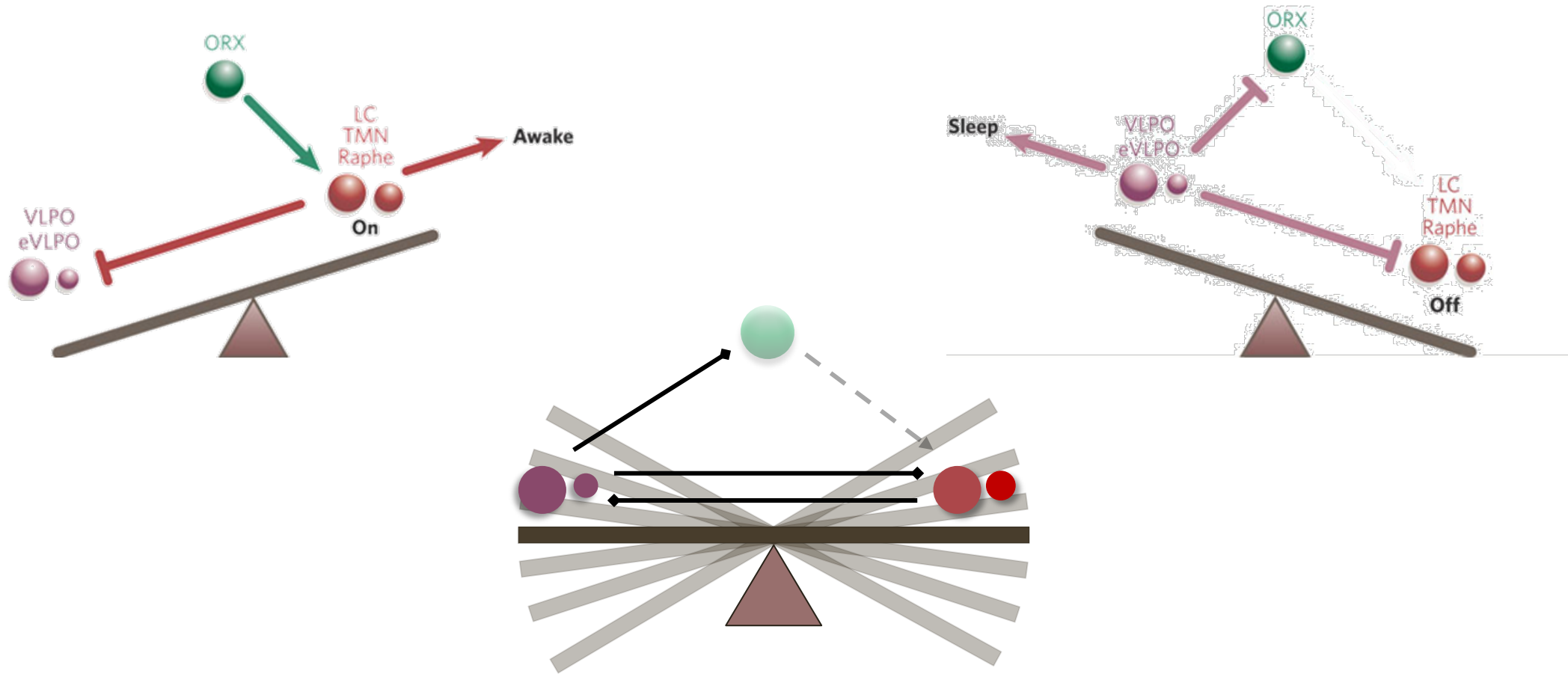
Orexinergic Sleep-Wake Centers of the Brain Implicated in Sleep & Psychiatric Disorders

The Consequences of Losing Orexin



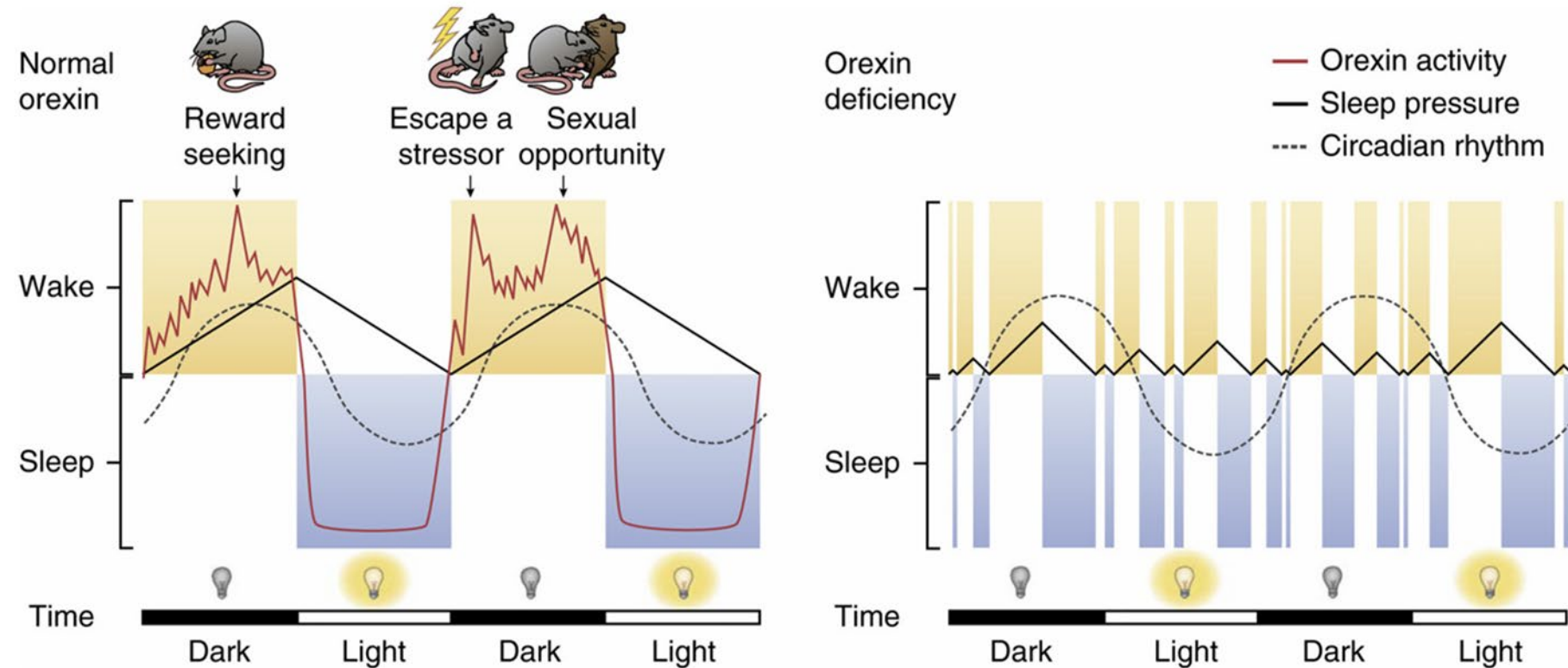
pLH/vPAG = posterior lateral hypothalamus/ventral periaqueductal grey; [e]VLPO = [extended] ventrolateral preoptic area; MAs = monoamines; ORX = orexin; SLD = sublaterodorsal; vIPAG/LPT = ventrolateral periaqueductal grey/lateral pontine tegmentum; SII = spinal inhibitory interneuron; vM = ventral medulla

