IN PARTNERSHIP WITH Sleep Research Society Foundation

Psych Congress MasterClass

Neurobiology of Orexin Agonism: The Final Frontier of Sleep-Wake Disorders in Psychiatry

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Faculty Disclosures

- **David Plante, MD, PhD:** Advisory Board – Alkermes PLC, Apnimed, Centessa, Harmony Biosciences, Jazz Pharma, Takeda Pharmaceuticals U.S.A; Consultant – Aditum Bio (Terminated), Alkermes PLC, Centessa, Harmony Biosciences, Jazz Pharma, Takeda Pharmaceuticals U.S.A., Teva Pharmaceuticals Australia (Terminated)
- **Chelsie Monroe, PMHNP-BC:** Advisory Board – AbbVie, Axsome, Alkermes, Bristol Myers Squibb, Neurocrine Biosciences, Otsuka, Teva Pharmaceuticals; Speakers Bureau – AbbVie, Alkermes, Axsome, Bristol Myers Squibb, Intracellular Therapeutics, Neurocrine Biosciences, Otsuka, Teva Pharmaceuticals

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Learning Objectives

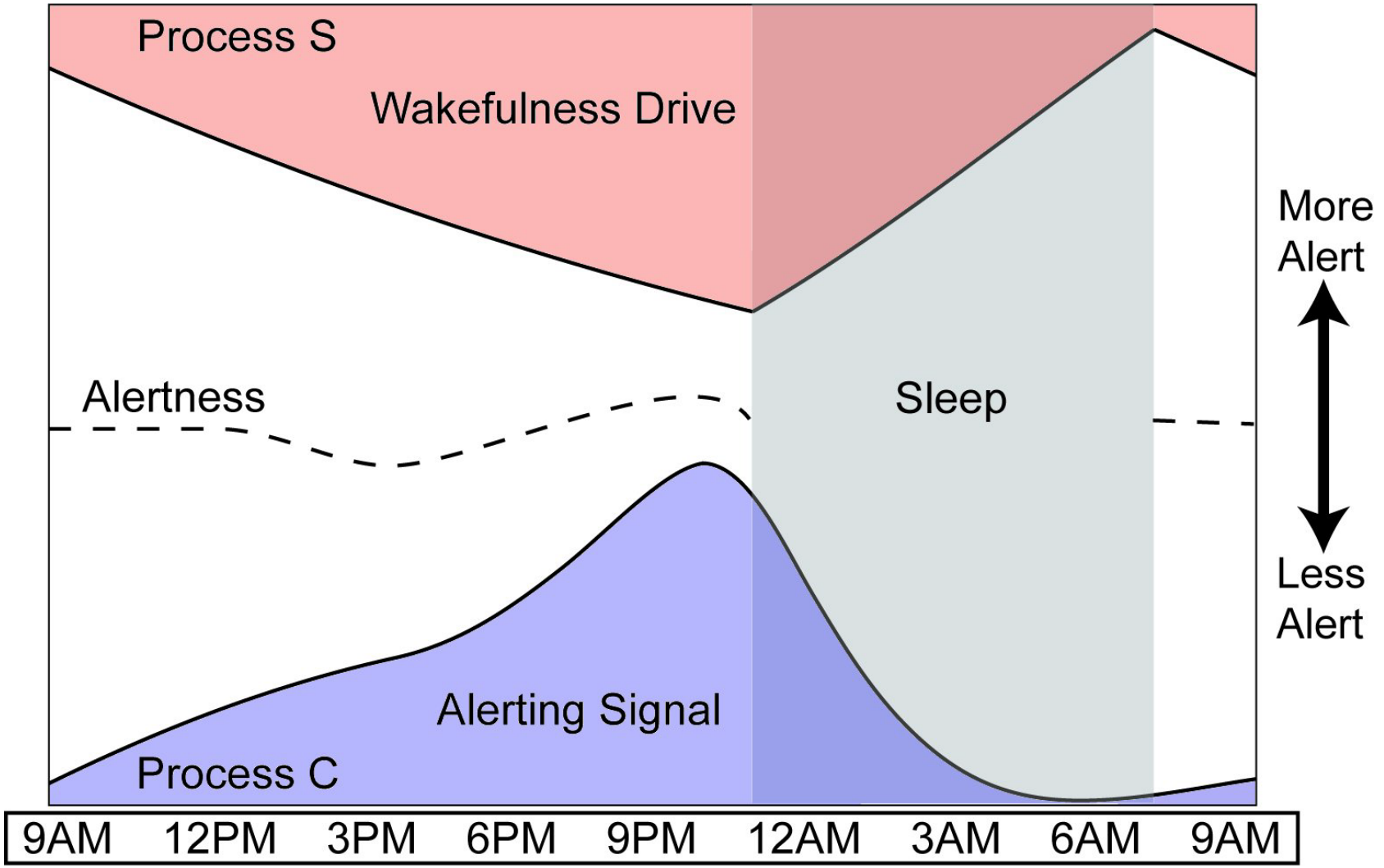
1. Describe the pathophysiology of narcolepsy and its comorbidity with psychiatric conditions
2. Implement strategies for detecting narcolepsy in patients with comorbid psychiatric conditions
3. Assess the role of psychiatry clinicians alongside sleep specialists in the care of patients with narcolepsy
4. Evaluate the mechanisms of action, available clinical evidence, and potential therapeutic implications associated with emerging orexin receptor agonists for narcolepsy

