Moving Beyond Sleep: The Broader Connection Between the Orexin System and Psychiatric Disorders

TOTAL CME

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TOTAL CME

Disclosures of Conflicts of Interest

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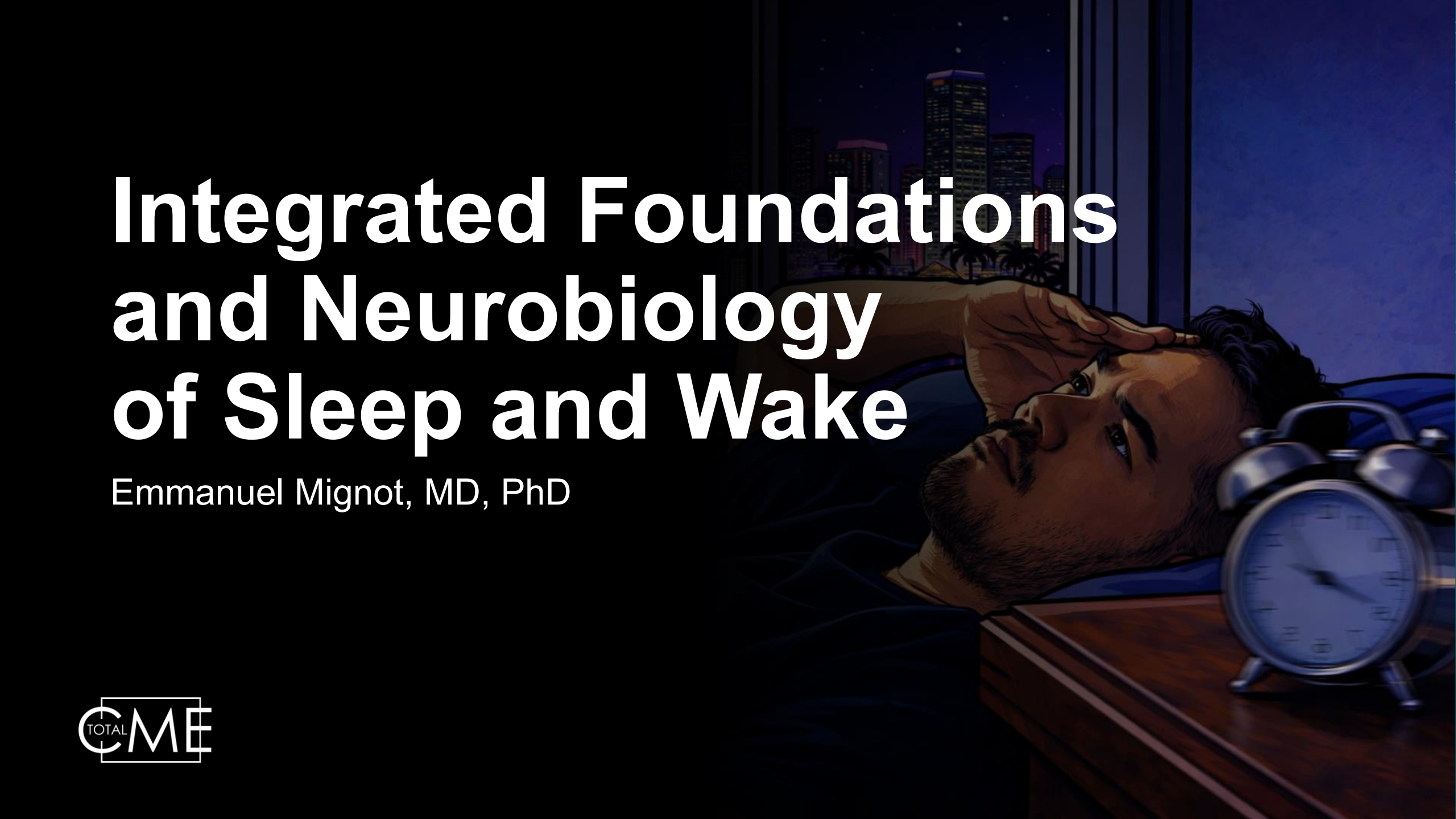
Contracted Researcher: research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute

Learning Objectives

- Understand how orexin-mediated pathways involved in arousal, REM regulation, and reward contribute to co-occurring sleep disturbances and psychiatric disorders
- Implement validated, bidirectional screening pathways that systematically apply validated screening tools in order to detect coexisting sleep and psychiatric disorders
- Evaluate the clinical trial data surrounding safety, efficacy, and adverse event monitoring of new and emerging orexin receptor agonists

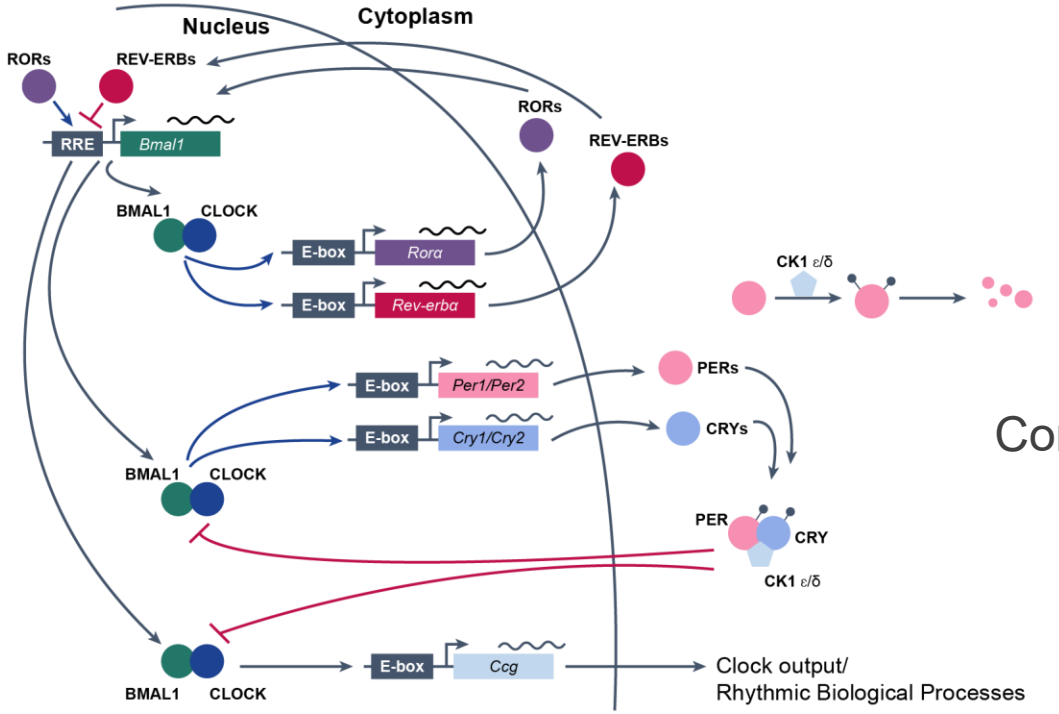
Integrated Foundations and Neurobiology of Sleep and Wake

Emmanuel Mignot, MD, PhD

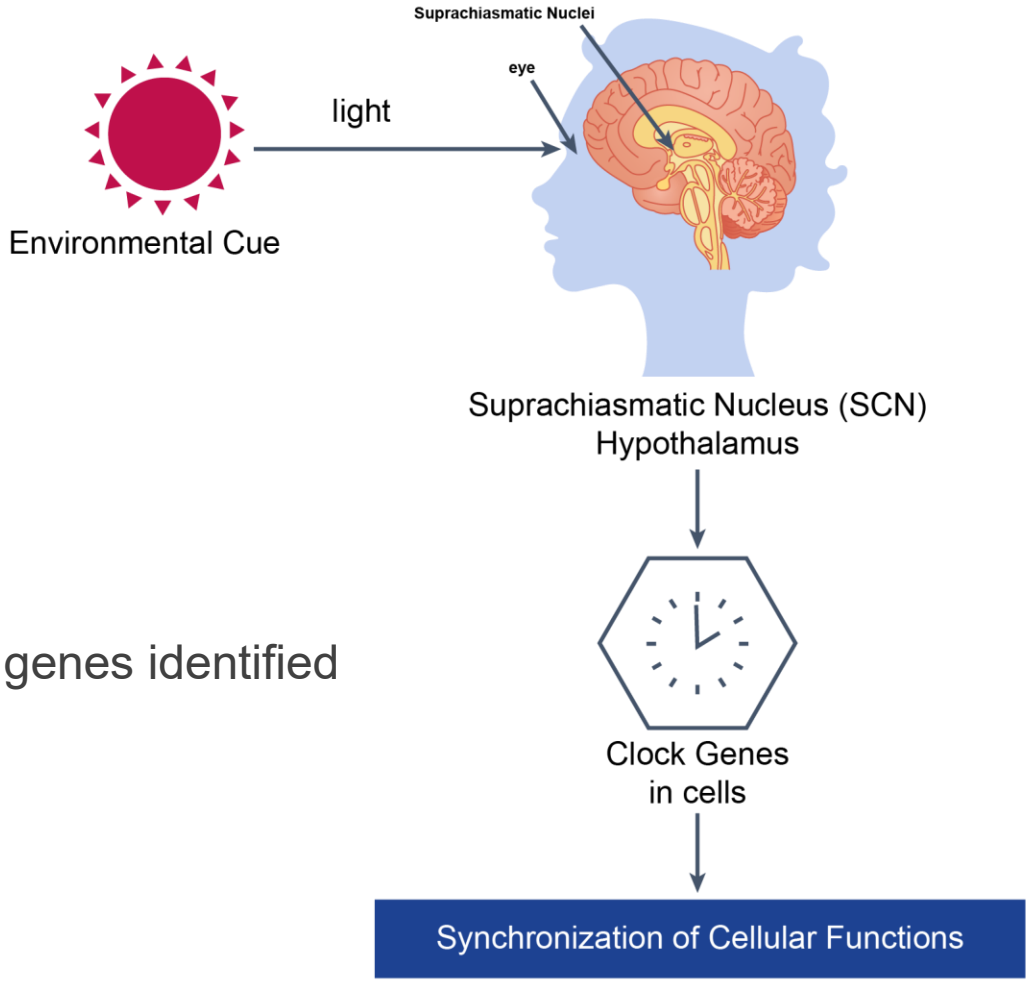


Circadian Clock Is Well Understood

4,256/7497 = 57% of genes are cycling



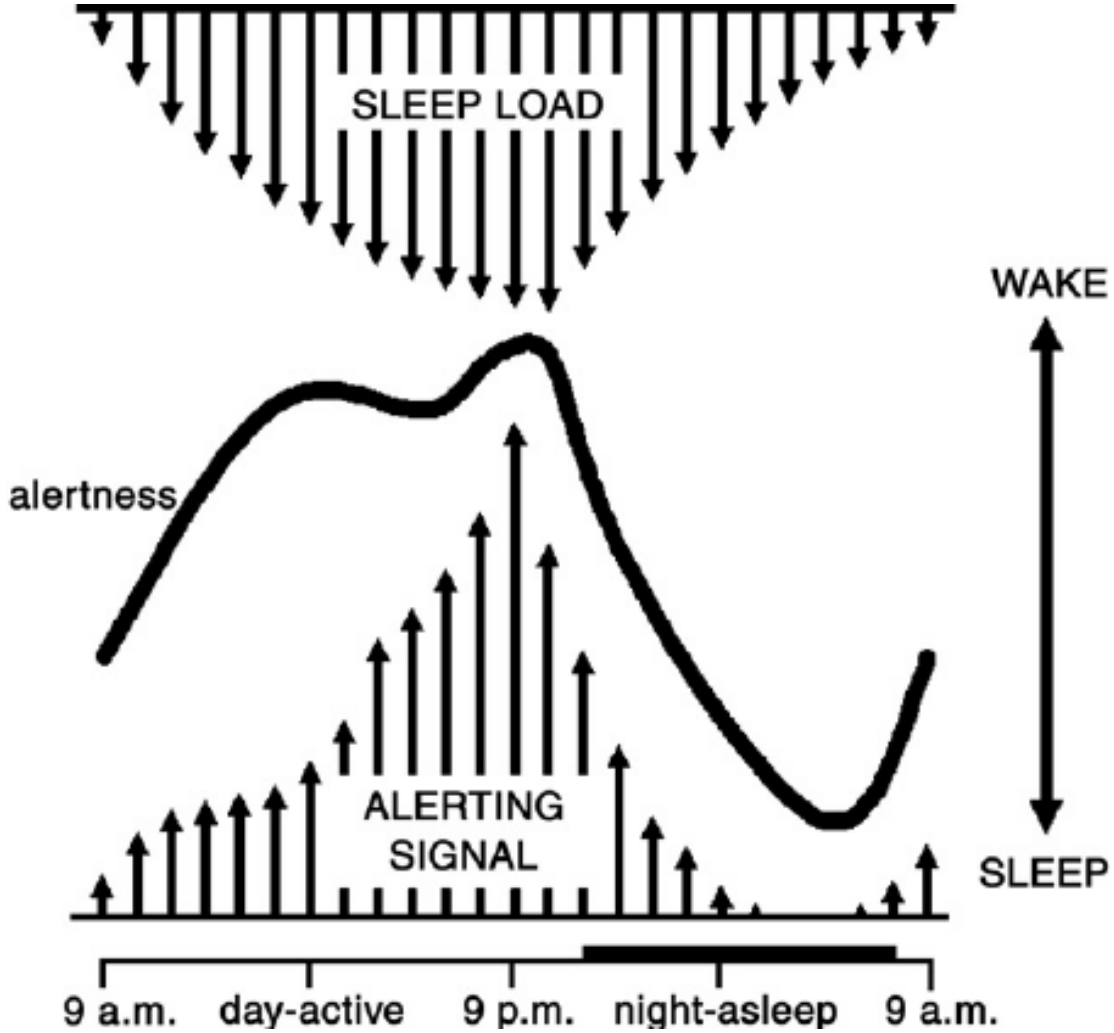
Core genes identified



Zhang R, et al. *Proc Natl Acad Sci U S A*. 2014;111(45):16219-16224.