Sleep-State Instability



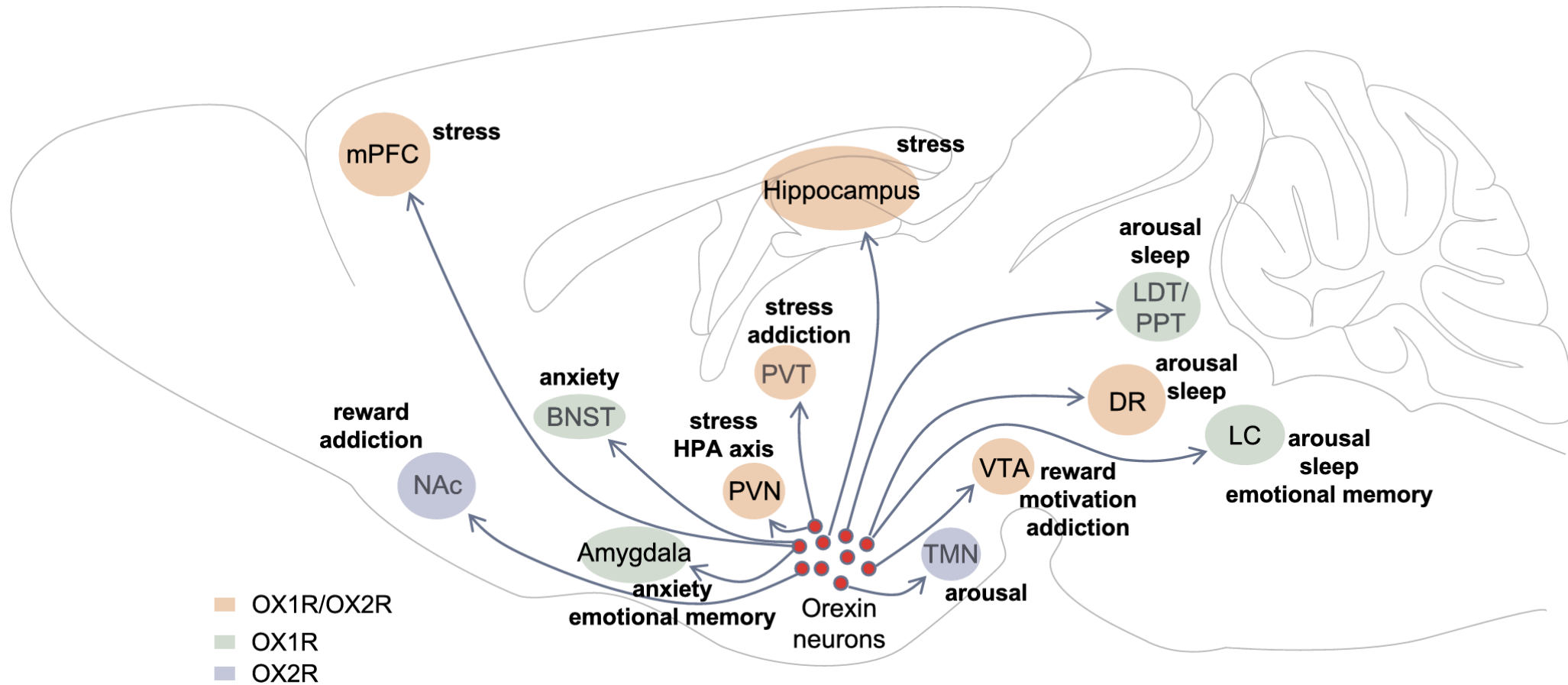
ORX = orexin; [e]VLPO = [extended] ventrolateral preoptic area; LC = locus coeruleus; TMN = tuberomammillary nucleus

Sleep/Wake and Motivation



Loss of Orexin: **Narcolepsy** = unstable transitions (sleep intrudes into wake, and vice versa)

Orexin Projections



mPFC = medial prefrontal cortex; NAc = nucleus accumbens; BNST = bed nucleus of the stria terminalis; PVN = paraventricular nucleus; PVT = paraventricular nucleus of the thalamus; VTA = ventral tegmental area; DR = dorsal raphe.

Sargin D. *Neuropharmacology*. 2019;154:68-78.

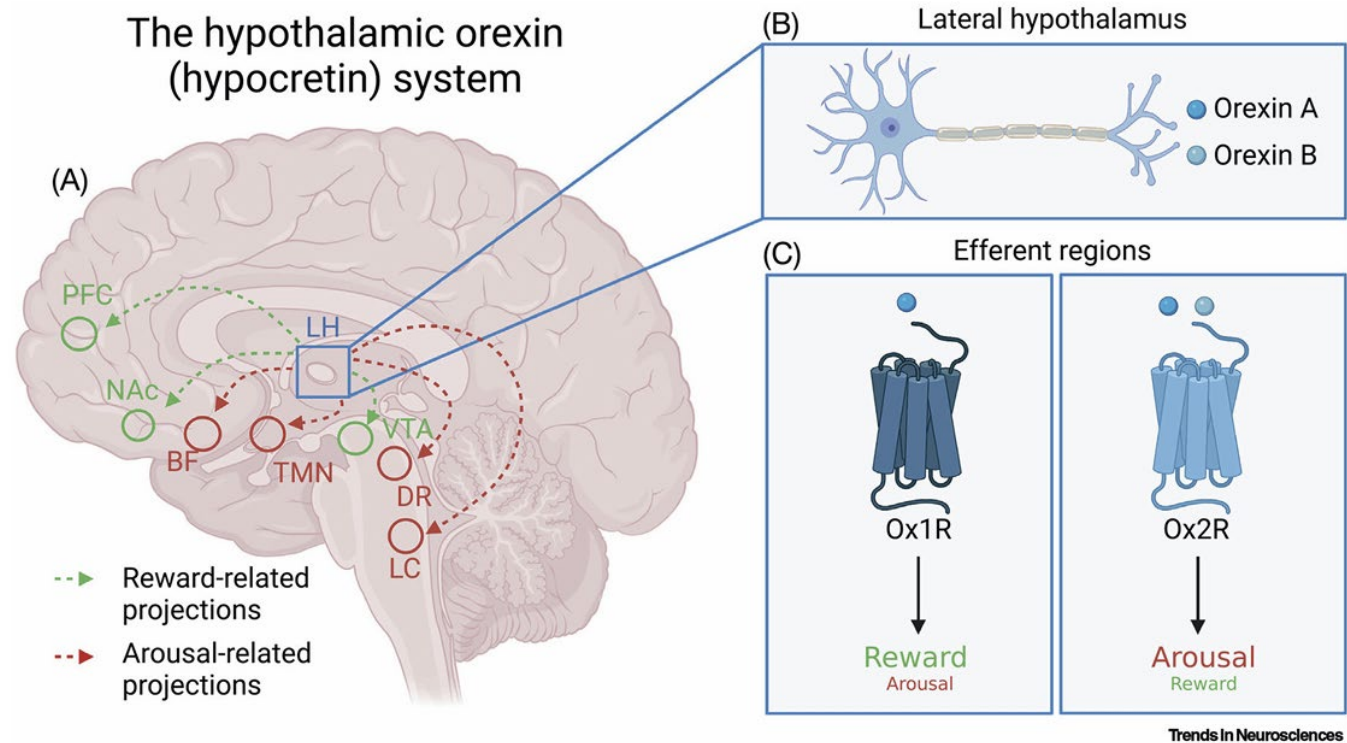
Orexin: Functions & Mechanisms

Orexins (A & B): Neuropeptides from dorsolateral hypothalamus

Receptors: ORX1 (reward/motivation)
ORX2 (sleep/wake)

Roles: Sleep/wake cycles, arousal, feeding, reward-seeking, cognition, stress, motor activity, autonomic regulation

Co-Transmission: Many orexin neurons also contain glutamate, which can signal independently