Neurobiology of Sleep-Wake Disorders

Interaction of Process C and S

Homeostatic sleep drive

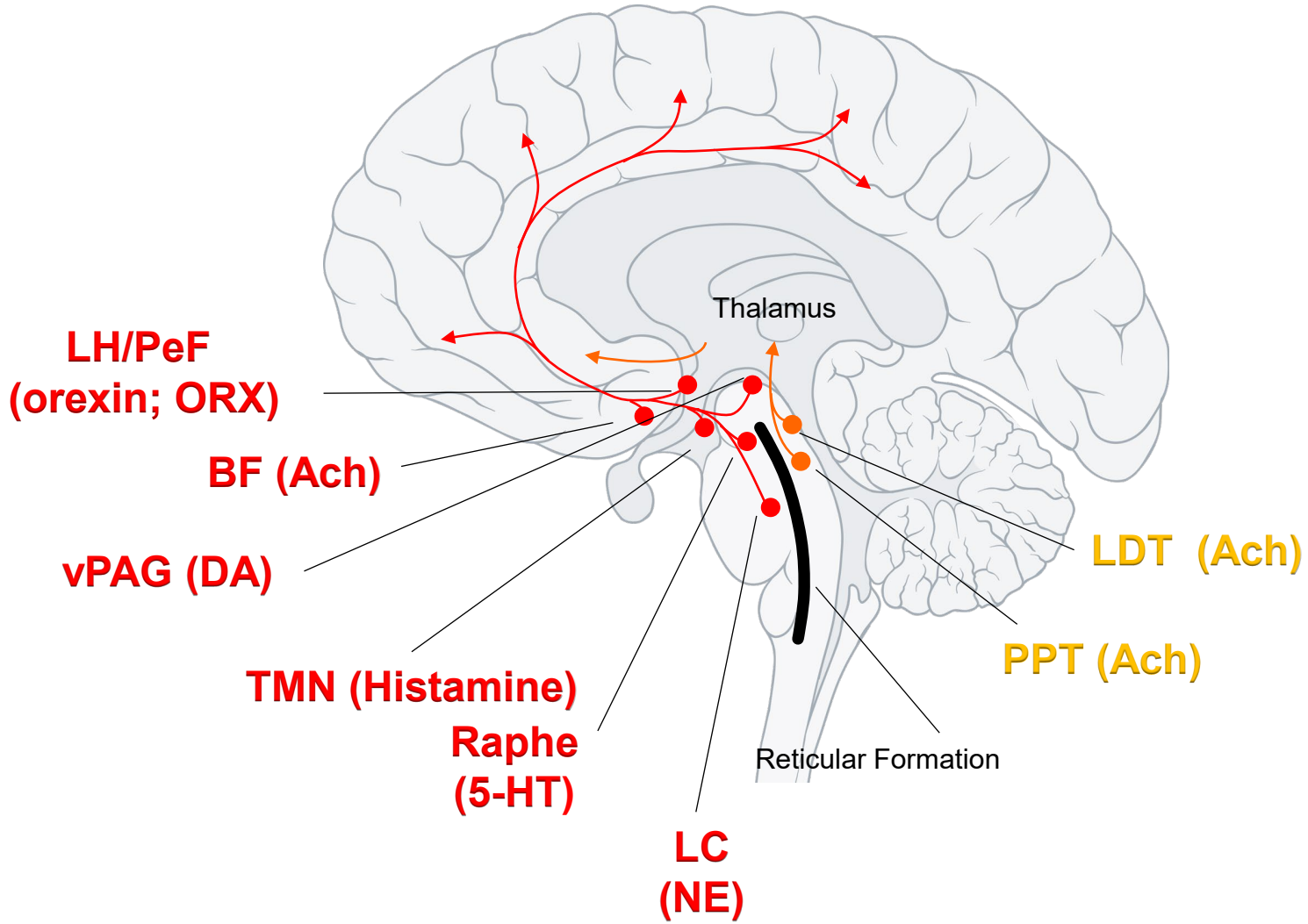
Circadian alerting signal



Process C=Circadian

Process S=Homeostatic

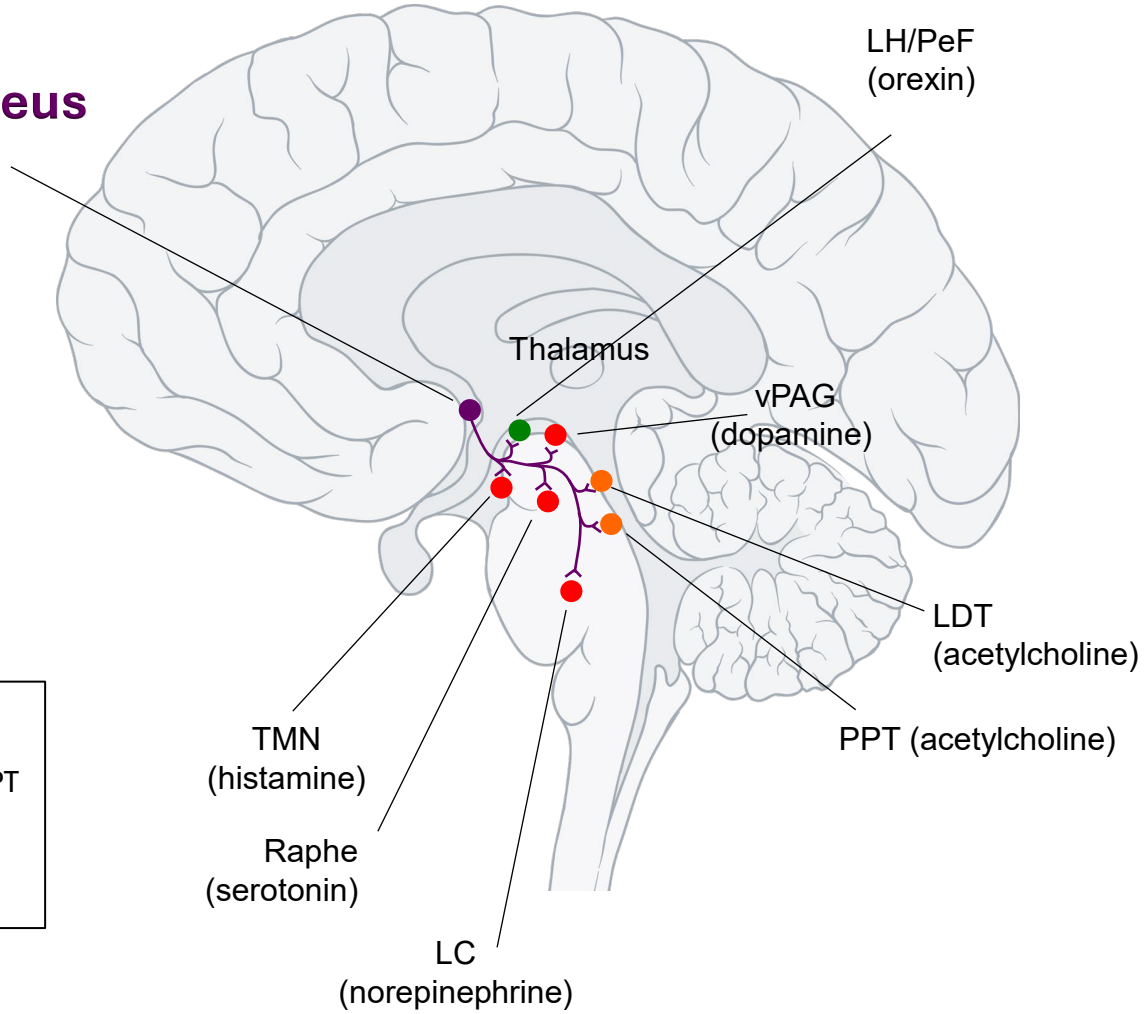
The Ascending Arousal Mechanism



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

VLPO Inhibits Ascending Arousal System

Ventrolateraral Preoptic Nucleus (VLPO)