Sleep Homeostasis Is Not Understood

- Sleep and circadian physiology interact to maintain wakefulness during the day and control sleep during the night
- In the cortex and hypothalamus combined, 4811/11078 = 43% of genes are sleep debt dependent, with about 1,520 (13%) sleep debt specific
- No core gene identified



Mackiewicz M, et al. *Physiol Genomics*. 2007;31(3):441-457.

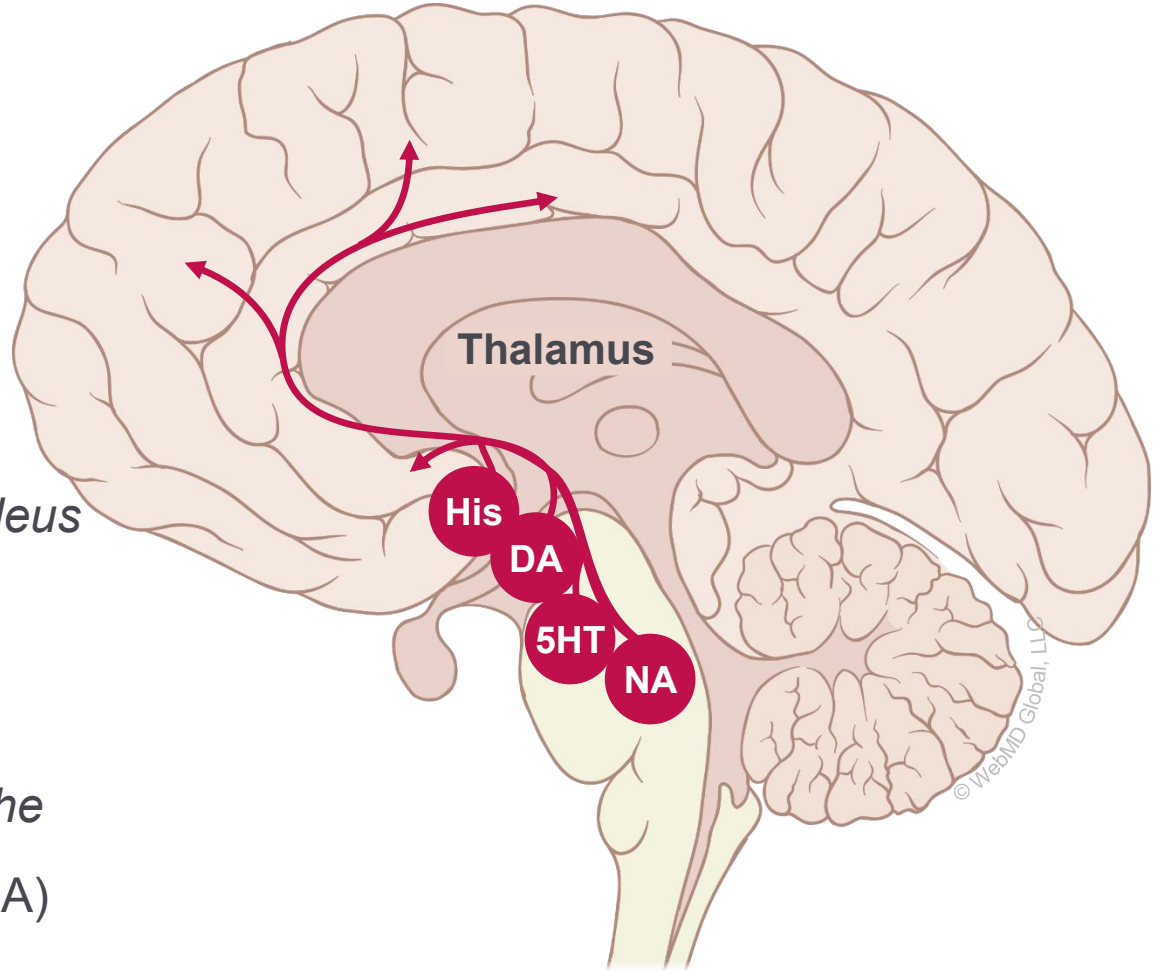
Wake-Promoting Pathways
Monoamines

Histamine (His)
Tuberomammillary nucleus

Dopamine (DA)
Ventral tegmental area

Serotonin (5HT)
Dorsal and median raphe

Noradrenaline (NA)
Locus coeruleus



5HT and NE
- Decreased firing in sleep
- Absent tone in REM sleep

Dopamine:
- Changes in pattern of firing

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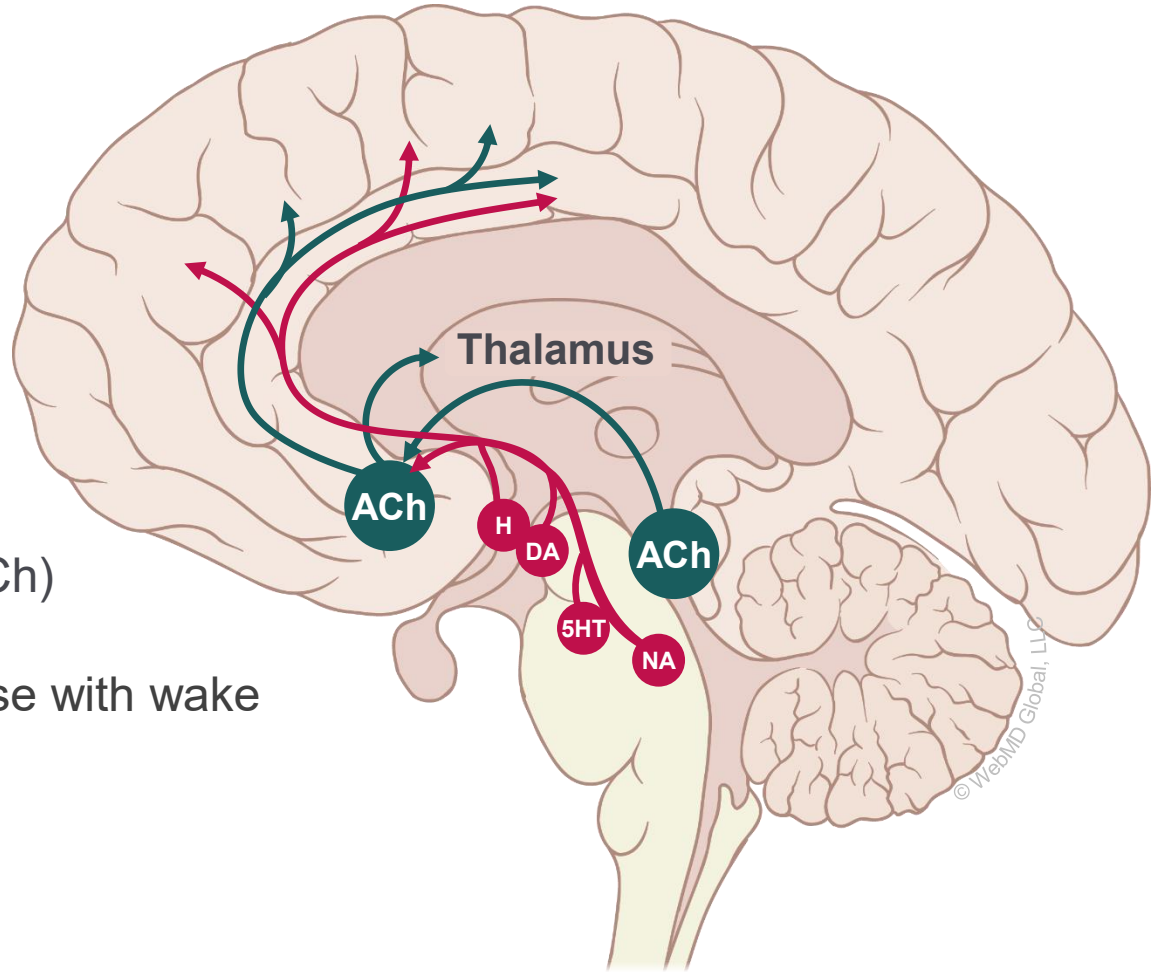
Scammell TE, et al. *Neuron*. 2017;93(4):747-765.

Wake-Promoting Pathways
Cholinergic



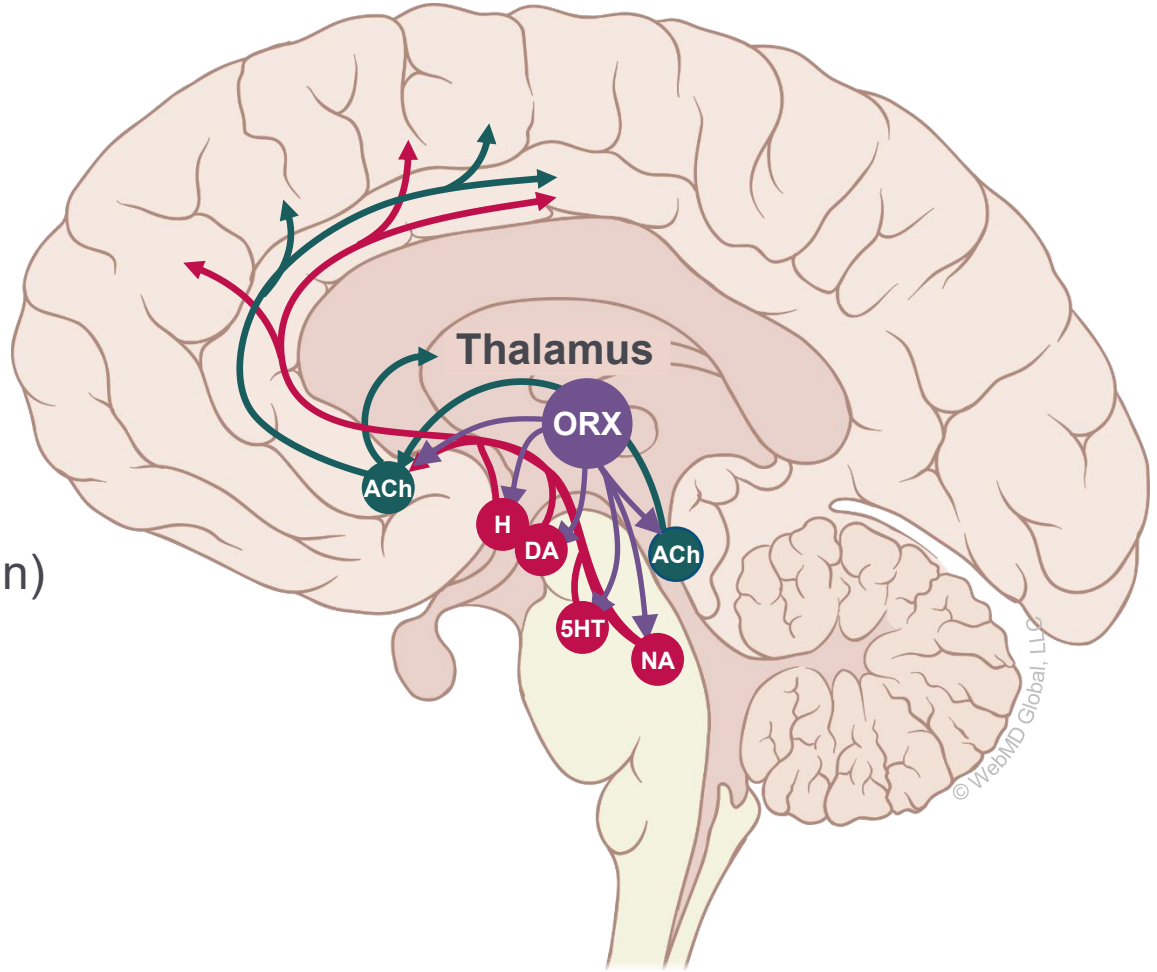
Acetylcholine (ACh)
Basal forebrain
- Increase firing/release with wake

Acetylcholine (ACh)
Pedunculopontine and laterodorsal tegmental nuclei
- Increased firing/release with wake and REM sleep

5HT, serotonin; ACh, acetylcholine; DA, dopamine; H, histamine; NA, noradrenaline.
Scammell TE, et al. *Neuron*. 2017;93(4):747-765.