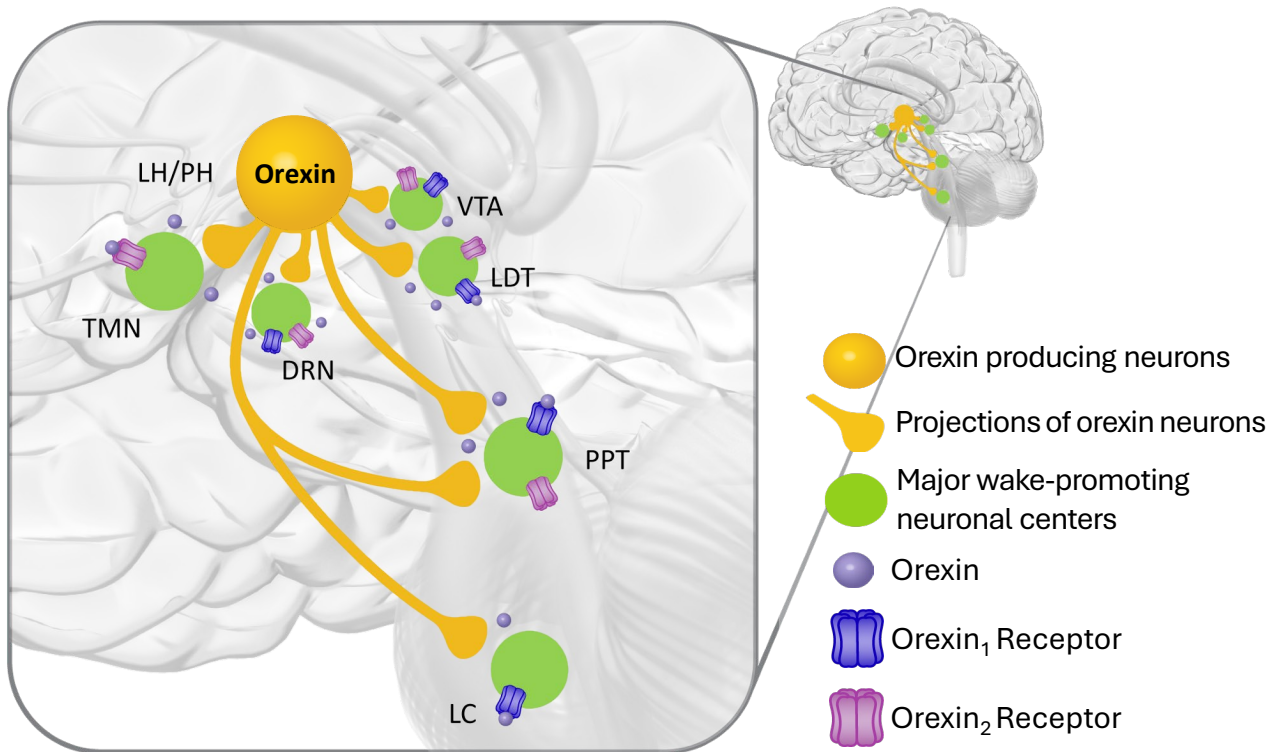
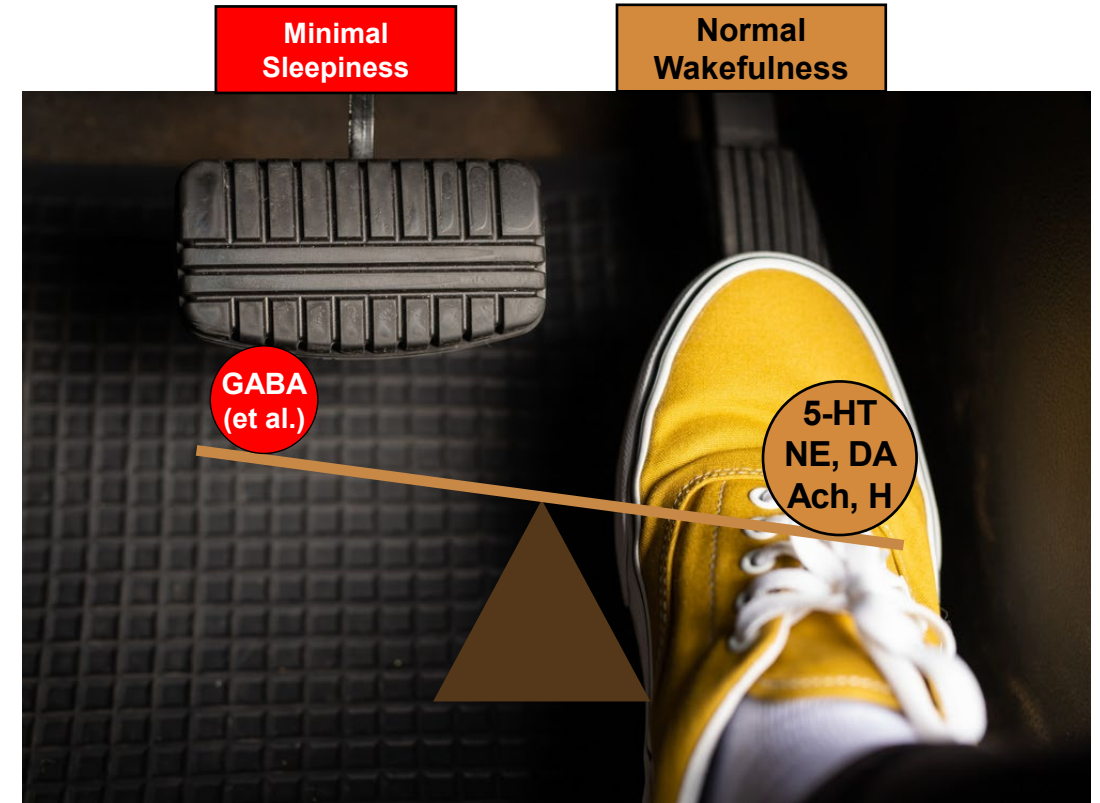
Key Learning Points



- Orexin feeds into several monoaminergic systems central to wake and behavioral state regulation
 - **Orexin promotes motivational activation synergistically across monoamine systems**
- Orexin deficiency (as in NT1) results in state instability
- Selective orexin-2 receptor (Ox2R) agonists are the result of decades of scientific progress in the mechanistic understanding of sleep neurocircuitry

Emerging Therapies Targeting the Orexin Pathway

The Normal Orexin System



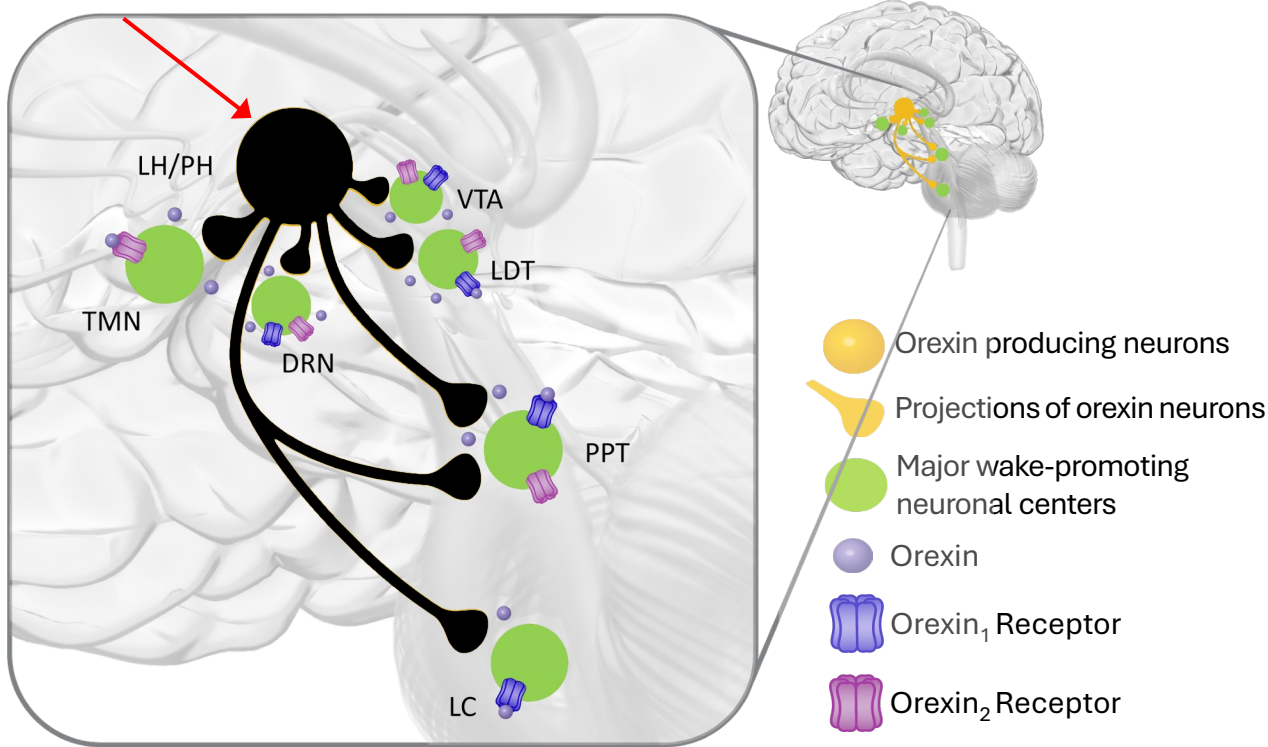
Orexin stabilizes the wake-promoting neurotransmitter centers of the brain to produce wakefulness

DRN = dorsal raphe nucleus; PPT = pedunculopontine tegmental nucleus; LDT = laterodorsal tegmental nucleus; LH/PH = lateral/posterior hypothalamus; TMN = tuberomammillary nucleus; VTA = ventral tegmental area.