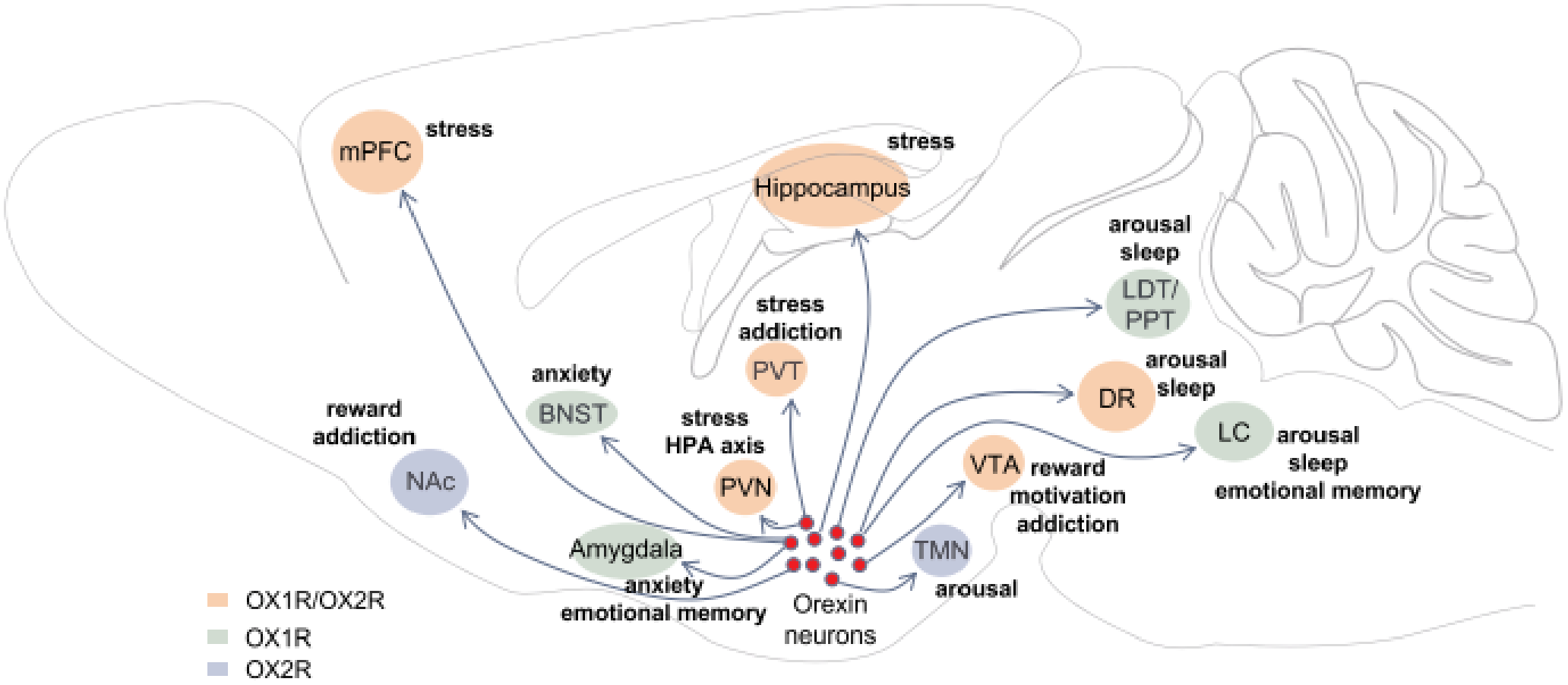


- GABA (majority) and galanin
- Projections to TMN, Raphe, LC, vPAG LDT and PPT
- Innervates LH/ PeF neurons containing orexin

***Promotes sleep via inhibition of AAS**

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

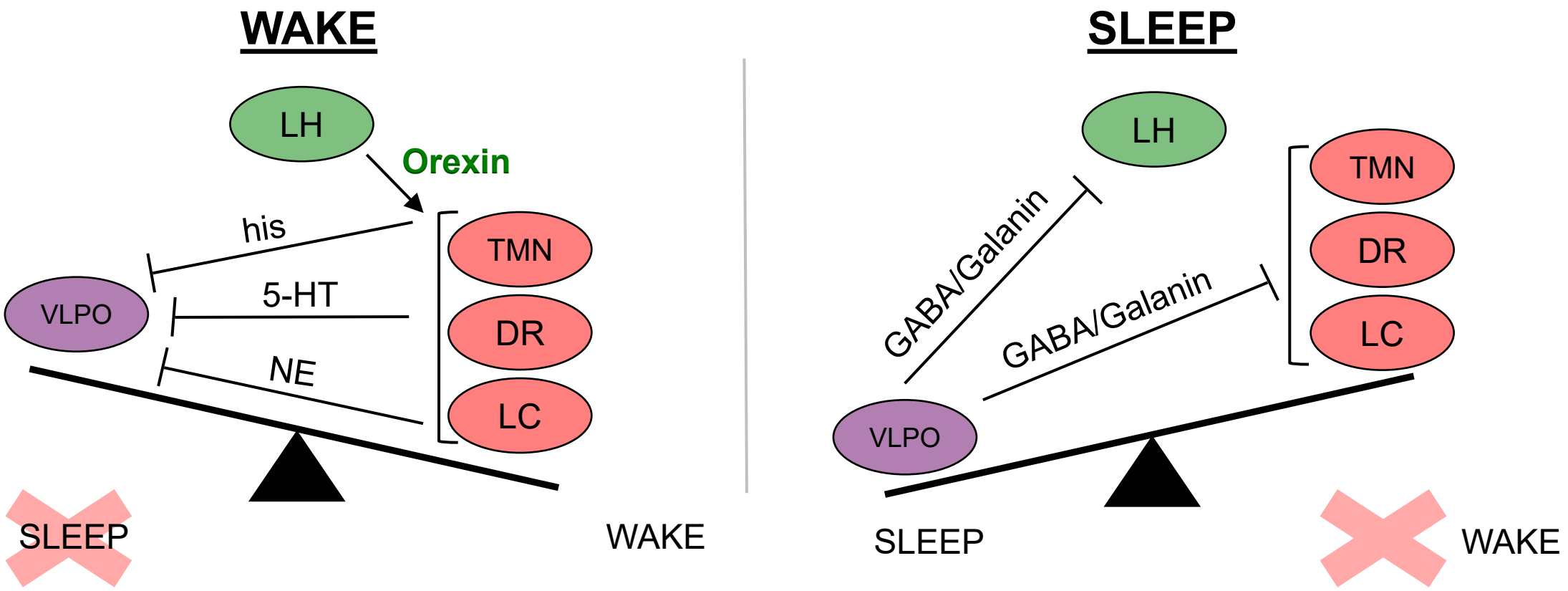
Orexin Projections



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.