Wake-Promoting Pathways
Orexin

ORX (orexin/hypocretin)
Lateral hypothalamus

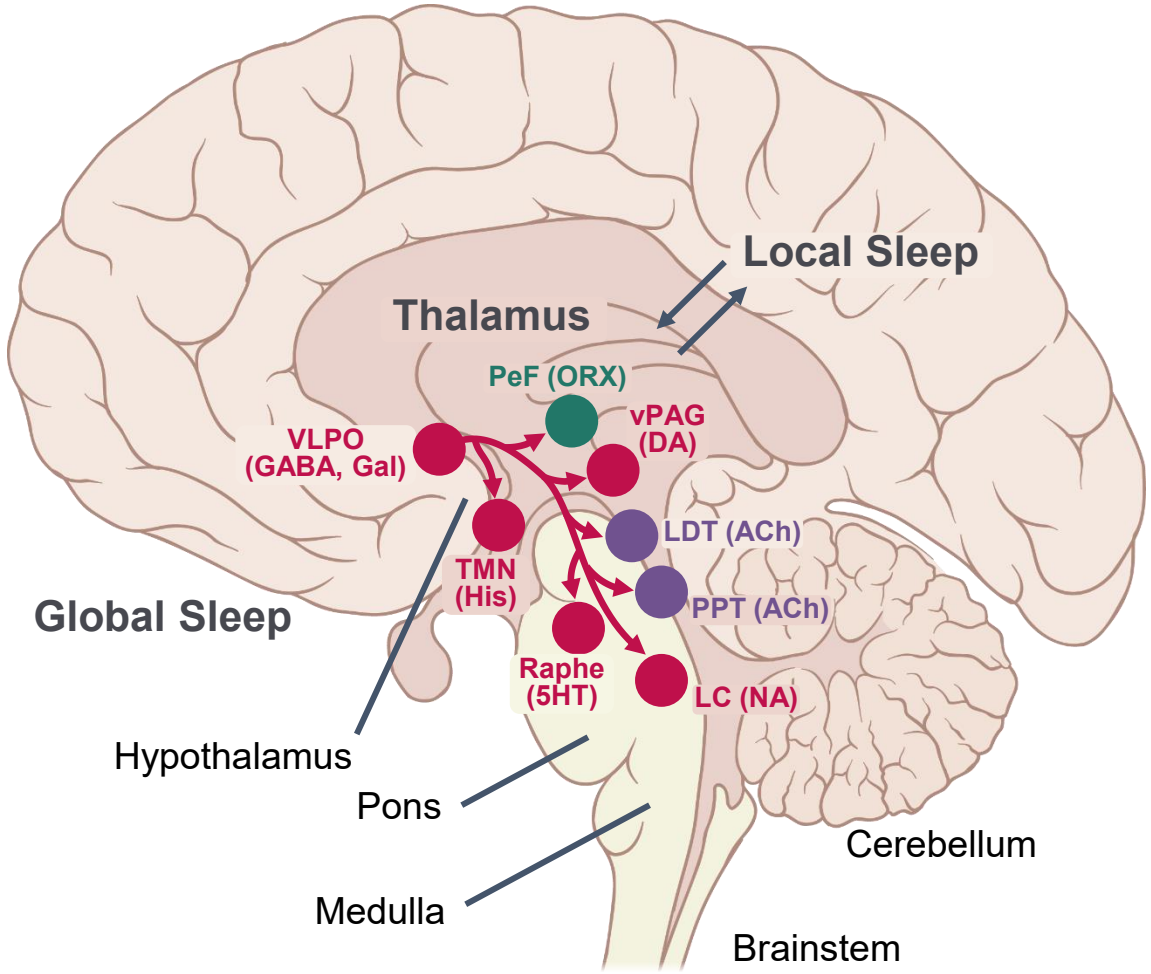


- Increases with sleep deprivation to fight sleepiness
- Increases in the evening with the circadian drive for alertness
- Stimulates acetylcholine and all monoamines
- 2 receptors with different distributions (OX1R and OX2R)

5HT, serotonin; ACh, acetylcholine; DA, dopamine; H, histamine; NA, noradrenaline; ORX, orexin.
Scammell TE, et al. *Neuron*. 2017;93(4):747-765.

Sleep-Promoting Pathways

Preoptic Area, Thalamus; General Excitatory/Inhibitory Tone

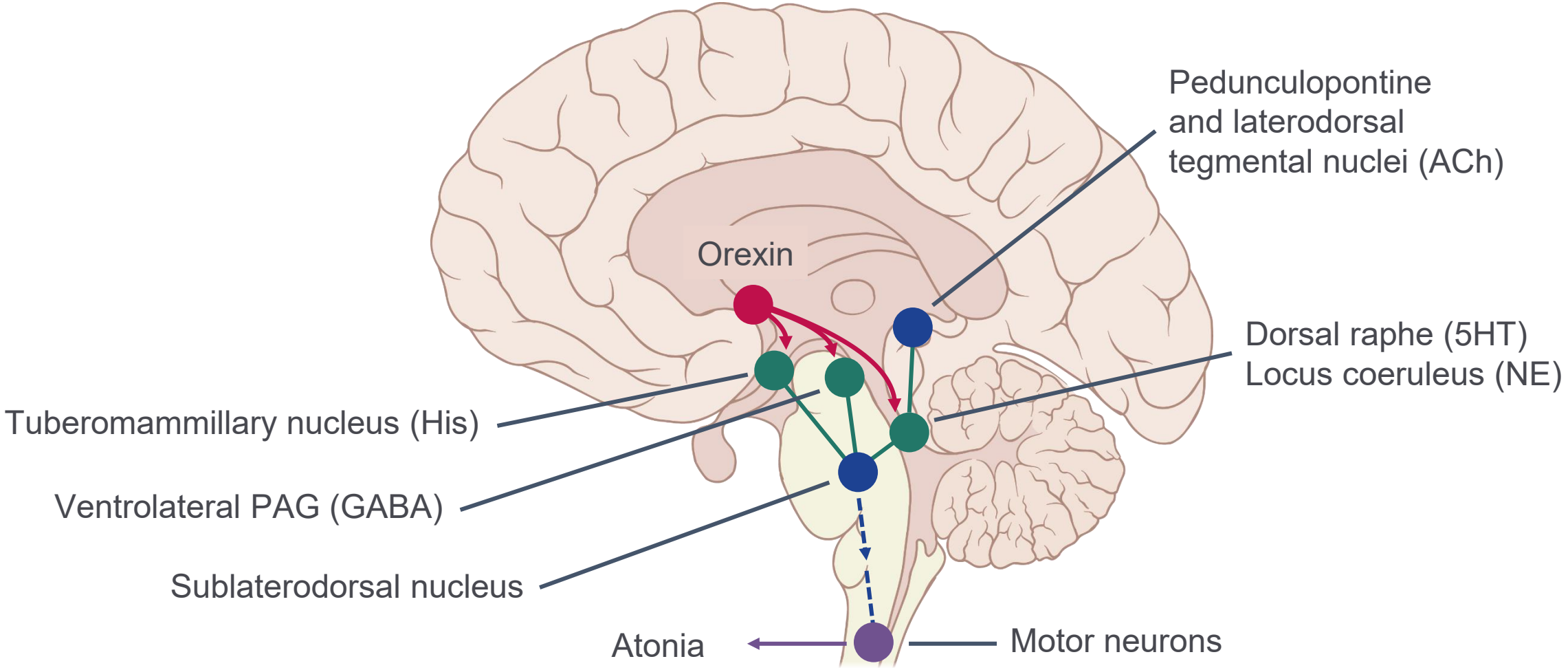


- GABAergic: widespread brain inhibition
- Local sleep through thalamocortical pathways
- VLPO and MnPO GABAergic systems inhibiting wake-promoting neurons

5HT, serotonin; ACh, acetylcholine; DA, dopamine; H, histamine; NA, noradrenaline; ORX, orexin.
Scammell TE, et al. *Neuron*. 2017;93(4):747-765.

REM-Regulating Pathways

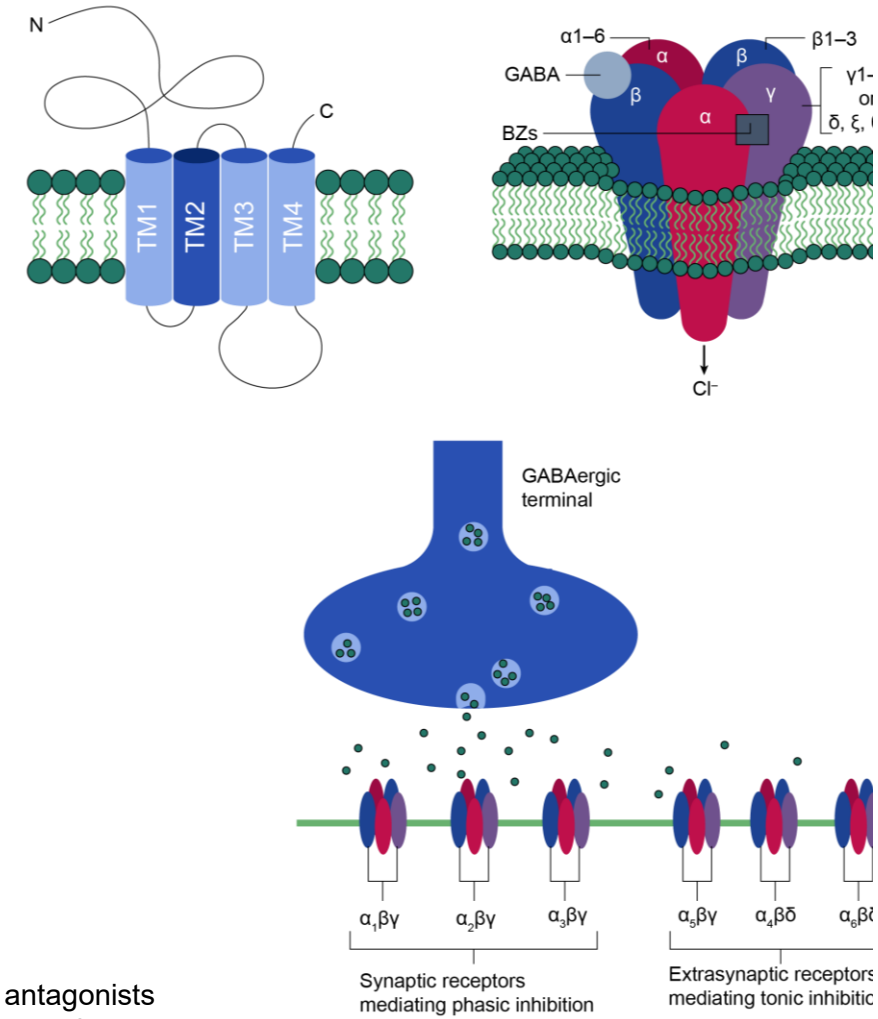
Orexin, Acetylcholine, Monoamines



Monteiro S, et al. *Sleep and Vigilance*. 2018;2:33-38.

Main Sleep-Promoting Drugs

- GABAergic GABA-A chloride channel allosteric enhancers
  - ✓ Barbiturates, alcohol, allo-progesterone
  - ✓ Benzodiazepines
  - ✓ Z-Drugs, zolpidem, zaleplon, zopiclone (some specificity)
- Anti-H1 histamines
  - ✓ OTC Tylenol PM, doxepine, many antipsychotics and tricyclics
- 5HT2 blockers
  - ✓ Trazodone, mirtazapine, often with anti-H1 effects
- GABA-B agonists
  - ✓ GHB, baclofen
- Alpha-2 delta calcium channel modulators/gabapentin
- Orexin antagonists (OXR2/OXR1 dual: DORA)
  - ✓ Suvorexant, lemborexant, daridorexant, vornorexant (Japan)



5HT2 antagonists
H1 antagonists
OXR1/OXR2 antagonists
$\alpha 2\delta$ channel blockers

Farrant M, Nusser Z. *Nat Rev Neurosci*. 2005;6(3):215-229.

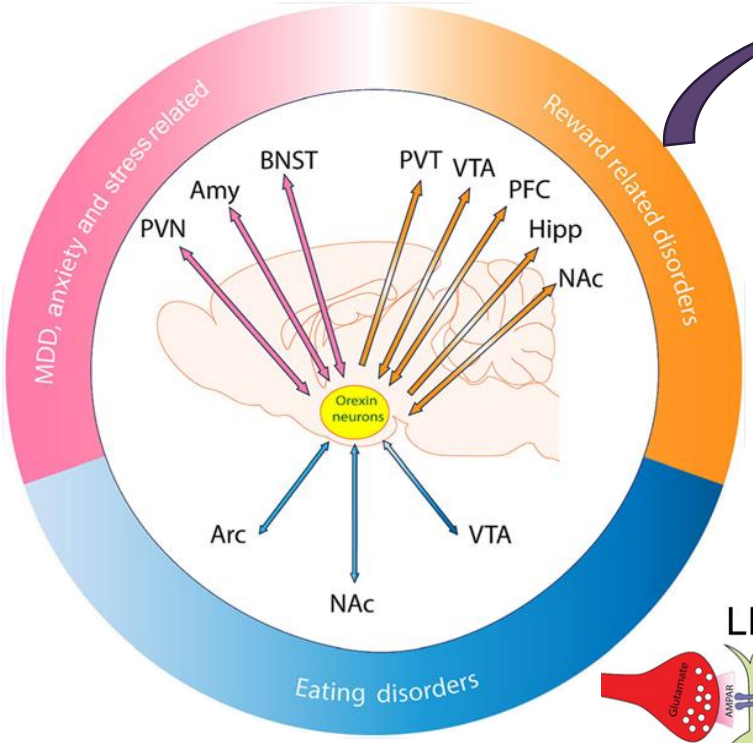
Main Wake-Promoting Drugs

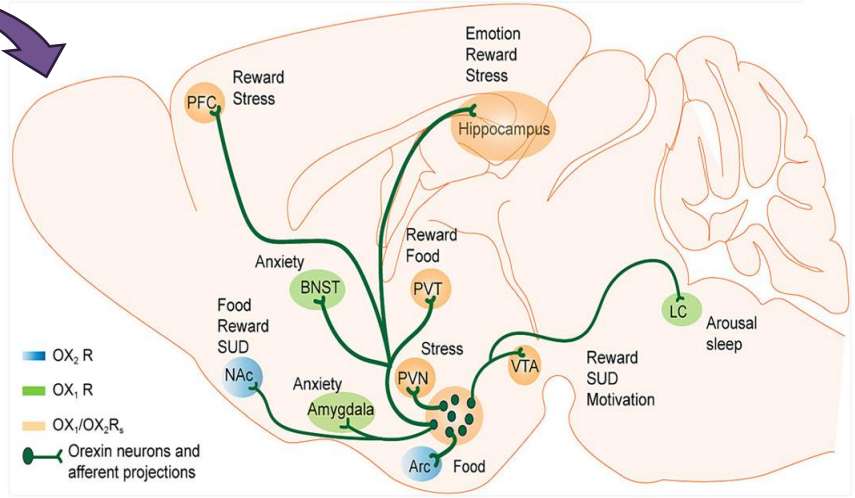
- Dopaminergic-releasing agents (some with adrenergic effects)
  - ✓Methylphenidate
  - ✓Amphetamine
- Dopamine reuptake blockers (some with adrenergic effects)
  - ✓Solriamfetol
  - ✓Modafinil
- Adenosine A1 blockers
  - ✓Caffeine
- Orexin OXR2 agonists (none with OXR1 effects)
  - ✓Oveporexton
  - ✓Alixorexton
  - ✓Others to follow