Sakurai T. *Nat Rev Neurosci*. 2007;8(3):171-181. Marcus JN, et al. *J Comp Neurol*. 2001;435(1):6-25. Scammell TE, et al. *Annu Rev Pharmacol Toxicol*. 2011;51:243-266. Morin CM, et al. *Nat Rev Dis Primers*. 2015;1:15026.

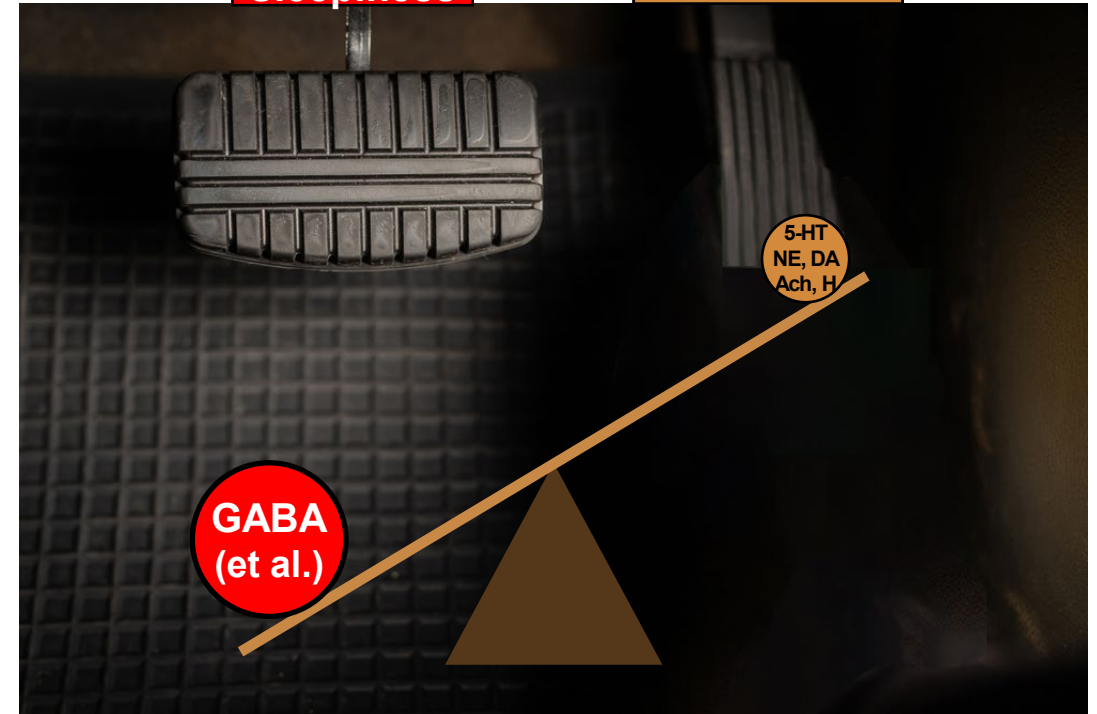
Mechanism of Orexin Agonists in NT1

Deficiency of
Orexin Neurons



**Extreme
Sleepiness**

**Poor/inconsistent
Wakefulness**



Deficiency of orexin neurons produces unrelenting sleepiness and intermittent cataplexy

Turn Down for What?

The Long Road to Turning Orexin Up

2001–2014

1

ANTAGONISTS COME FIRST

- **SB-334867-A**: first selective orexin receptor antagonist (2001)
- **Suvorexant**: first dual orexin receptor antagonist approved (2014)

Smart D, et al. *Br J Pharmacol*. 2001;132:1179-1182; Brisbare-Roch C, et al. *Nat Med*. 2007;13:150-155; FDA. Belsomra Drug Approval Package. 2014; Nagahara T, et al. *J Med Chem*. 2015;58:7931-7937; Takeda. TAK-925 World Sleep Congress Data. 2019; Takeda. TAK-994 Clinical Program Update. 2021; Dauvilliers Y, et al. *N Engl J Med*. 2023;389:309-321; Arnett A. *Sleep Review*. November 30, 2023.

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MID-2010s–2019

2

AGONIST PROOF OF CONCEPT

- **YNT-185**: preclinical evidence for wake promotion, but limited bioavailability
- **Danavorexton (TAK-925)**: human wake promotion, but required a 9-hour IV infusion

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EARLY 2020s

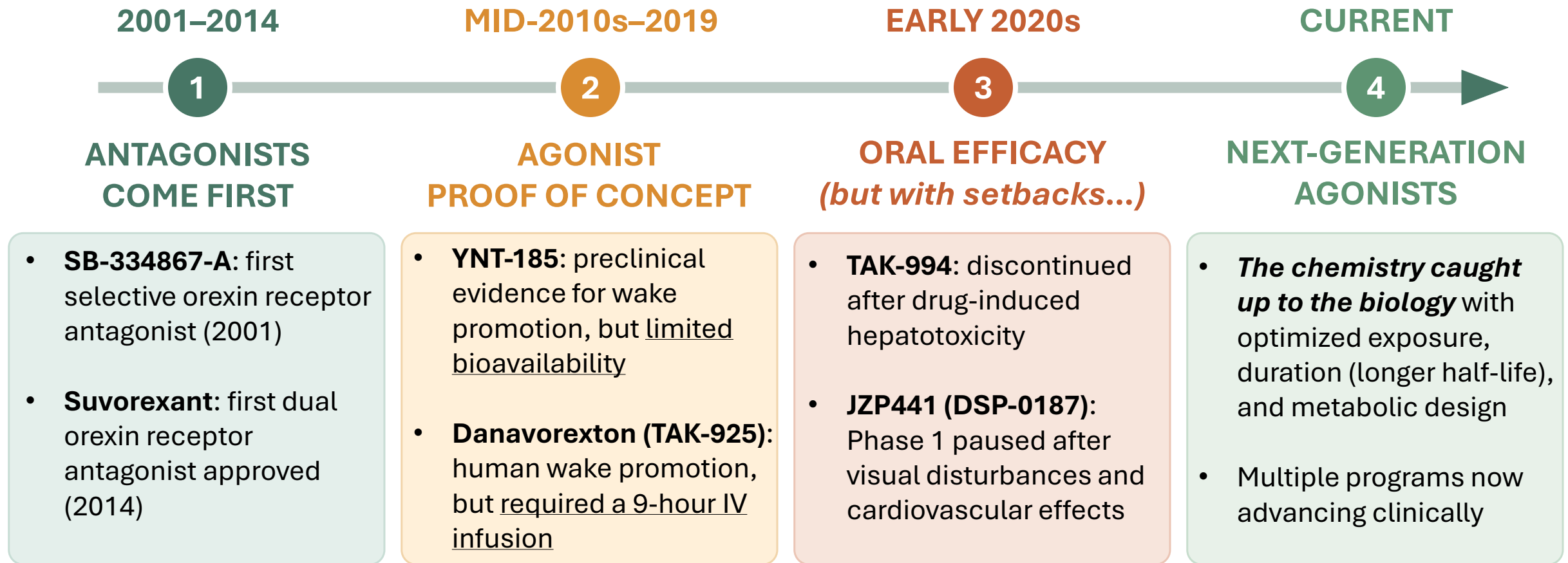
3

ORAL EFFICACY (*but with setbacks...*)

- **TAK-994**: discontinued after drug-induced hepatotoxicity
- **JZP441 (DSP-0187)**: Phase 1 paused after visual disturbances and cardiovascular effects