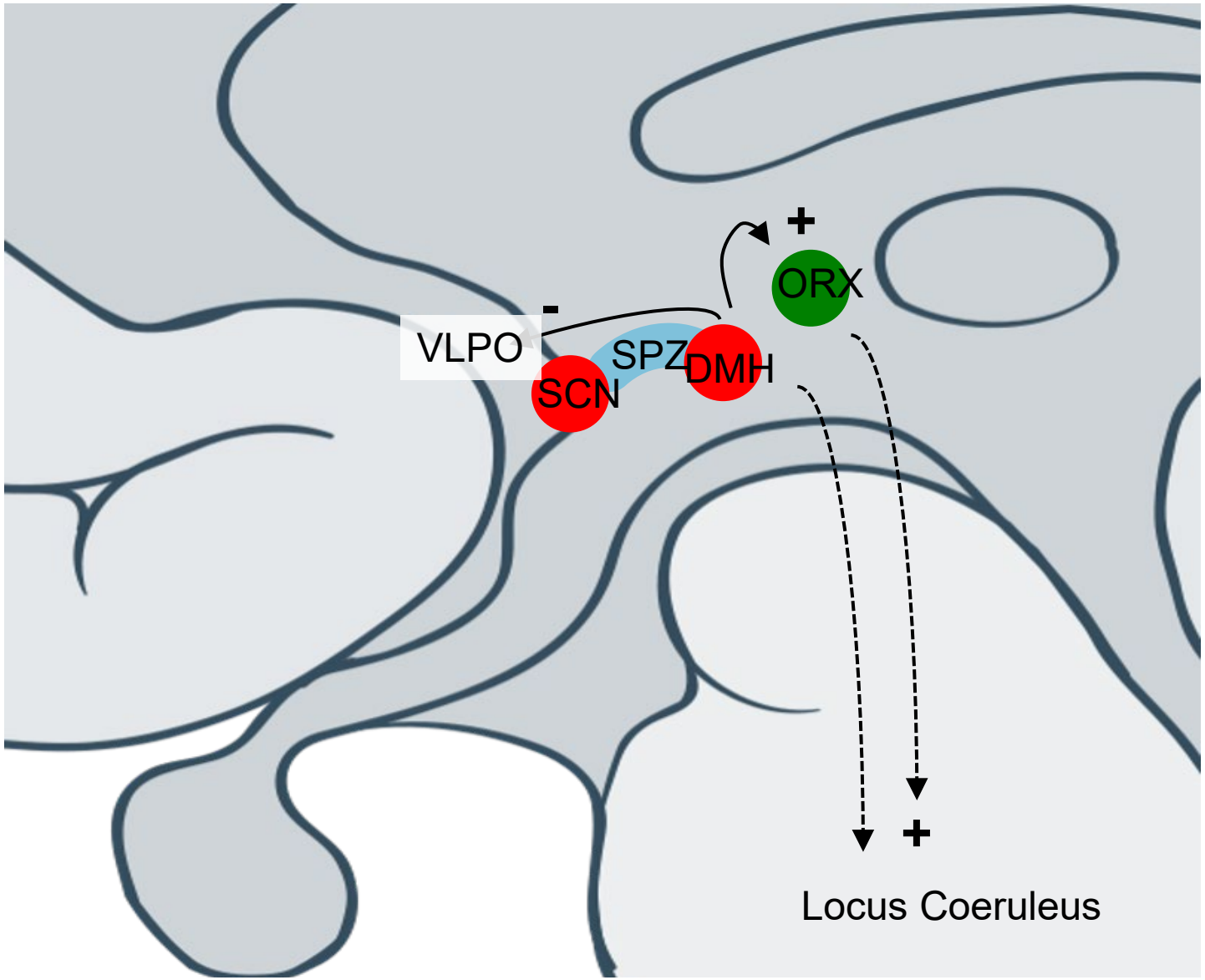
Flip-Flop Switch Model



Model allows for rapid vigilance state transitions

Orexin neurons serve as the "finger on the switch" to maintain state

Circadian Influence of Sleep-Wake Rhythms



SPZ = subparaventricular zone; DMH = dorsomedial nucleus of hypothalamus; SCN = suprachiasmatic nucleus; REM = rapid eye movement.