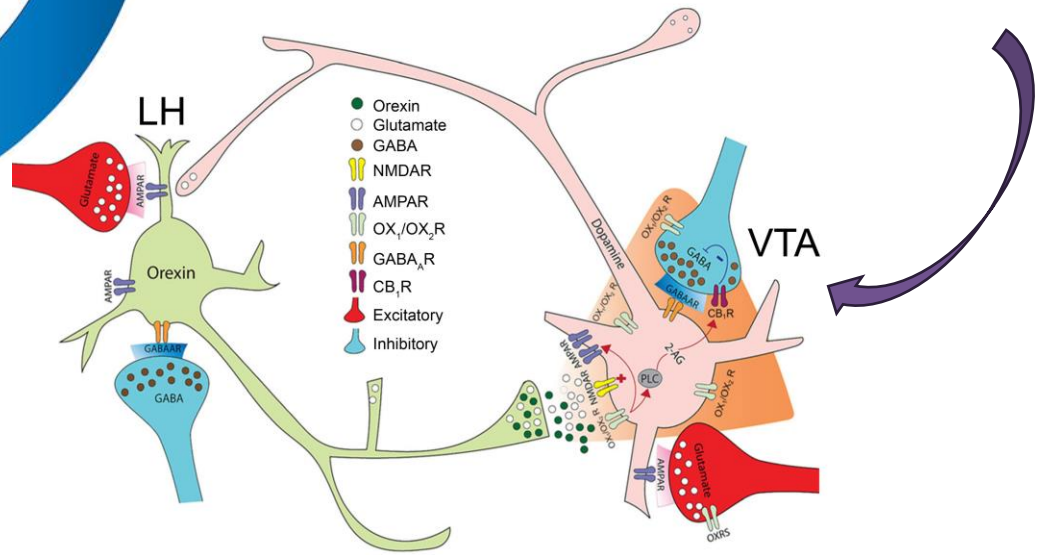
The Sleepy Patient in Psychiatric Disorders: Psychiatric Insights

Roger S. McIntyre, MD, FRCPC

Orexin as a Brain-Wide Integrator of Reward, Stress, and Metabolic Control





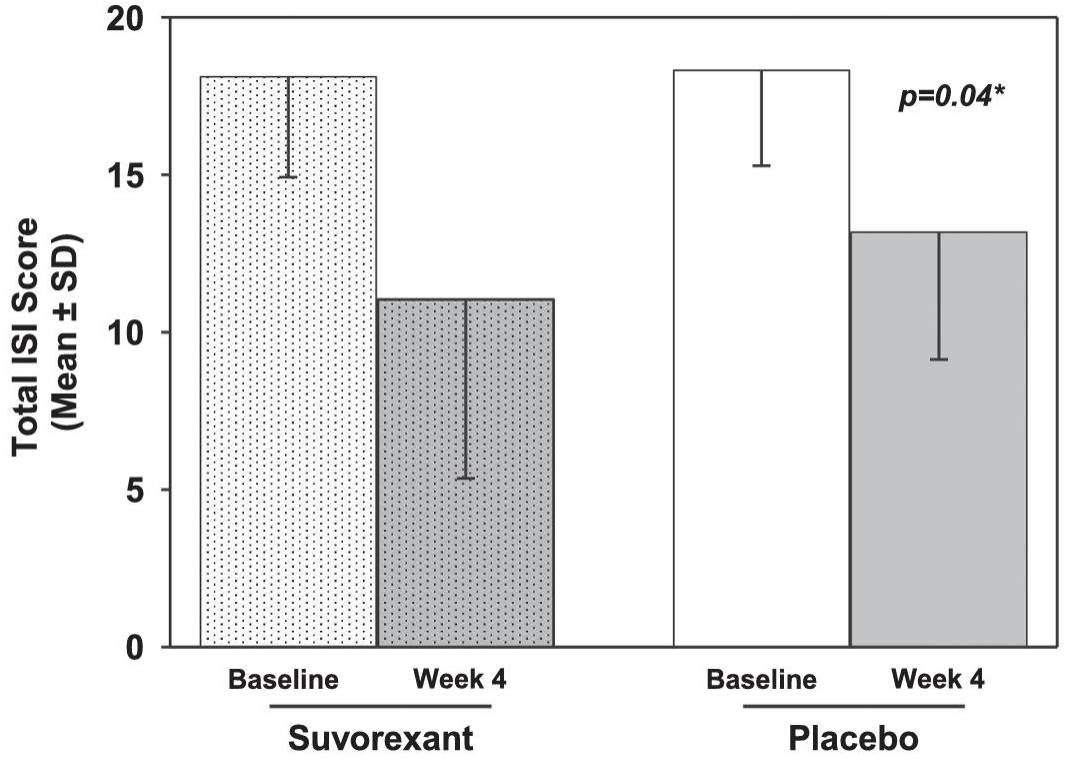


- Orexin links reward metabolism mood and stress circuits
- Ventral tegmental area is a key orexin target for reward seeking
- Orexin acts mainly as a modulatory non-synaptic signal
- OX1 and OX2 receptors vary by region enabling specialized effects

Mohammadkhani A, et al. *Br J Pharmacol*. 2024;181(22):4430-4449.

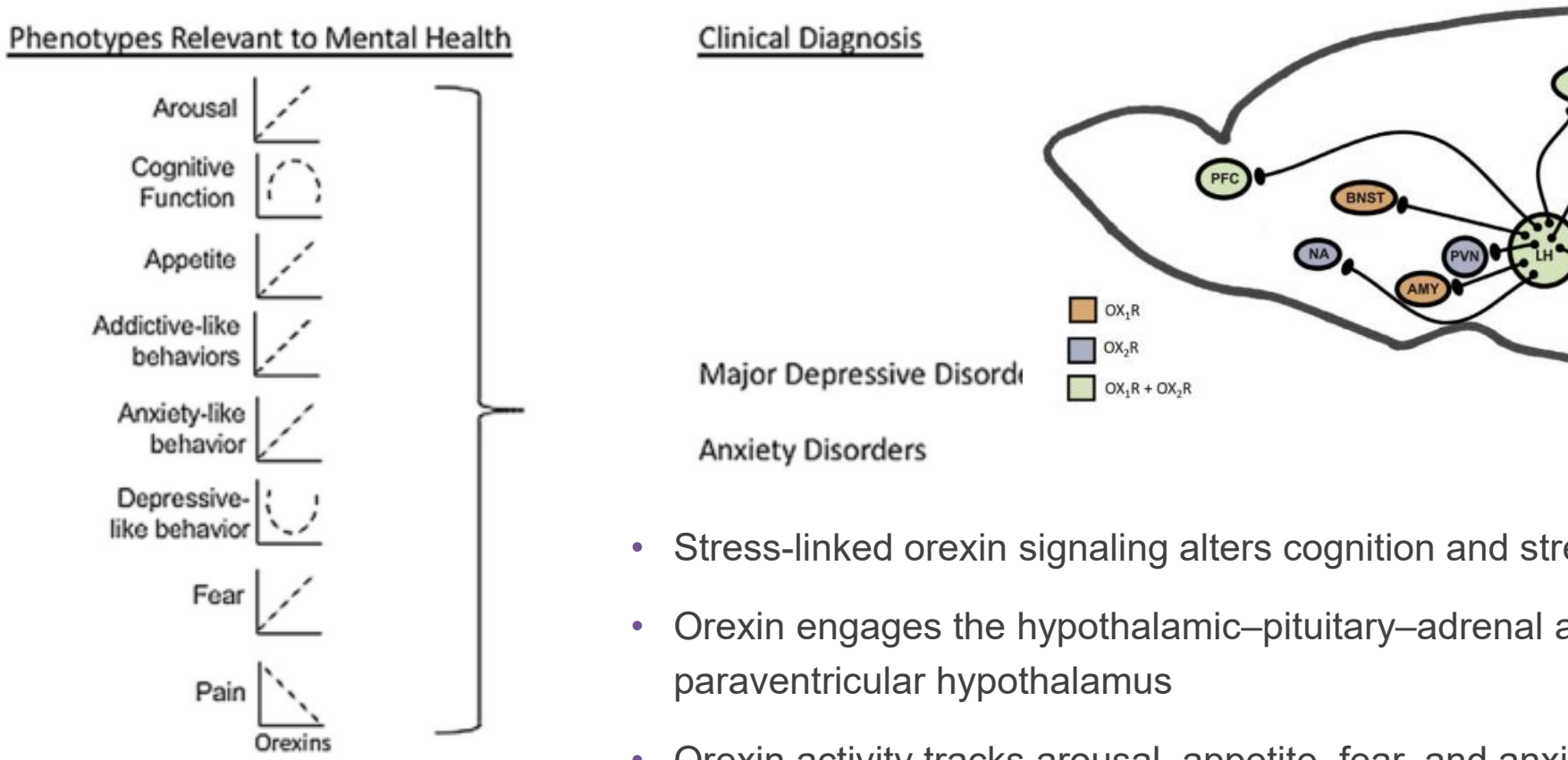
A Double-Blind, Randomized, Placebo-Controlled Trial of Suvorexant for the Treatment of Vasomotor Symptom–Associated Insomnia Disorder in Midlife Women

Insomnia severity assessed using Insomnia Severity Index (ISI) at baseline and end of treatment (Week 4) by suvorexant (n = 27) and placebo (n = 29) treatment arm



Rahman SA, et al. *Sleep*. 202245(3):zsac007.

Orexin Stress Circuitry Shapes Mood and Anxiety



- Stress-linked orexin signaling alters cognition and stress-induced reward seeking
- Orexin engages the hypothalamic–pituitary–adrenal axis via the paraventricular hypothalamus
- Orexin activity tracks arousal, appetite, fear, and anxiety- and depressive-like phenotypes linked to major depressive disorder and anxiety disorders

Grafe LA, Bhatnagar S. *Front Neuroendocrinol*. 2018;51:132-145.

The Impacts of Trauma and Stress on Orexin Signaling and Expression

Acute trauma/stress exposure

- ↑ Orexin neuronal activation in the lateral hypothalamic area
- ↑ Orexin concentrations in the hypothalamus, brainstem, thalamus, and amygdala
- ↑ Prepro-orexin, OX1R, in the posterior hypothalamus
- No significant change in OX2R

Chronic trauma/stress exposure

- ↑ Orexin expression and concentration in the hypothalamus
- Prior stress exposure is associated with increased orexin receptor responsivity

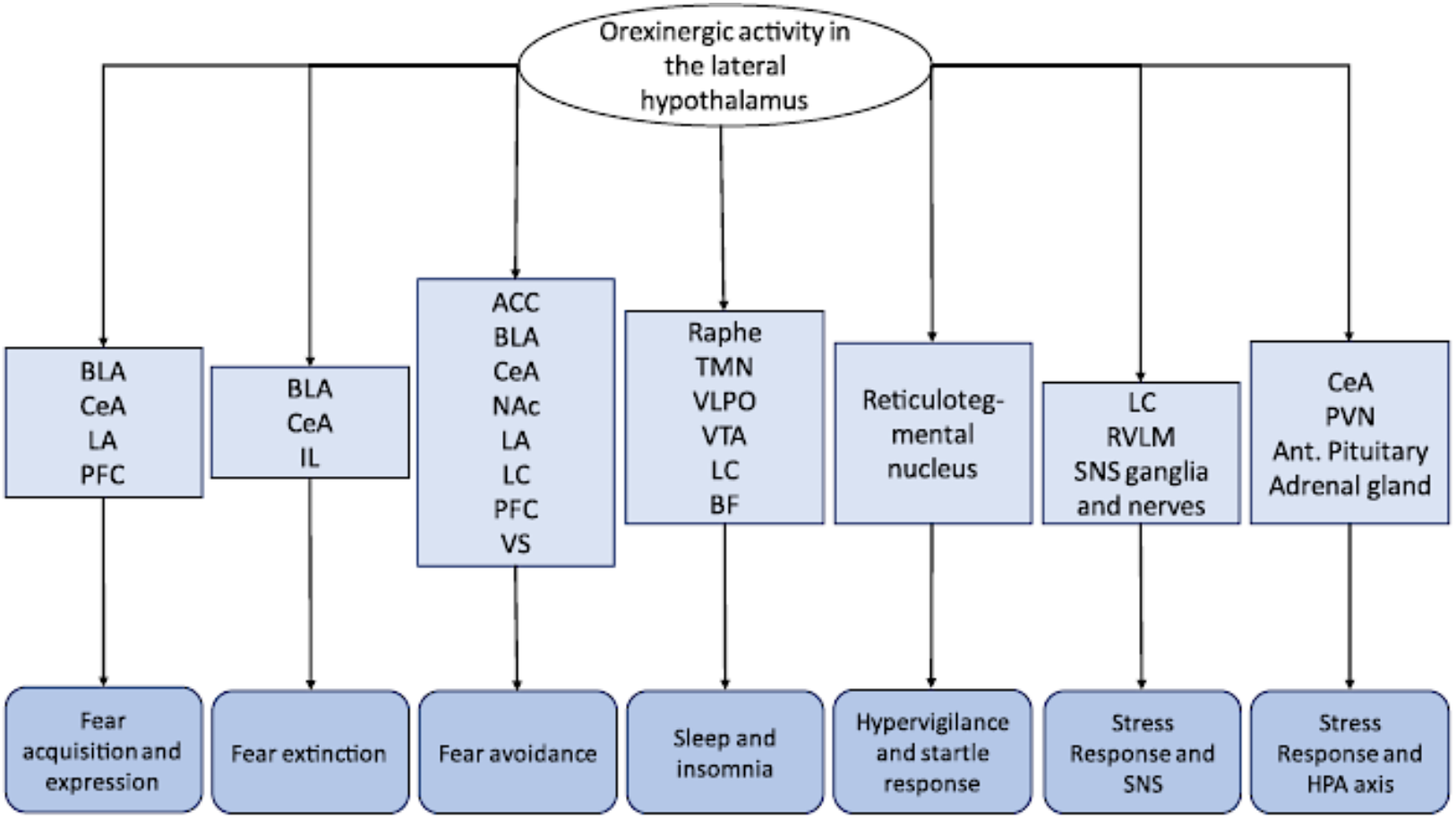
Childhood trauma exposure

- Limited evidence
- ↑ Plasma orexin B in adults
- No significant change in plasma orexin A
- Associated with Major Depressive Disorder

TOTAL CME

Xiao K, et al. *Psychiatry Res.* 2026;363:117222.