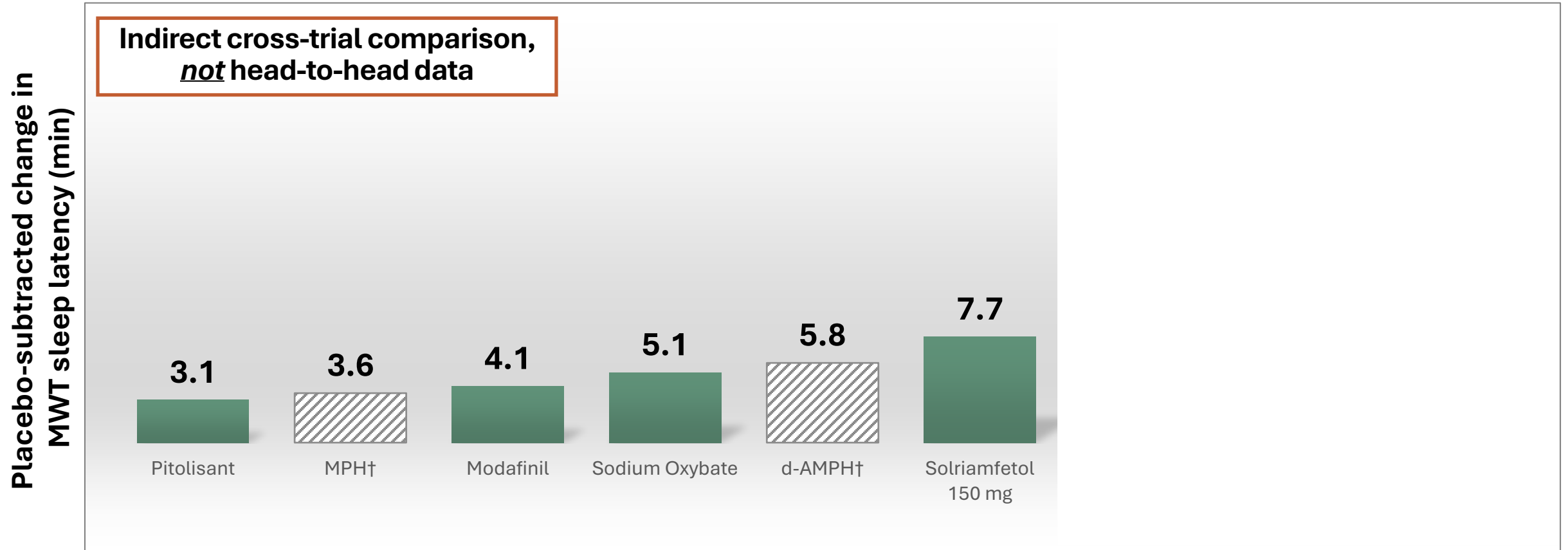
Turn Down for What?

The Long Road to Turning Orexin Up



Smart D, et al. *Br J Pharmacol*. 2001;132:1179-1182; Brisbare-Roch C, et al. *Nat Med*. 2007;13:150-155; FDA. Belsomra Drug Approval Package. 2014; Nagahara T, et al. *J Med Chem*. 2015;58:7931-7937; Takeda. TAK-925 World Sleep Congress Data. 2019; Takeda. TAK-994 Clinical Program Update. 2021; Dauvilliers Y, et al. *N Engl J Med*. 2023;389:309-321; Arnett A. *Sleep Review*. November 30, 2023.

Orexin Agonists Set New Standards in Wake Promotion for Narcolepsy

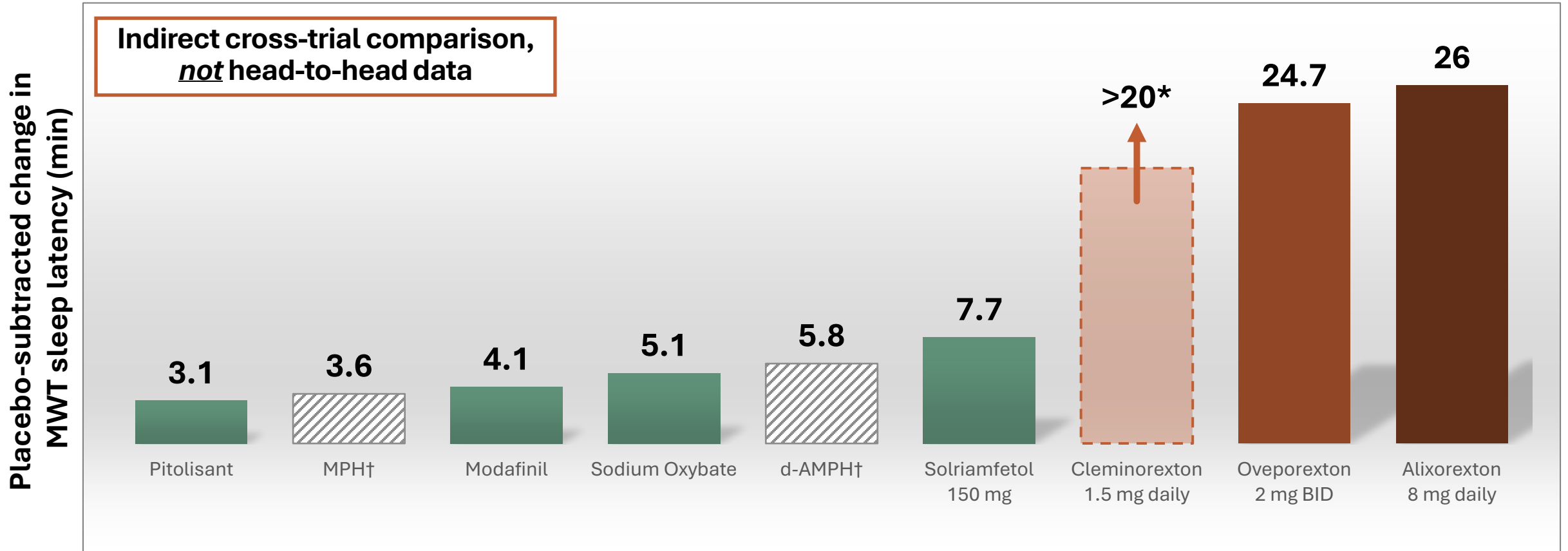


†Uncontrolled change from baseline, as no placebo-controlled MWT data available;

MWT=Maintenance of Wakefulness Test; MPH=methylphenidate; d-AMPH=dextroamphetamine

Maski et al. J Clin Sleep Med. 2021;17:1895-1945; Mitler and Hajdukovic. Sleep. 1991;14:218-220; Thorpy et al. Ann Neurol. 2019;85:359-370; Centessa Pharmaceuticals. Phase 2a CRYSTAL-1 study of clemimorexton (ORX750). Data cutoff 9/23/2025. Presented 11/5/2025; Dauvilliers et al. N Engl J Med. 2025;392:1905-1916; Plazzi et al. Lancet Neurol. 2026;25:889-899.

Orexin Agonists Set New Standards in Wake Promotion for Narcolepsy



†Uncontrolled change from baseline, as no placebo-controlled MWT data available; *Bar marks a lower bound, as exact mean not yet reported.

MWT=Maintenance of Wakefulness Test; MPH=methylphenidate; d-AMPH=dextroamphetamine

Maski et al. J Clin Sleep Med. 2021;17:1895-1945; Mitler and Hajdukovic. Sleep. 1991;14:218-220; Thorpy et al. Ann Neurol. 2019;85:359-370; Centessa Pharmaceuticals. Phase 2a CRYSTAL-1 study of cleminorexton (ORX750). Data cutoff 9/23/2025. Presented 11/5/2025; Dauvilliers et al. N Engl J Med. 2025;392:1905-1916; Plazzi et al. Lancet Neurol. 2026;25:889-899.