Suprachiasmatic Nucleus (SCN) promotes wake and suppresses REM/sleep

Broad Mechanisms of Sleep-Wake Medications

- **Promote Wake**
  - Support components of the arousal mechanism
  - Inhibit systems that promote sleep

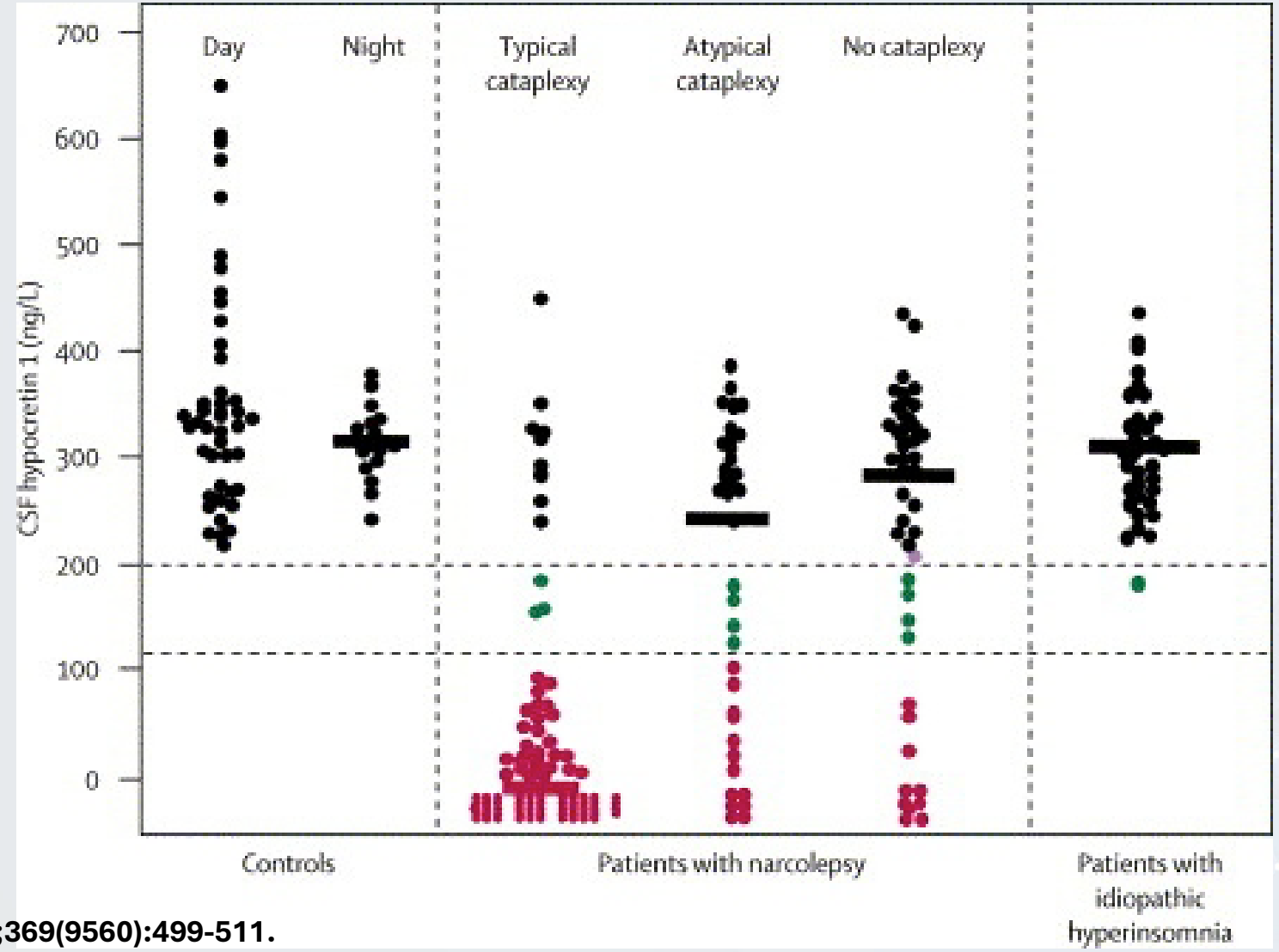
- **Promote Sleep**
  - Block components of the arousal mechanism
  - Activate systems that promote sleep