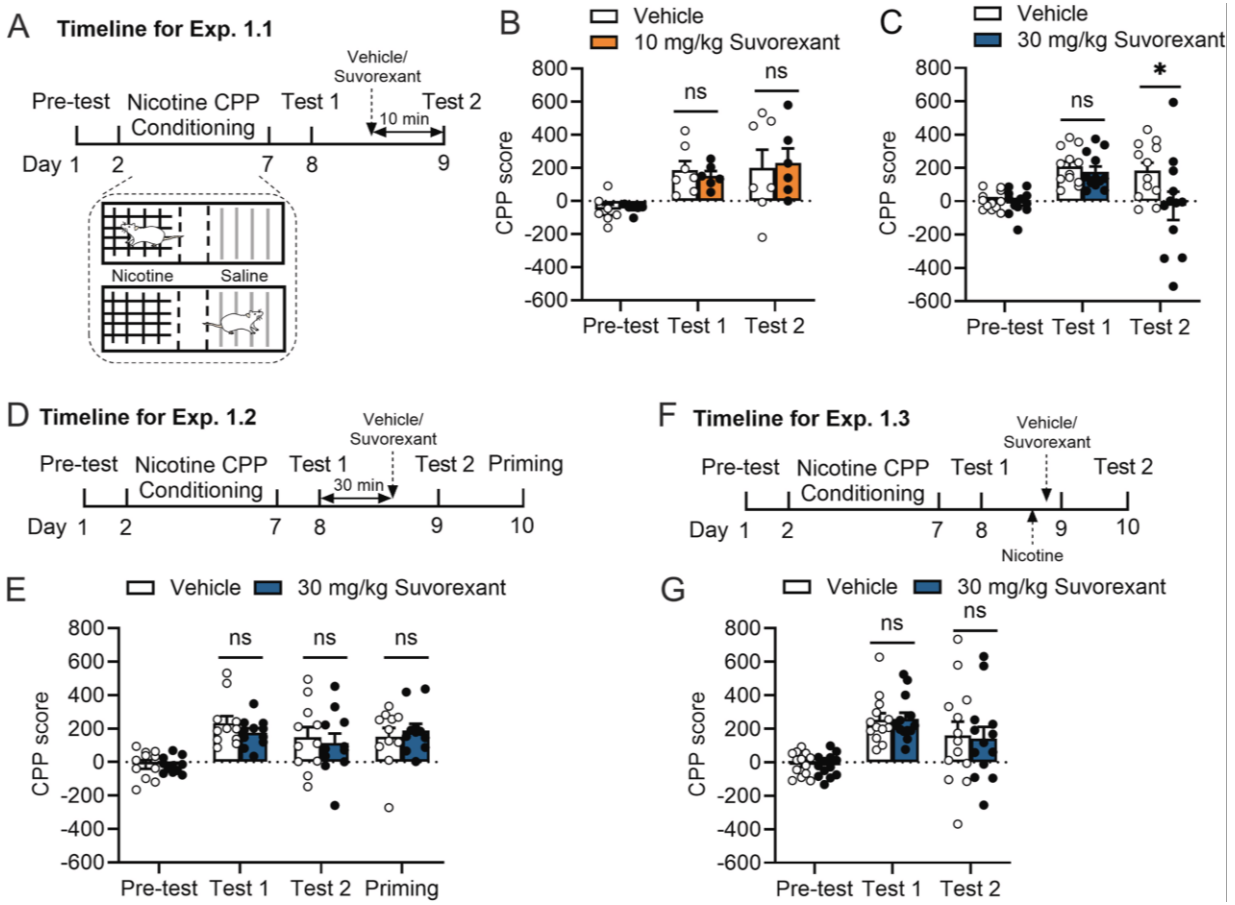
Orexigenic Outputs From Lateral Hypothalamus



Kaplan GB, et al. *Brain Res Bull.* 2022;186:106-122.

Suvorexant Disrupts the Expression and Retrieval of Nicotine Reward Memory

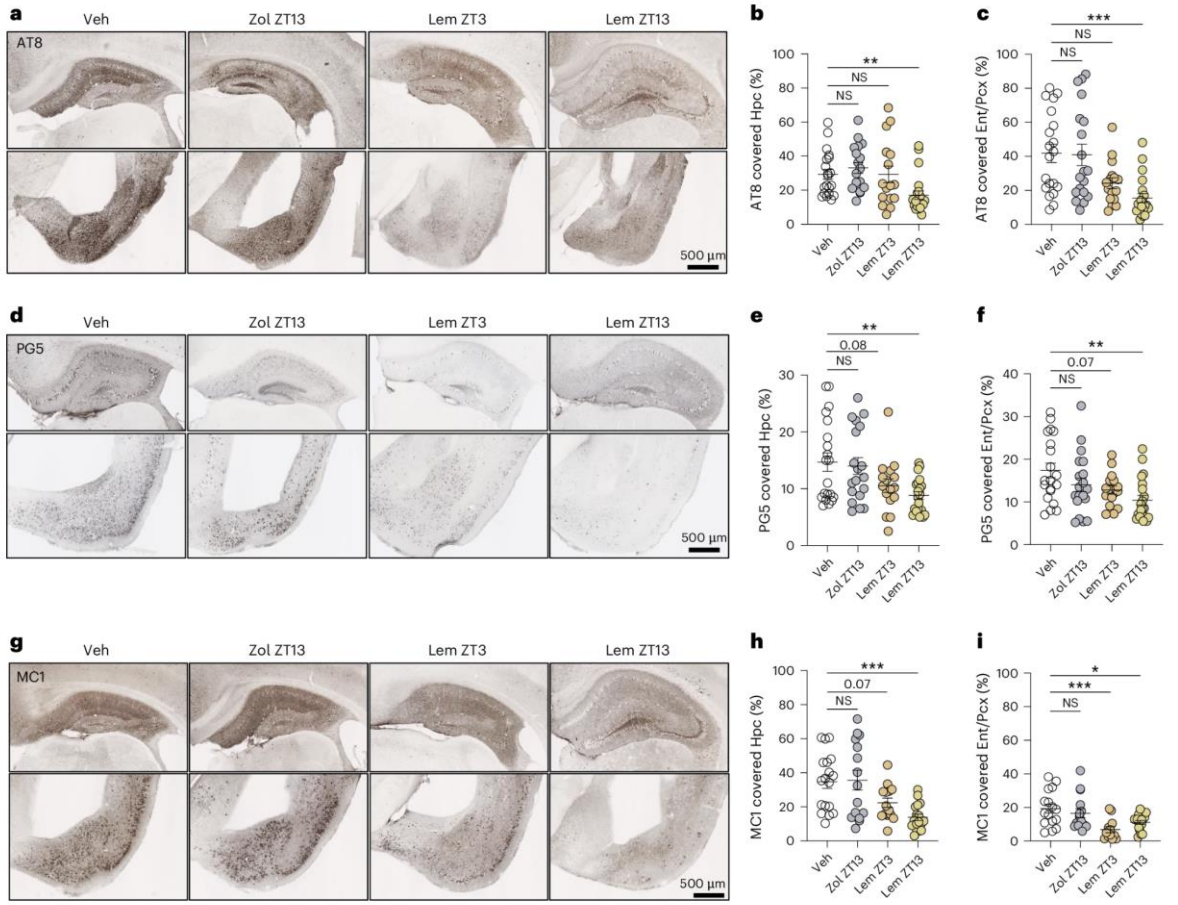
Suvorexant attenuated the retrieval but had no effect on the reconsolidation of nicotine reward memory



Cui P, et al. *Neuropharmacology*. 2025;276:110523.

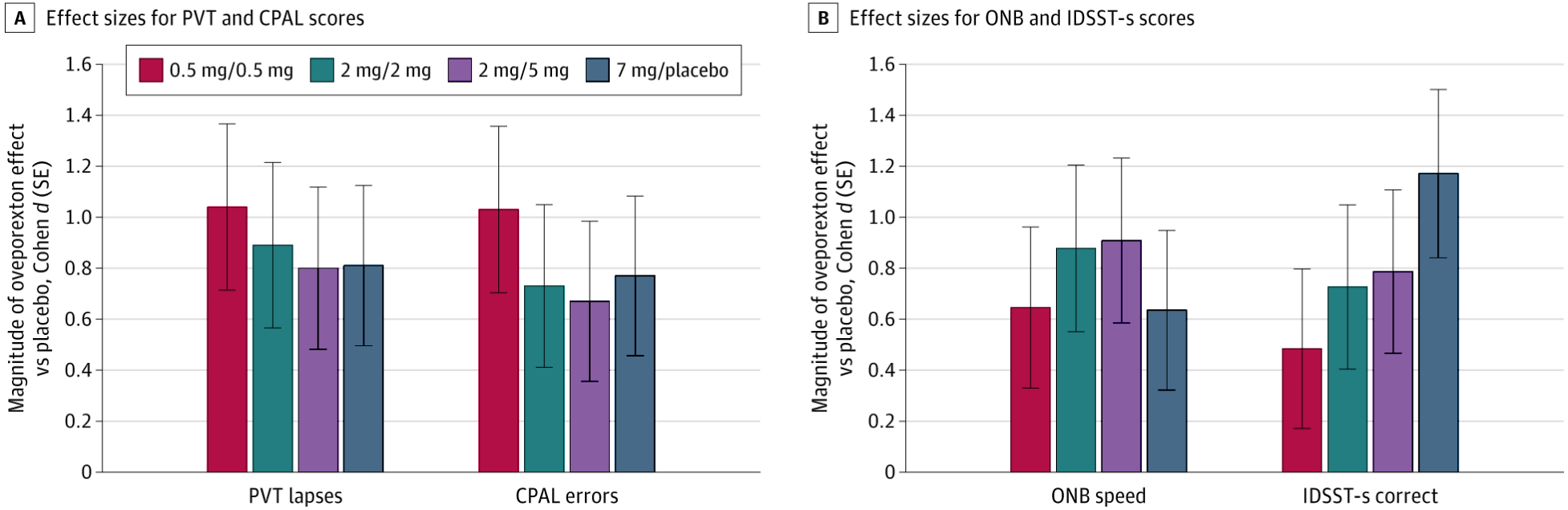
Lemborexant Ameliorates Tau-Mediated Sleep Loss and Neurodegeneration in Males in a Mouse Model of Tauopathy

Lemborexant treatment reduces hyperphosphorylated pathological tau in male P301S/E4 mice



Parhizkar S, et al. *Nat Neurosci*. 2025;28(7):1460-1472.