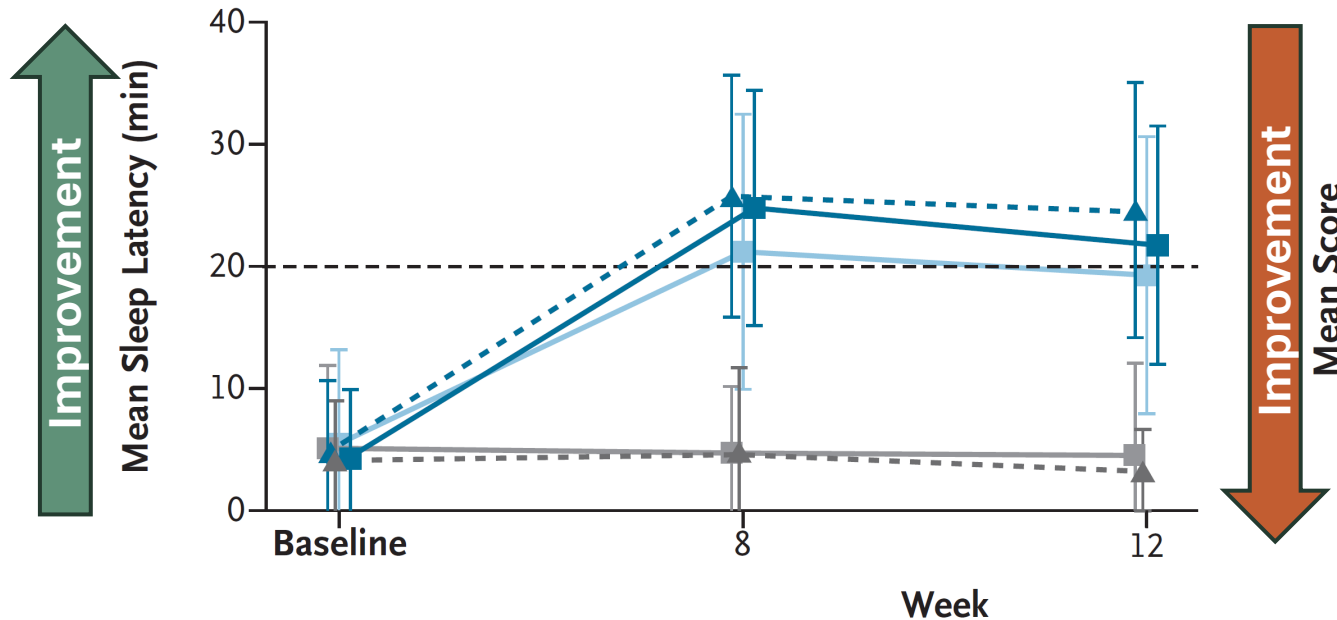
Overporexton

Oveporexton (TAK-861) Improved Sleep Latency and Daytime Sleepiness in Two Phase 3 Trials

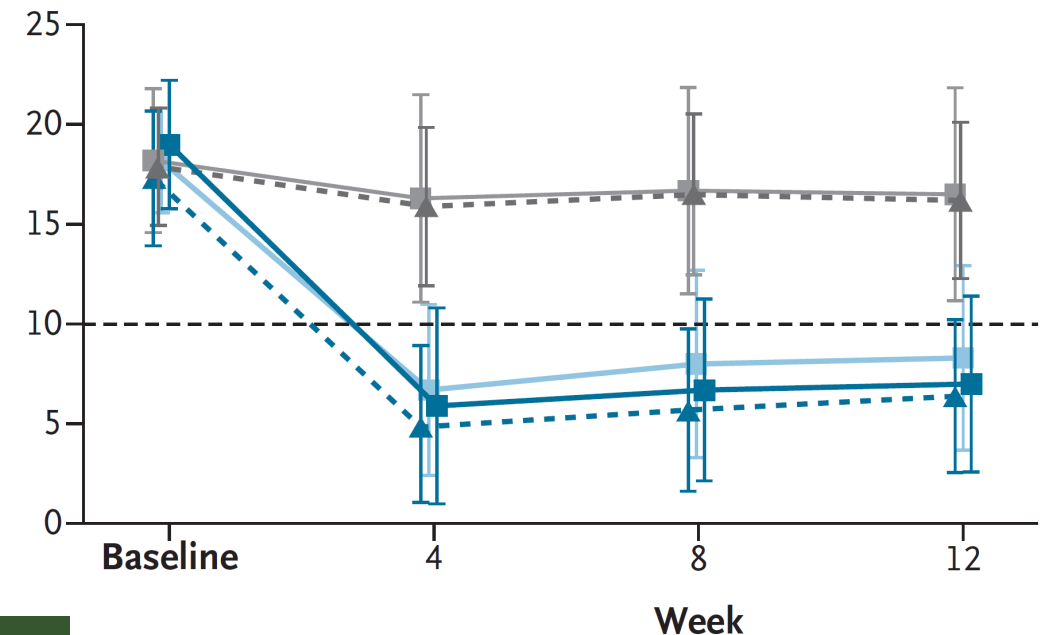
First Light Trial: Oveporexton, 1 mg twice daily Oveporexton, 2 mg twice daily Placebo

Radiant Light Trial: Oveporexton, 2 mg twice daily Placebo

Daytime Sleep Latency (Both Trials)



Daytime Sleepiness (Both Trials)



Oveporexton **reduced weekly cataplexy episodes by ~80% at Week 12**, compared with 28%–39% with placebo across the two Phase 3 trials ($P < .001$)

FDA Approval for NT1 in August 2026
(availability pending scheduling, November 2026)



All doses across both trials at Week 12 timepoints were significant ($p < 0.001$) vs placebo

Dauvilliers Y, Mignot E, Antczak J, et al. Oveporexton for narcolepsy type 1: results from two phase 3 trials. *N Engl J Med*. Published September 9, 2026.

Oveporexton: Phase 3 Safety and Tolerability

Adverse Event	Placebo (N=76)	Oveporexton 1 mg BID (N=60)	Oveporexton 2 mg BID (N=136)
Insomnia	1%	55%	60%
Urinary frequency	5%	53%	58%
Urinary urgency	1%	15%	16%
Salivary hypersecretion	0%	8%	7%
Influenza	1%	5%	3%
Abdominal pain	0%	3%	1%
Oropharyngeal pain	0%	3%	1%
Paresthesia	0%	2%	2%
Rash	0%	0%	3%
Sinusitis	1%	5%	2%

Oveporexton: Phase 3 Safety and Tolerability

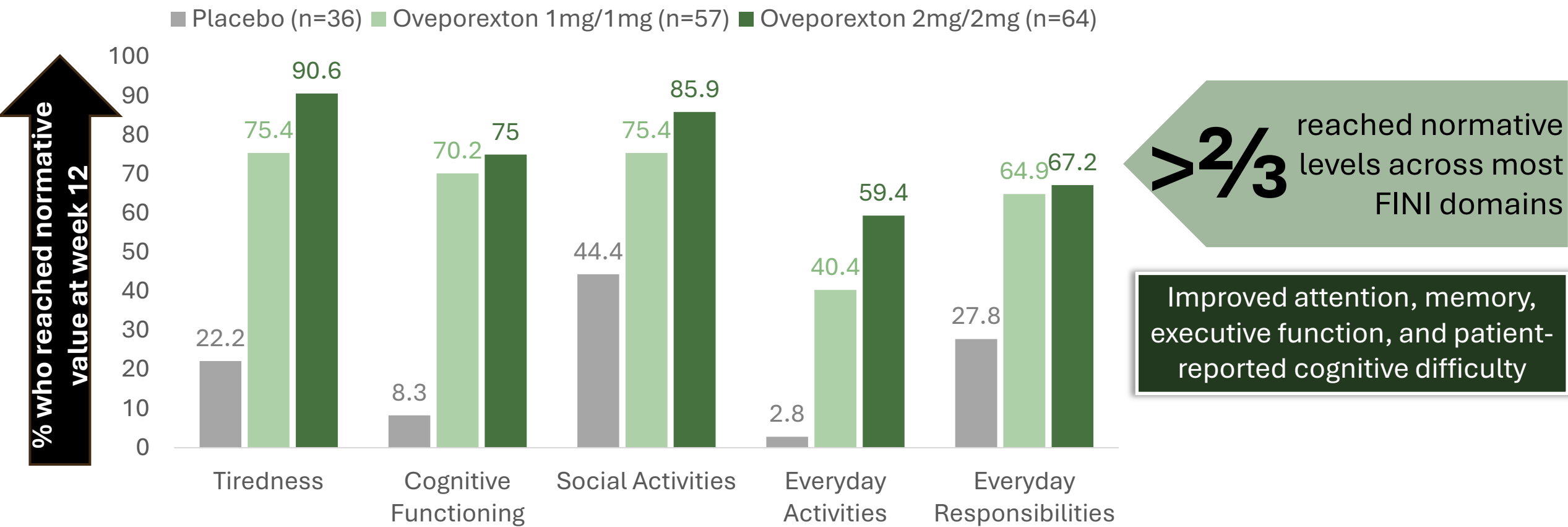
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Influenza	1%	5%	3%
Abdominal pain	0%	3%	1%
Oropharyngeal pain	0%	3%	1%
Paresthesia	0%	2%	2%
Rash	0%	0%	3%
Sinusitis	1%	5%	2%