Dual Orexin Receptor Antagonists (DORAs)

- **Suvorexant** (Belsomra®) – approved 2014
  - Half life ~12 hours
  - Typical adult dose 10-20 mg
- **Lemborexant** (Dayvigo®) – approved 2019
  - Half-life 17-55 hours
  - Typical adult dose 5-10 mg
- **Daridorexant** (Quviviq®) – approved 2022
  - Half life ~8 hours
  - Typical adult dose 25-50 mg

DORA = dual orexin receptor antagonist.

CSF Orexin/Hypocretin Is Decreased in Narcolepsy Type 1



CSF = cerebrospinal fluid.

Dauvilliers Y, et al. *Lancet*. 2007;369(9560):499-511.

Narcolepsy Type 1

- **<u>Cardinal symptoms</u>**
  - Excessive Daytime Sleepiness (sine qua non)*
  - Sleep Paralysis*
  - Hypnagogic/hypnopomic imagery*
  - Cataplexy*
  - Automatic Behaviors
  - REM phenomena (vivid dreams, dream enactment, etc.)
  - Disrupted nocturnal sleep

***Form narcoleptic "tetrad."**

Key Learning Points

- Orexin (hypocretin) is critically important in sleep-wake regulation, particularly in promoting wakefulness
- Orexin antagonists promote sleep by blocking action of orexin
- Persons with narcolepsy type 1 have presumably autoimmune loss of orexin-containing neurons, leading to clinical symptomatology, including excessive daytime sleepiness