Oveporexton Effect Size on Cognitive Measures

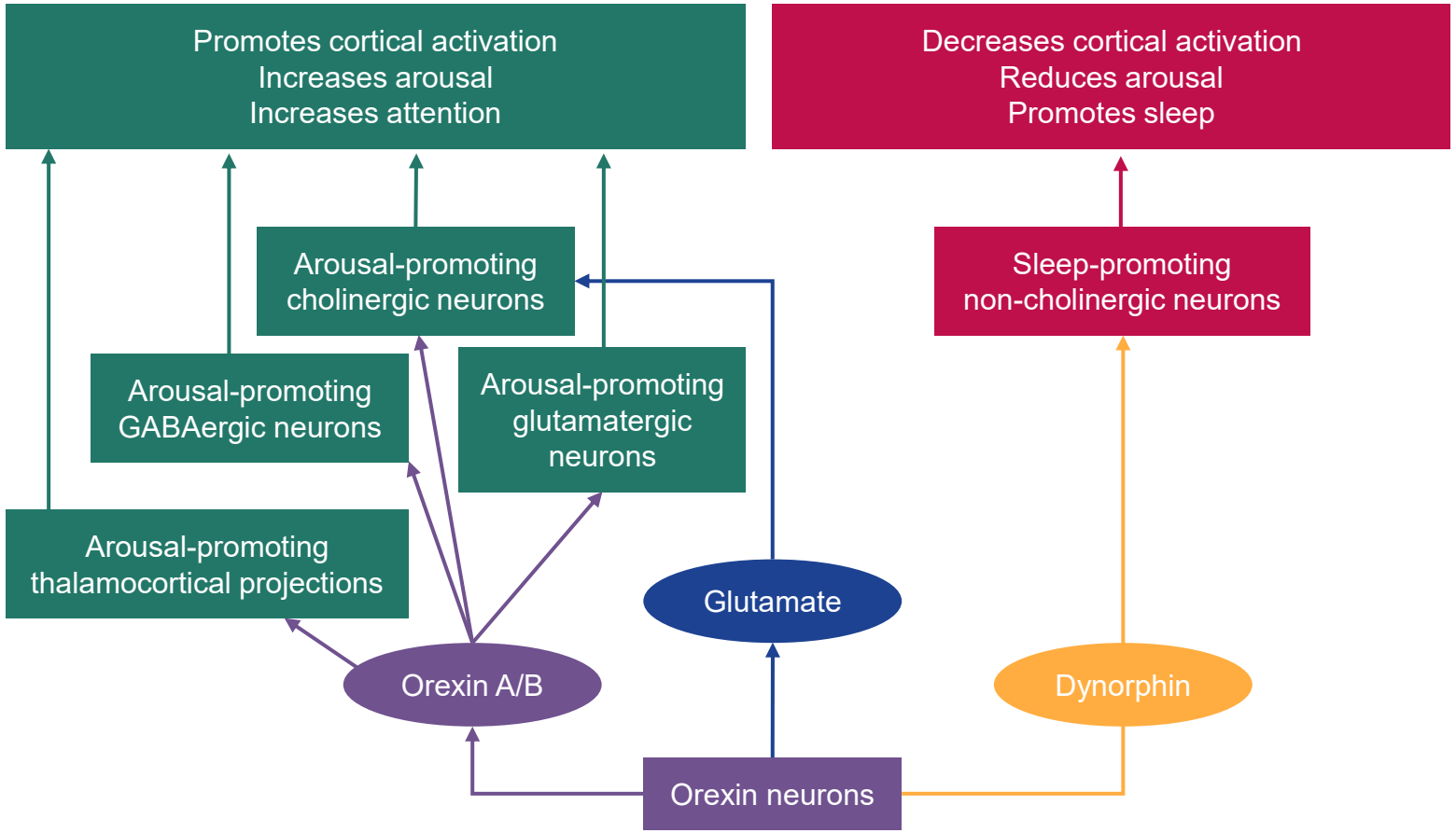


Effect sizes from constrained longitudinal data analysis and mixed-effects model for repeated measures models. The magnitude of the difference in mean changes from baseline with each dose of oveporexton compared to placebo was expressed as an effect size (Cohen *d*), where *d* = 0.2-<0.5 was classified as small, *d* = 0.5-<0.8 as medium, and *d* ≥0.8 as large effects. Signs for the effect sizes summarizing treatment group differences for Psychomotor Vigilance Task (PVT) lapses, Continuous Paired Associate Learning (CPAL) errors, and One Back test (ONB) logarithmic base 10 transformation (log10ms), where increasing values indicated worsening performance, were reversed so that all positive effect sizes indicated a drug-related improvement and vice versa. IDSST-s indicates International Digit Symbol Substitution Test–symbols.

TOTAL CME

Lammers GJ, et al. *JAMA Neurology*. 2026;83(2):145-152.

Orexin as the Arousal Attention Sleep Switch



- Orexin increases cortical activation arousal and attention
- Orexin recruits cholinergic gamma-aminobutyric acid and glutamatergic arousal networks
- Orexin neurons co-release glutamate for rapid excitation
- Dynorphin counterbalances arousal to promote sleep pathways

Toor B, et al. *Front Neurol Neurosci*. 2021;45:38-51.

Daridorexant for Adults with Attention Deficit Hyperactivity Disorder (ADHD) and Insomnia Disorder

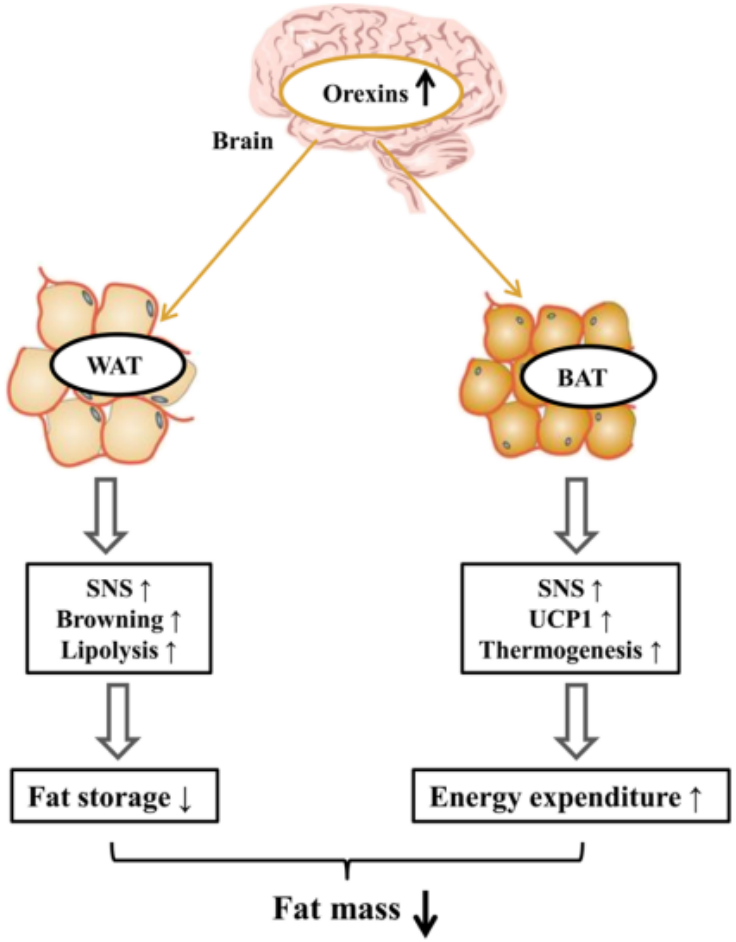
Secondary cognitive outcome measures in ADHD patients before and after daridorexant treatment.

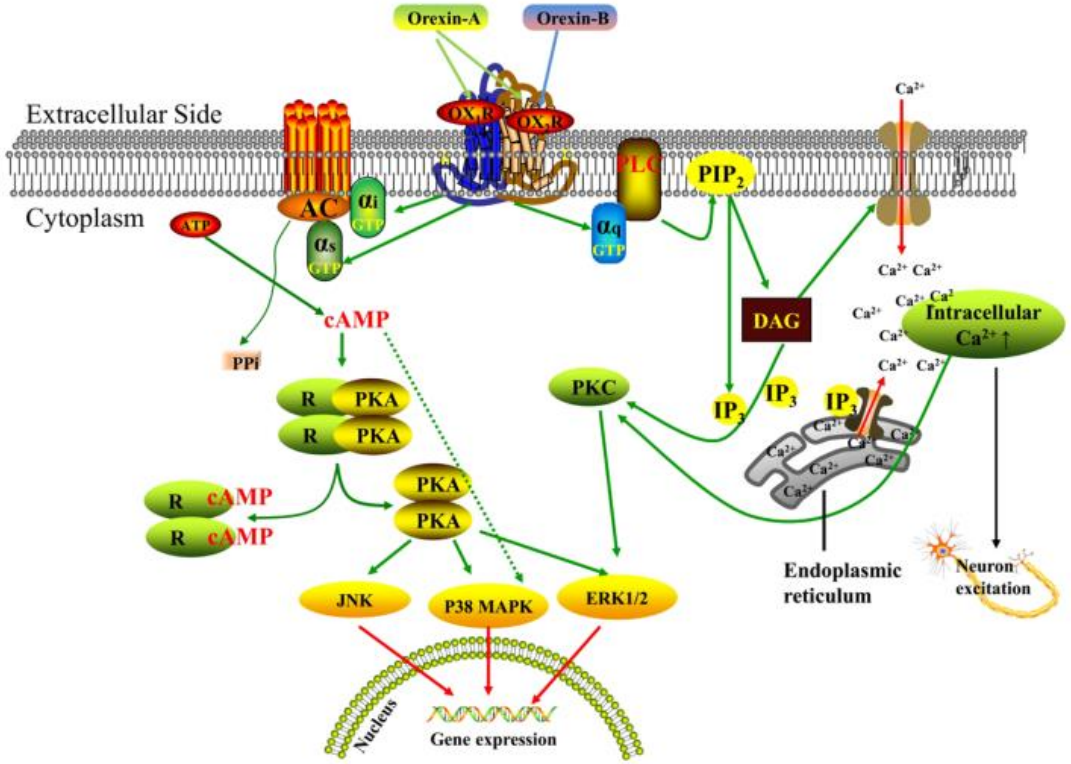
Measure	Pre-treatment (n: 24)	Post-treatment (n: 24)	Z	P	Effect Size (r)
detectability	52.5 [44.75; 67.25]	52 [43; 56.75]	−1.417399	0.156366	0.28
omissions	46 [45; 50.5]	46 [45; 48]	−1.047965	0.294655	0.21
commissions	55 [47.5; 67.5]	53 [43.25; 62.75]	−1.130361	0.258324	0.23
perseverations	48 [46; 58]	48 [46; 58.75]	−0.222828	0.823669	0.04
HRT	44 [40; 46.75]	45 [38.5; 52]	0.244154	0.807112	0.04
HRT_SD	49.5 [42.5; 62.25]	47.5 [42.25; 52.75]	−2.178072	0.029401*	0.44
variability	48.5 [43.25; 59.5]	47.5 [44.25; 52.25]	−1.720236	0.085390	0.35
HRT_block_change	51 [45.25; 62]	49.5 [43.75; 54]	−2.085113	0.037059*	0.42
HRT_ISI_change	47 [40; 52.5]	50 [43.5; 56]	2.059140	0.039481*	0.42

Note. Data are expressed as median [interquartile range] for all variables. HRT = hit reaction time; SD = standard deviation; ISI = inter-stimulus interval. *$p < .05$. None of the pre–post changes survived FDR correction.

Grasso G, et al. *Compr Psychiatry*. 2026;148:152700.

Orexin Signaling Links Receptor Pathways to Energy Balance





- Orexin A engages both receptors; orexin B favors receptor 2
- G protein coupling drives cyclic AMP and phospholipase C signaling
- Calcium and kinase cascades shape gene expression and excitability
- Central orexin increases sympathetic fat burning via white fat browning and brown fat thermogenesis

AMP, adenosine monophosphate.

Liu L, et al. *ACS Omega*. 2020;5(1):547-555.

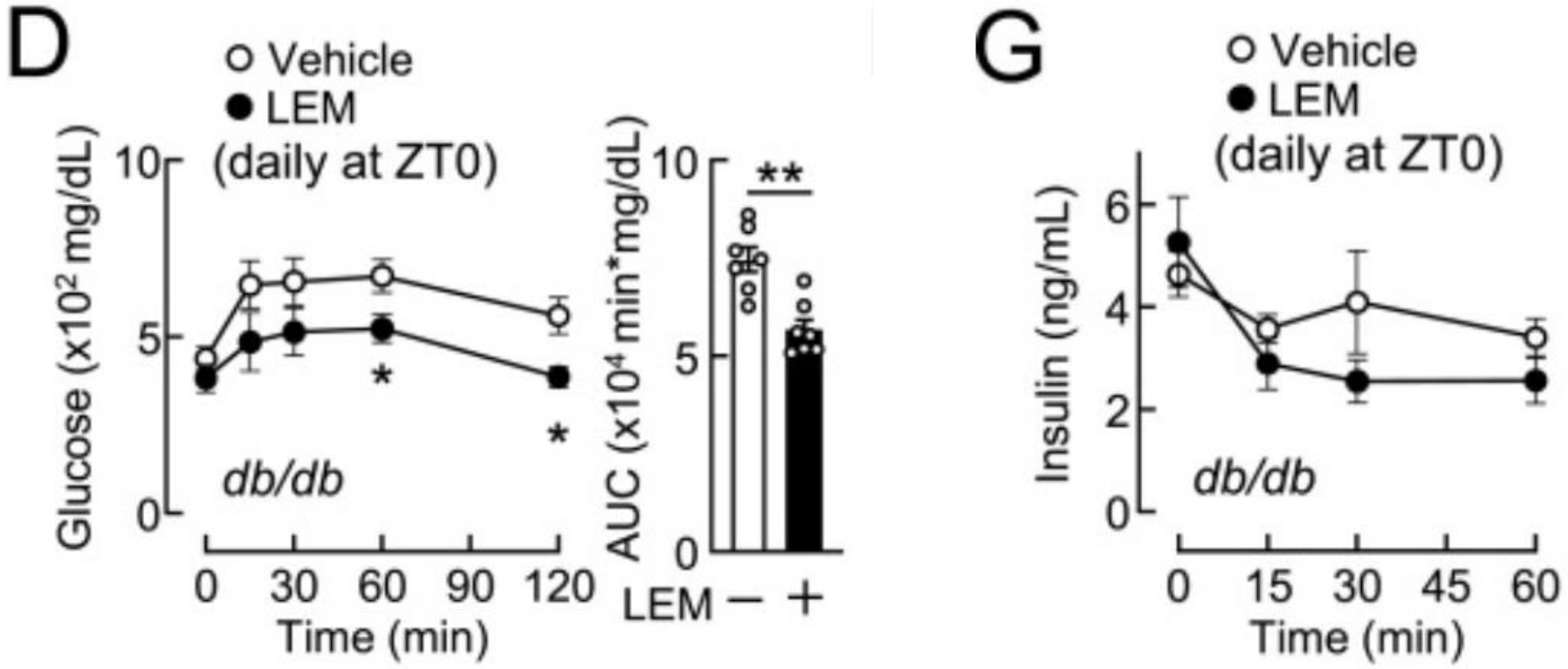
Evidence Implicating Orexins in Glucose-Insulin Homeostasis

- Orexins are produced and orexin receptors are expressed in the endocrine pancreas
- Orexins facilitate the transition of white adipose tissue to brown adipose tissue
- Orexins govern energy expenditure
- Orexins influence gluconeogenic activity
- Orexins modulate sleep architecture (ie, REM and non-REM sleep)
- Orexin receptor antagonism improves glucose-insulin homeostasis

Wong S, et al. *CNS Spectr*. 2026;31(1):e4.