~**90%** of insomnia events occurred within the first 2 days of treatment initiation; 4% began between days 2 and 7

Majority of cases (~63%) resolved **within 1 week of onset**; ~17% were ongoing at study completion

No events led to treatment discontinuation or were classified as serious adverse reactions

Oveporexton Restored Cognition and Functioning Toward Normative Levels in Two Phase 3 Studies



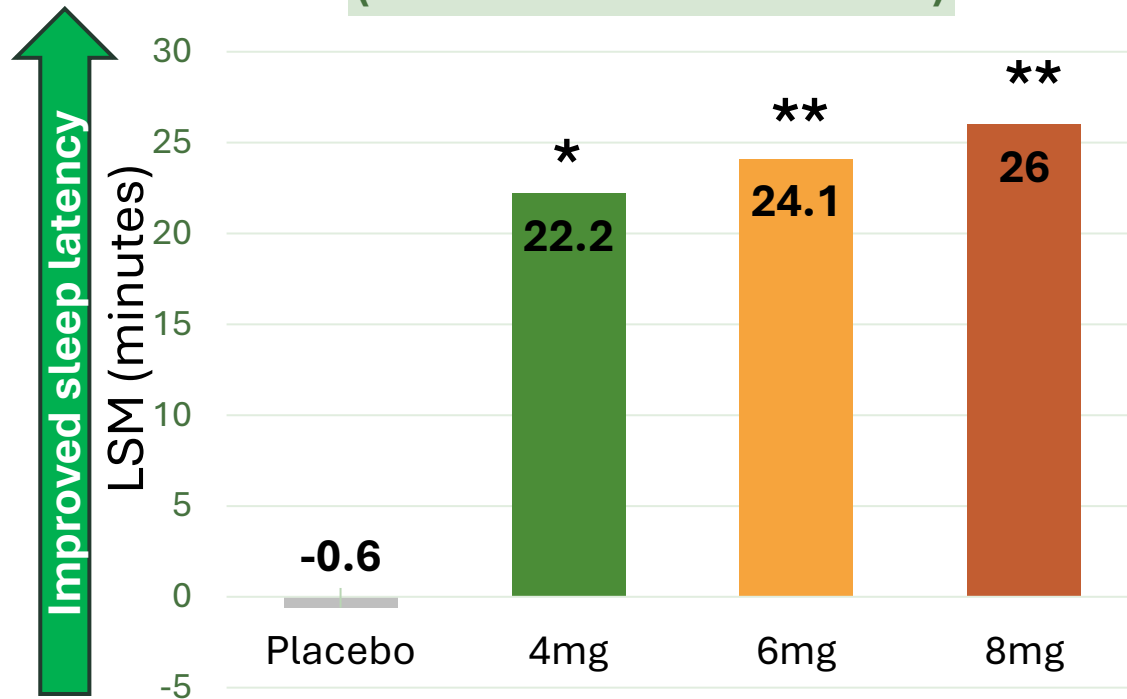
Note: results shown from one Phase 3 study (First Light); findings are relatively comparable across both studies

FINI=Functional Impacts of Narcolepsy Instrument
Pizza F, et al. Oveporexton (TAK-861) improves cognitive symptoms in patients with narcolepsy type 1: Results from two randomized, placebo-controlled phase 3 trials; Plazzi G, Dauvilliers Y, Pizza F, et al. Effect of the oral orexin receptor 2 agonist oveporexton (TAK-861) on functional impacts of narcolepsy type 1: Results from two phase 3 studies. Poster presented at: SLEEP 2026; June 14-17, 2026; Baltimore, MD

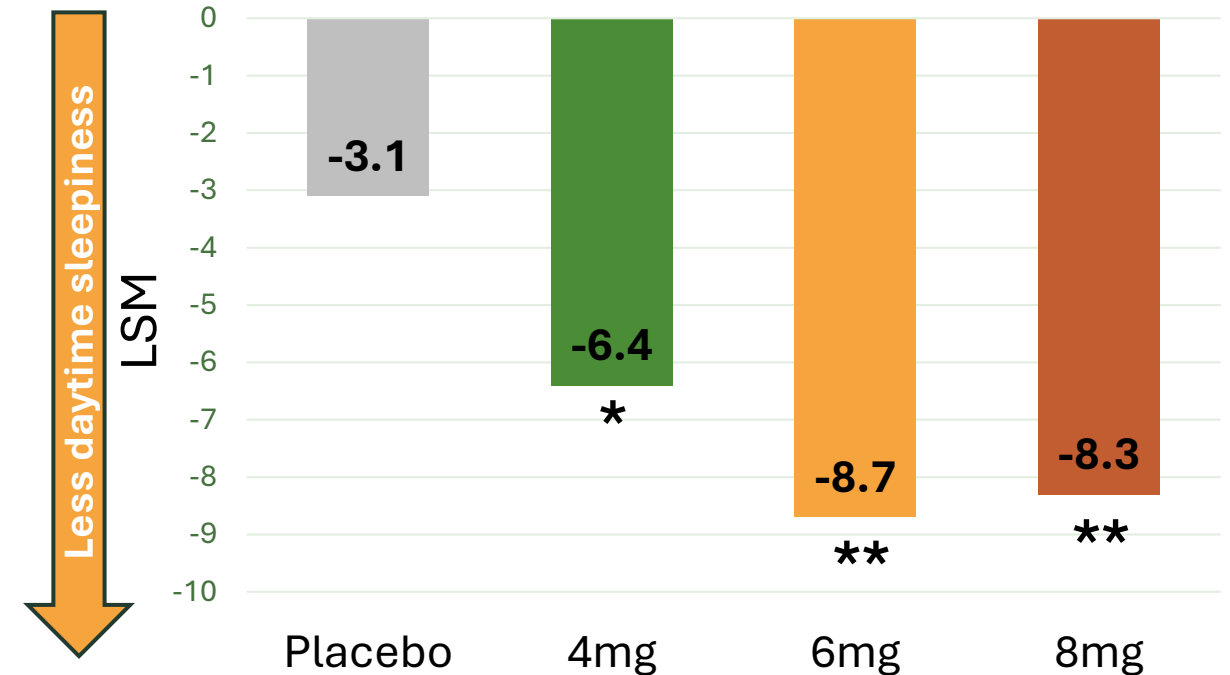
Alixorexton

Once Daily Alixorexton (ALKS-2680) Showed Efficacy for Improving Sleep Latency and Daytime Sleepiness

Daytime Sleep Latency
(Δ from baseline to Week 6)



Daytime Sleepiness
(Δ from baseline to Week 6)



*p=0.01 vs placebo; **p<0.0001 vs placebo.

LSM=least squares mean.

Plazzi G, et al. *Lancet Neurol*. Published online August 24, 2026.

Alixorexton: Safety and Tolerability

Adverse Event	Placebo (N=23)	Alixorexton 4 mg (N=23)	Alixorexton 6 mg (N=22)	Alixorexton 8 mg (N=24)
Urinary frequency	4%	65%	50%	55%
Insomnia	0	17%	32%	28%
Salivary hypersecretion	0	22%	23%	25%
Urinary urgency	4%	9%	18%	15%
Blurry vision	4%	9%	5%	15%

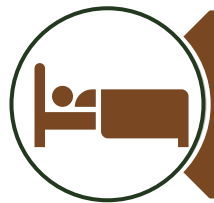
Alixorexton Improved Cognition and Fatigue Beyond Core NT1 Symptoms



Reduced overall NT1 symptom burden, with significant improvements across all alixorexton doses at week 6



Improved patient-reported cognitive functioning, with approximately 90% reporting no or minimal cognitive impairment at week 6



Meaningfully reduced fatigue, with mean PROMIS-Fatigue scores reaching normative levels at week 6