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

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

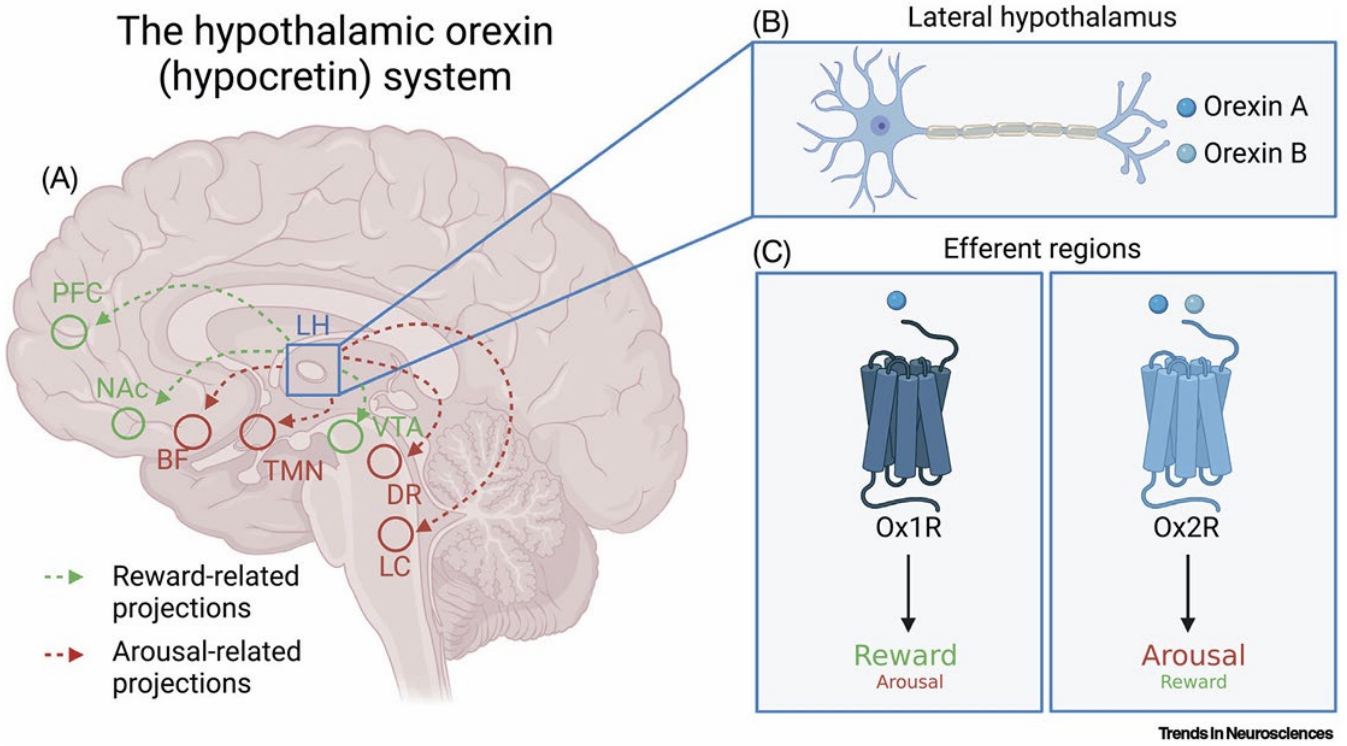
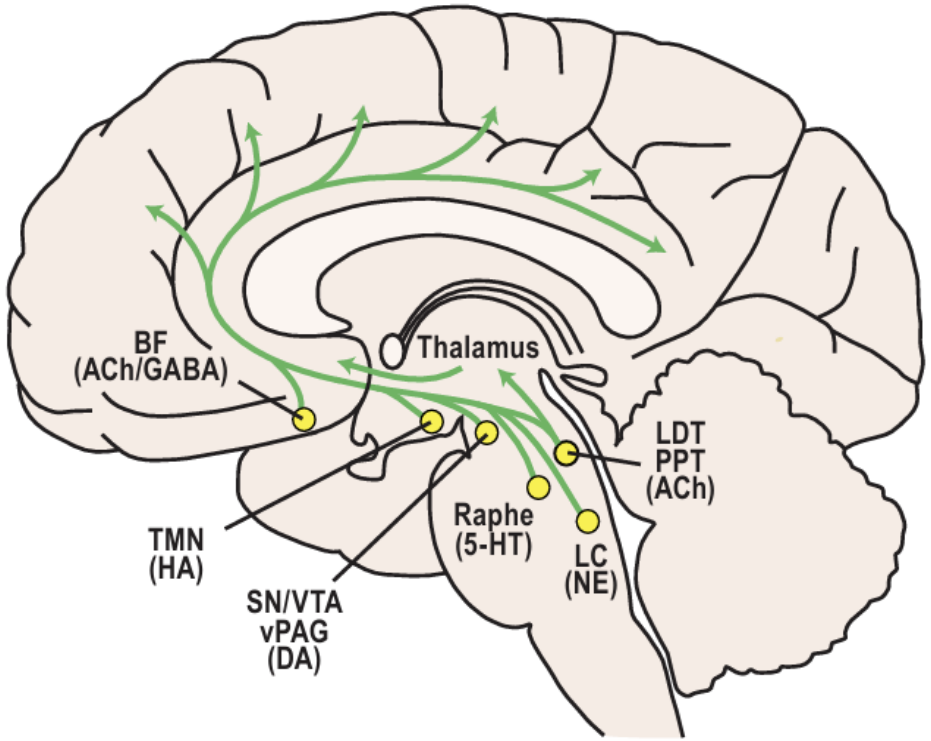


Figure 1. An overview of the orexin (hypocretin) system and its receptors.

Mahler SV, et al. *Nat Neurosci*. 2014;17(10):1298-1303. Schöne C, Burdakov D. *Front Behav Neurosci*. 2012;6:81. Mehr JB, et al. *Trends Neurosci*. 2021;44(11):852-855. Saper CB, Fuller PM. *Curr Opin Neurobiol*. 2017;44:186-192. España RA, Scammell TE. *Sleep*. 2011;34(7):845-858.

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 neurobiology from a clinical perspective. Sleep, 34(7), 845–858. https://doi.org/10.5665/SLEEP.1112