Resting-Phase Administration of Lemborexant Ameliorates Sleep and Glucose Tolerance in Type 2 Diabetic Mice

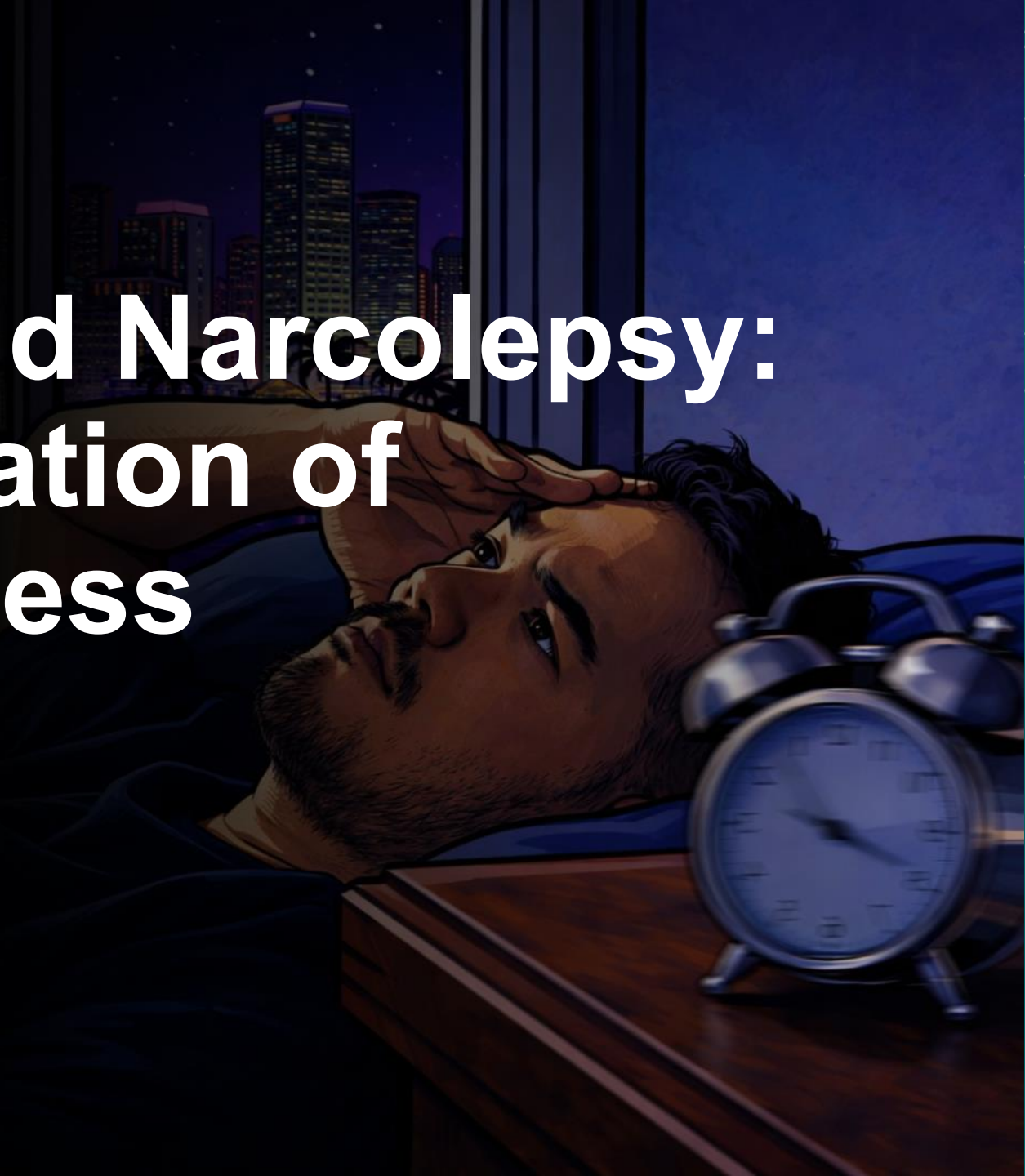
Improving effects of daily resting-phase administration of lemborexant on glucose intolerance in *db/db* mice



Tsuneki H, et al. *Eur J Pharmacol*. 2023;961:176190.

Hypersomnia and Narcolepsy: Clinical Presentation of Daytime Sleepiness

Emmanuel Mignot, MD, PhD



Typical Case: Narcolepsy or Narcolepsy-Like

- Daytime sleepiness manifests as:
  - ✓Sleep attacks, automatic behaviors
  - ✓Feels better after napping, but does not last
- Cataplexy:
  - ✓Brief muscle weakness, triggered by mirth, joking
- REM sleep dysregulation:
  - ✓Vivid dreaming, persistent memory of it, sometimes “half-sleep hallucinations”
  - ✓Sleep paralysis—but many people without narcolepsy have that
- Insomnia in the middle of the night, restless sleep
- Weight gain, especially if rapid onset

> Cause: Orexin deficiency

Diagnosis Can Be Biochemical or Electrophysiological

- HLA-DQB1*06:02 positive vs 25% population
- Low CSF orexin, gold standard, if HLA positive
- PSG-MSLT consistently positive (92% vs 4% false positive)
  - ✓PSG SOREMP (REM latency ≤15 min)
  - ✓MSL <8 min
  - ✓≥2 SOREMP naps
- Deep learning of PSG indicates mixed REM sleep/stage 1 stages

> Cause: Orexin deficiency

TOTAL CME

PSG-MSLT, polysomnography multiple sleep latency test; SOREMP, sleep-onset REM periods.

Narcolepsy Type 2 (NT2) or Idiopathic Hypersomnia (IH)

- Daytime sleepiness manifests as
  - ✓ Sleep inertia in the morning and after naps
  - ✓ Nonrestorative naps
  - ✓ Brain fog
- No cataplexy
- REM sleep dysregulation is variable

2 variants

- Long sleep duration: >11 hrs/day with prolonged naps
- Or hypersomnolence MSLT SL ≤ 8 min (with ≥2 SOREMP = NT2; ≤2 SOREMP = IH)
  - Note: 23% of population has SL ≤8 min; not stable trait

Sometimes hard to differentiate from depression or clinophilia

Periodic Hypersomnia (Kleine-Levin Syndrome)

- Teen or young adult
- Sudden episode of 15-20 hrs daily sleep lasting a few weeks (often hospitalized) that reverses to normal but then reoccurs unpredictably
- Profound cognitive abnormalities
  - ✓Severe feeling of derealization
  - ✓Mutism, does not talk
  - ✓Disinhibition, infantile behavior, hyperphagia, hypersexuality
- Entirely reversible but reoccur randomly
- Spontaneously improves ~10 years after onset; disease “burns” out

> Cause: Genetics suggest overlap with bipolar and circadian abnormalities; often responds to lithium

Treating the Sleepy Patient

Emmanuel Mignot, MD, PhD

Roger S. McIntyre, MD, FRCPC

Narcolepsy Type 1, NT2, and IH

NT1

Orexin deficiency

Diagnosis
- **Cataplexy**
- MSLT SL<8 ≥2 SOREMP
- HLA-TCR factors
- Deep learning predictions
- Autoimmune basis

Treatment
- Treated with stimulants, antidepressants, sodium oxybate

≠

NT2

No simple cause

Diagnosis
- MSLT SL <8 ≥2 SOREMP
- Not reproducible

Treatment
- Treated with stimulants, sodium oxybate

=

IH

No simple cause

Diagnosis
- MSLT SL <8 ≥2 SOREMP
- Not reproducible

Treatment
- Treated with stimulants, sodium oxybate

OTHER DISORDERS

eg, sleepiness in depression and treated OSA
- Treatment with stimulants (on or off label)

0.05% (US ~175,000): The obvious

1%-4% (US ~17M): The main opportunity

TOTAL CME

Management of Narcolepsy or Hypersomnia

Definite cataplexy or orexin deficiency

Behavioral Methods:
- Scheduled naps
- Fixed wake-up time
- Regular sleep schedule

No/Atypical Cataplexy No orexin deficiency

Oxybate (GHB): effective on all symptoms; variable administration (bedtime, 2-3x)

May add **modafinil, solriamfetol, methylphenidate, amphetamine, pitolisant** for *sleepiness* as described on the right side of slide

May add additional *anticataplexy* agents:
- **Venlafaxine XR** 75-300 mg/day
- **Fluoxetine** 20-60 mg/day
- **Pitolisant** 17.8-35.6 mg/day

If no response, reevaluate cataplexy; measuring CSF orexin

Treat sleepiness with **modafinil** 200-600 mg/day; **R-modafinil** up to 250 mg/day; **pitolisant** up to 35.6 mg/day; **solriamfetol** up to 150 mg; can add pulse 5-10 mg **methylphenidate**

If insufficient consider:

Oxybate 4.5 g to 9 g

Methylphenidate SR up to 60 mg/day

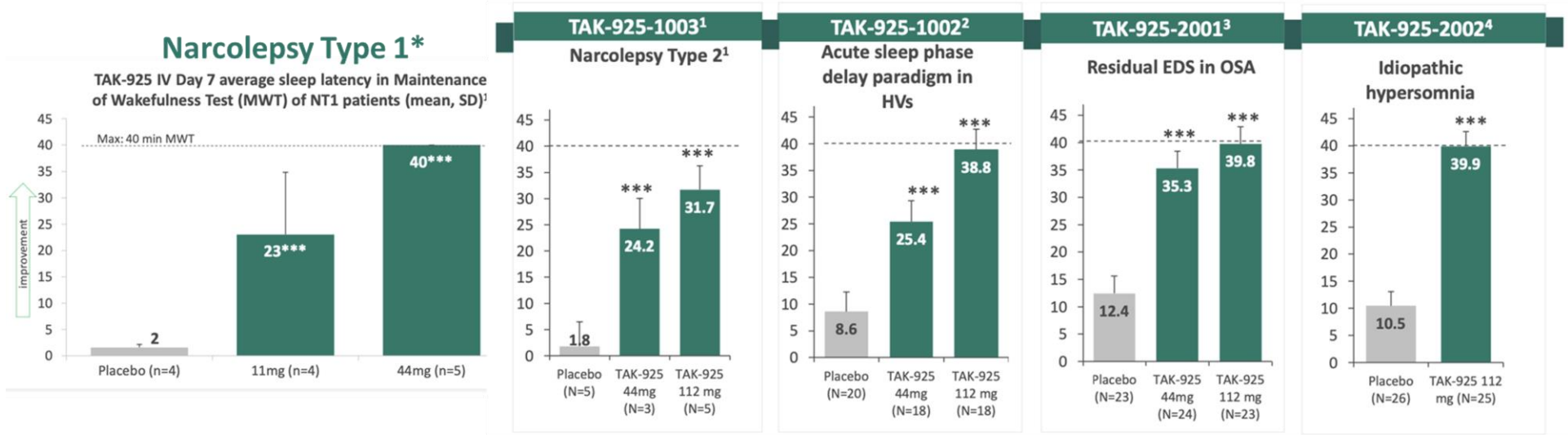
Dextroamphetamine SR up to 60 mg/day

SR is important to reduce abuse potential

NT1 polypharmacy for life
NT2/IH: can change/improve and must re-evaluate regularly

POC Achieved for NT1, NT2, IH, rEDS in OSA and Sleep-Deprived Healthy Subjects: Danavorexton (TAK925)

MWT



Efficacy Endpoint: mean sleep onset latency (min) and 95% CI

Safety profile: No serious adverse events or TAEs leading to D/C or deaths. Increases of urinary events and BP/HR have been observed

* Four participants who received TAK-925 44 mg experienced drug-related TEAEs: pollakiuria (n = 4), salivary hypersecretion (n = 1) and hyperhidrosis (n = 1)

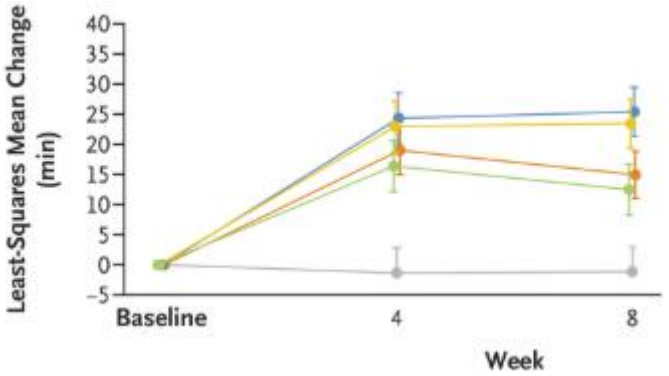
+ Active on all narcolepsy symptoms

Evans R, et al. *PNAS*. 2023;119(35)e2207531119.