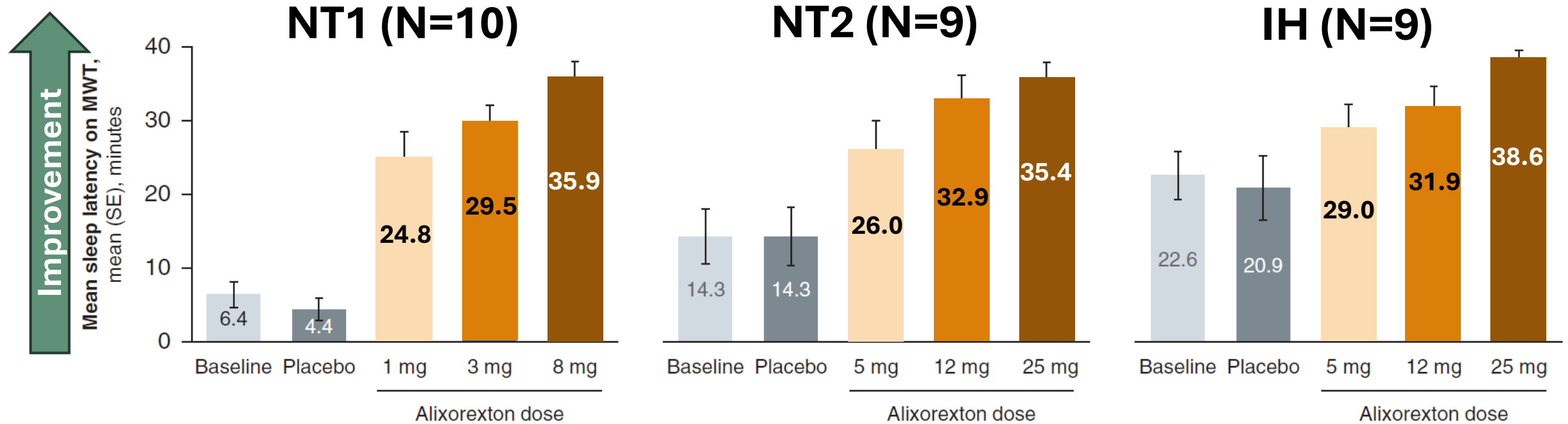
April 2026: Phase 3 studies have been initiated, evaluating once-daily and split-dose regimens

Exploratory endpoints; nominal P values were not adjusted for multiplicity.

Dauvilliers Y, et al. Improvement in patient-reported disease severity, cognitive functioning, and fatigue in patients with narcolepsy type 1 treated with alixorexton, an orexin 2 receptor agonist, in the Vibrance-1 phase 2 study. Poster presented at: American Academy of Neurology Annual Meeting; April 2026; Chicago, IL

Beyond NT1:

Alixorexton Shows Proof of Concept for NT2 and IH



Alixorexton demonstrated dose-dependent improvements in wakefulness across NT1, NT2, and IH

Cleminorexton

Cleminorexton (ORX750) Shows Early Proof-of-Concept Across Narcolepsy Types

As of data cut-off in September 2025*:

N=55 participants with NT1, NT2 and IH have been dosed during a 2-week crossover study

Most common TEAEs ($\geq 10\%$) across all cohorts were pollakiuria (51%), insomnia (22%), dizziness (13%), & headache (11%)

NT1

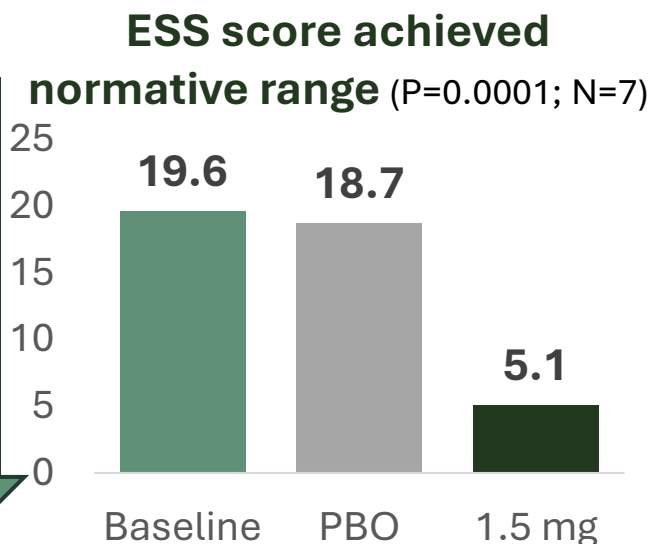
>20-minute change

from baseline in mean sleep latency (1.5mg dose vs placebo; $P=0.0026$; $N=6$)

87%

relative reduction in weekly cataplexy rate (1.5 mg dose vs placebo; $P=0.0025$; $N=7$)

improvement



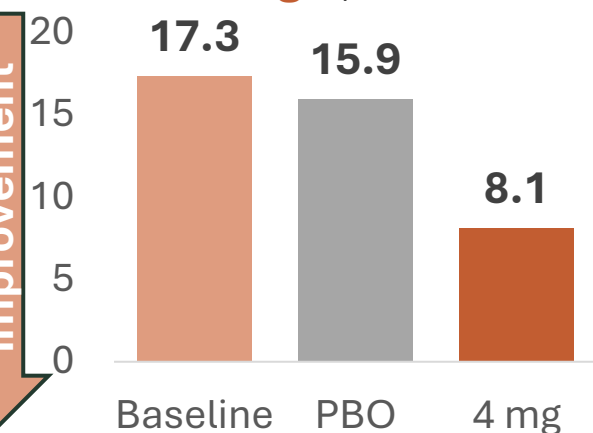
NT2

>10-minute change

from baseline in mean sleep latency (4mg dose vs placebo; $P=0.0193$; $N=10$)

ESS score achieved normative range ($P=0.0023$; $N=10$)

improvement



*Phase 2a efficacy findings are preliminary and currently company-reported; no peer-reviewed results available

ESS, Epworth Sleepiness Scale; PBO, placebo; TEAE, treatment-emergent adverse event.

Centessa Pharmaceuticals. Phase 2a CRYSTAL-1 study of cleminorexton (ORX750). Data cutoff September 23, 2025. Presented November 5, 2025.

Ongoing Studies for Cleminorexton

Ongoing Studies

**SAPPHIRE: Registrational Phase 2/3
study recruiting in NT1 and NT2**

N≈222 (ages 18-70)

12-week treatment period

Recruiting

**CRYSTAL-1: Phase 2a trial for NT1,
NT2, and IH**

N≈248 (ages 18-65)

12-week treatment period

Recruiting

Long-term OLE ongoing

New and Emerging OX2R Agonists... and Indications?

BP-205

Phase 1 SAD completed in healthy volunteers

Rapid absorption ($T_{\max}$ 30–75 min)

25-h half-life → once-daily dosing potential

Generally well tolerated; no serious/severe TEAEs

Next: MAD data Q4 2026; Phase 1b sleep-deprivation data expected early 2027; Phase 2 planned mid-2027

Lu AH69593

*Ongoing Phase 1b study;
no data available yet*

July 2026: FDA granted fast-track designation

Multiple companies have signaled an intent to study agonists for neuropsychiatric indications beyond narcolepsy and idiopathic hypersomnia, and ALKS 7290 is currently in phase 2 for ADHD

<https://clinicaltrials.gov/study/NCT07755410>. Accessed 9-14-2026. Harmony Biosciences. Harmony Biosciences announces record Q2 2026 revenue and shares initial clinical data for its orexin-2 agonist BP-205 reinforcing potential best-in-class profile. Published August 4, 2026. Accessed August 25, 2026; H. Lundbeck A/S. Lundbeck receives FDA Fast Track designation for Lu AH69593, an investigational orexin 2 receptor agonist for narcolepsy. News release. July 23, 2026. Accessed July 25, 2026.



Key Learning Points

- Results from two phase 3 trials of oreporexton demonstrated **significant reductions in weekly cataplexy episodes at Week 12** versus placebo in patients with narcolepsy type 1
 - Oreporexton also improved wakefulness, daytime sleepiness, cognition, and daily functioning, with a generally favorable safety and tolerability profile
- Early findings with alixorexton and clemnorexton support the potential of OX2R agonists to improve symptoms across narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia
- OX2R agonists are being investigated in ongoing studies in sleep disorders, as well as other indications

Faculty Discussion: Understanding Narcolepsy Through the Patient Experience

Patient experience of symptom onset

Diagnostic journey and barriers to timely recognition

Patient interactions and gaps in screening/communication

Ongoing burden and treatment priorities from the patient perspective



Q&A