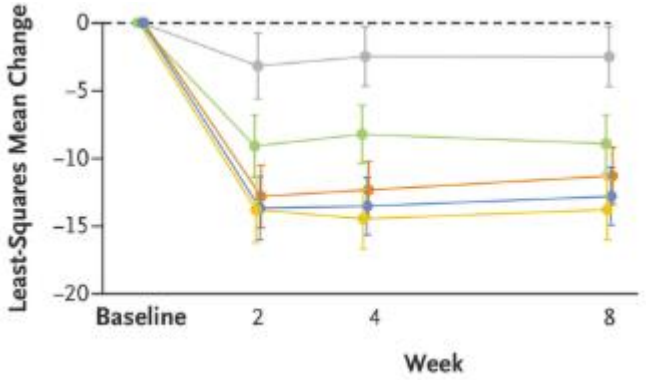
Oveporexton, an Oral Orexin Receptor 2–Selective Agonist, in Narcolepsy Type 1

Efficacy Endpoints

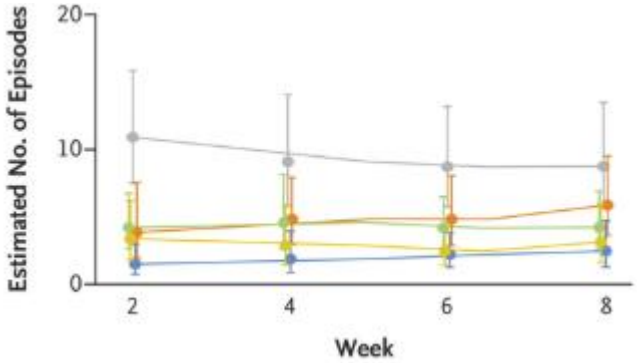
Change From Baseline in Average Sleep Latency on MWT



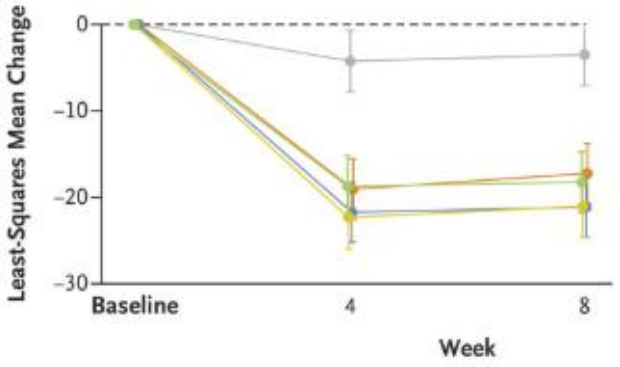
Change From Baseline in EES Total Score



Weekly Cataplexy Rate



Change From Baseline in NSS-CT Total Score

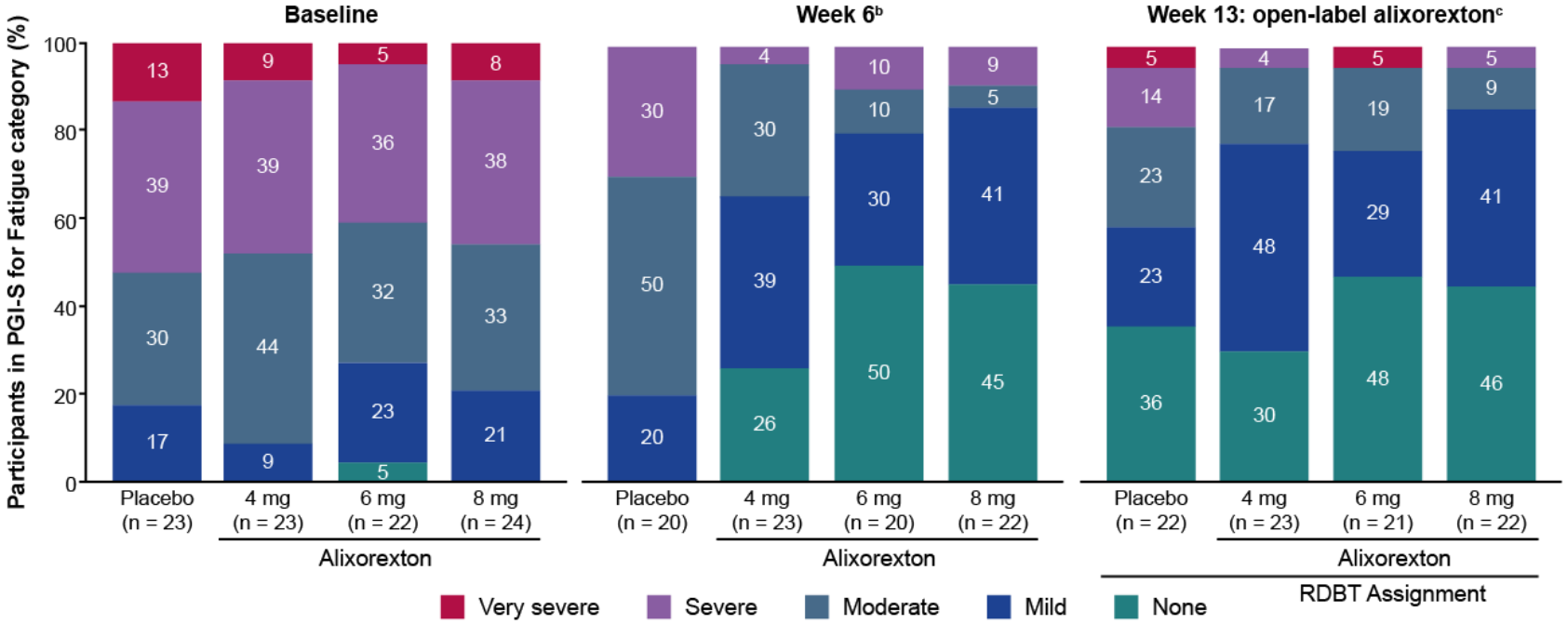


Dauvilliers Y, et al. *N Engl J Med*. 2025;392(19):1905-1916.

OXR2 agonists have positive cognitive effects

Most participants treated with alixorexton reported no or mild cognitive impairment at weeks 6 and 13

PGI-S for Cognition[a] categorical change from baseline through week 13



[a]The PGI-S for Cognition is a single-item measure that asks patients to rate the severity of their cognitive impairment at a given point in time. [b]At week 6, all doses of alixorexton were significantly different from placebo ($P = 0.0015$ for the 4 mg dose, $P = 0.0004$ for the 6 mg dose, and $P < 0.0001$ for the 8 mg dose, all nominal.) [c]All participants who entered the OLE were started on alixorexton 6 mg, with dose adjustment permitted for the first 2 weeks of the OLE. Participants are shown throughout the OLE by their original RDBT period randomization assignment. Dauvilliers Y, et al. AAN 2026; poster 14-002.

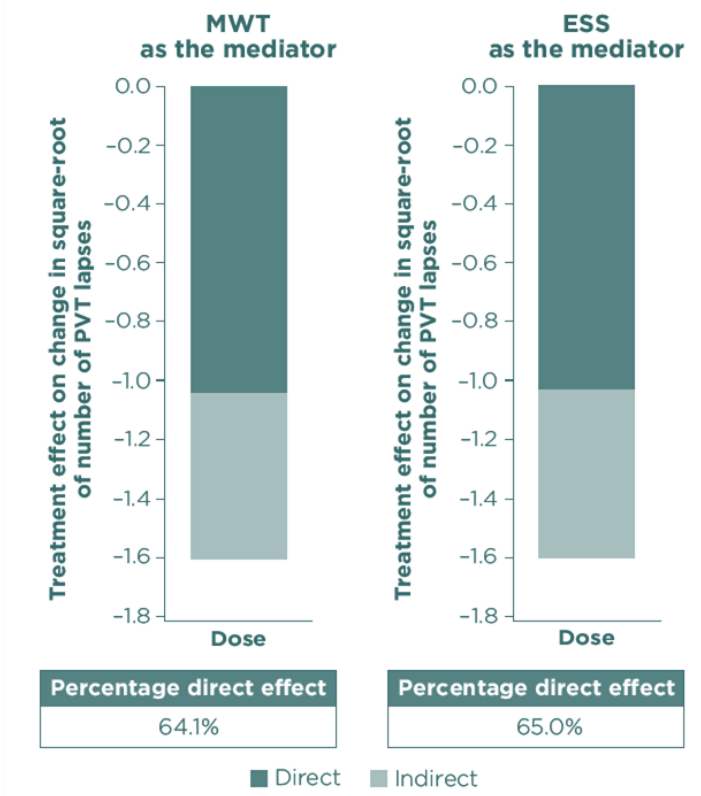
Are cognition effects mediated by Sleepiness effects?

How much of oveporexton's effects on PVT lapses (attention) can be mediated by effects on objective (MWT) and subjective (ESS) sleepiness?

Answer of mediation analysis

~65%

Figure 5. Direct and indirect treatment effects of TAK-861 on number of PVT lapses



Treatment effects on PVT with change in MWT as the mediator or change in ESS as the mediator show a large part of the improvement in sustained attention was a direct effect of TAK-861. Data analysed as change in square-root of PVT from baseline.

Plazzi G, et al. ESRS Sleep Europe 2024. P1257.

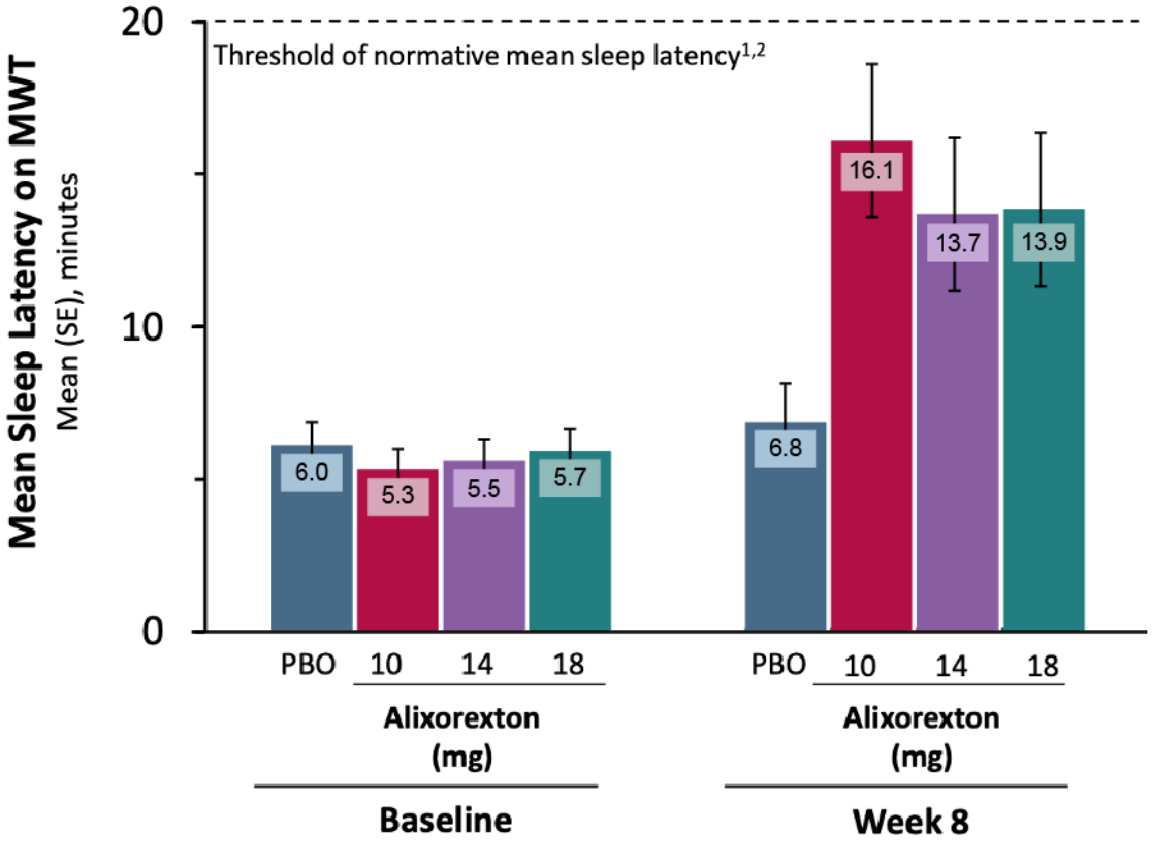
What About Safety, Tolerability, and Other Factors?

- **Side effects across all orexin agonists**
  - Urinary urgency
  - Insomnia (no clear effect on DNS in NT1)
  - +/- minor visual disturbances
  - No clear BP/HR effects
- **AEs appear largely transient**
- **Potential DEA scheduling**
- **Long term effects**
  - In NT1 the first few days, then the first month, then stable in LTE.

TOTAL CME

Plazzi G, et al. ESRS Sleep Europe 2024. P1257.

Orexin agonists also effective in Narcolepsy type 2 Improvements in MWT Mean Sleep Latency at All Doses with Alixorexton



Primary Endpoint Analysis at Week 8

Change from baseline at Week 8 (minutes)[a]	PBO (N = 24)	Alixorexton once daily 10 mg (N = 23)	14 mg (N = 22)	18 mg (N = 24)
LSM	**1.6**	**10.8**	**8.3**	**8.2**
(95% CI of LSM)	(-2.6, 5.7)	(6.5, 15.1)	(4.1, 12.5)	(4.1, 12.4)
LSM difference vs PBO		**9.3**	**6.7**	**6.7**
(95% CI of LSM difference)		(3.3, 15.2)	(0.9, 12.6)	(0.9, 12.4)
***P* value** (Adjusted for multiplicity)		NA[b]	**0.0485***	**0.0466***
***P* value** (Unadjusted for multiplicity)		0.0023	**0.0243***	**0.0233***

[a] ANCOVA model. Missing data were imputed using multiple imputation.
[b] Study employed hierarchical analysis procedure to control for multiplicity which precluded the assessment of statistical significance of the MWT endpoint at the 10 mg dose.
* Statistically significant following multiplicity adjustment.
CI, confidence interval; LSM, least squares mean; MWT, Maintenance of Wakefulness Test; PBO, placebo; SE, standard error.
Bogan R, et al. *Sleep.* 2026;49(1):A331-332.

Vibrance-3 (IH) (Alixorexton in Idiopathic Hypersomnia) Now Enrolling in the US

- n = 96 x 2
- **10, 14, 18 mg single dose and split dose**
- Primary: MWT
- Secondary: ESS and safety
- 8-week duration

TOTAL CME

ClinicalTrials.gov identifier: NCT06843590.

Concluding Remarks and Q&A

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