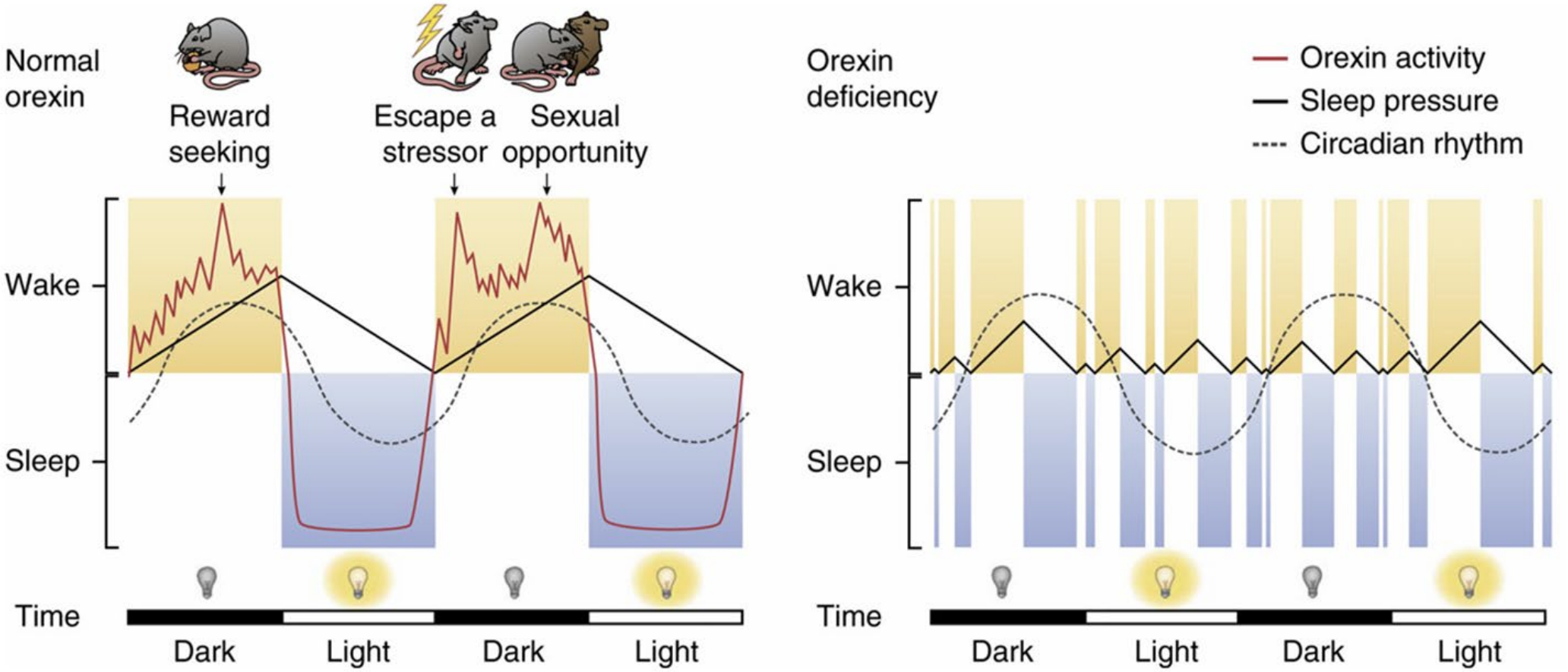
Neurotransmitter Implications in Wakefulness

NE	5-HT	HA	DA
The NE system is important in promoting arousal under conditions that require cognition or stress	Generally promotes wakefulness and suppresses REM sleep	Administration of H1 receptor agonist increases wakefulness while reducing NREM and REM sleep	Extracellular levels of DA are high in periods of wakefulness and lower during NREM sleep
LC activity too low = drowsy and inattentive LC activity too high = anxious and distractible		Administration of H1 receptor antagonists increases NREM and REM sleep (diphenhydramine and low-dose doxepin)	Drugs that increase DA signaling are used frequently to improve excessive daytime sleepiness

NREM = non-rapid eye movement.

España RA, Scammell TE. *Sleep*. 2011;34(7):845-858.

Sleep/Wake and Motivation



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

Mahler SV, et al. *Nat Neurosci*. 2014;17(10):1298-1303.

Effects of Commonly Used Drugs on Sleep and Waking

Drug Type	Pharmacologic Effect	Neurobiological Mechanism	Clinical Effects
SSRIs	Increase extracellular 5-HT	5-HT inhibits REM sleep-producing cells	Decreased REM sleep
TCAs	Increase extracellular 5-HT and NE	5-HT and NE inhibit REM sleep-producing cells	Decreased REM
Stimulants	Increase extracellular DA and NE	Increased DA and NE signaling	Increased wakefulness
Modafinil/Armodafinil	Increase extracellular DA	Increased DA signaling	Increased wakefulness
Benzodiazepines and sedative hypnotics	Enhance GABA signaling via GABA-A	GABA inhibits the arousal systems	Increased sleep
Classic antihistamines	Block HA H1 receptors	Reduced HA signaling	Increased sleep
Typical Antipsychotics	Block DA receptors	Reduced DA signaling	Increased sleep

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

España RA, Scammell TE. *Sleep*. 2011;34(7):845-858.

Orexin Promotes Adaptive Response to Stress/Anxiety and is Involved in Motivational Activation

Stress

- exposure to acute stressors **activates orexin neurons**
- Orexins have a role in sympathetic regulation and cardiovascular function in stress responses

Motivation

- Increased signaling may help to organize stress responses – **but only when motivated**
- In contrast, when a stressor is chronic, predictable, and impossible to escape, orexin system hypoactivity could yield depression-like, amotivational symptoms
- Orexins primarily promote learning and cognition that involves emotionally or motivationally relevant stimuli

Abreu AR, et al. *Brain Res*. 2020;1731:145942.

Mahler SV, et al. *Nat Neurosci*. 2014;17(10):1298-1303.

Orexins Have a Crucial Role in Facilitating Reward Seeking and May Be a Promising Strategy in Addiction Treatment

Numerous reports have since shown that *seeking* for all major addictive drugs involves ↑ orexin

- Drug addiction is associated with increased orexin activity; acute drug withdrawal also involves orexins.
- Suggests that orexin ***antagonists*** may be a promising treatment for substance use disorders

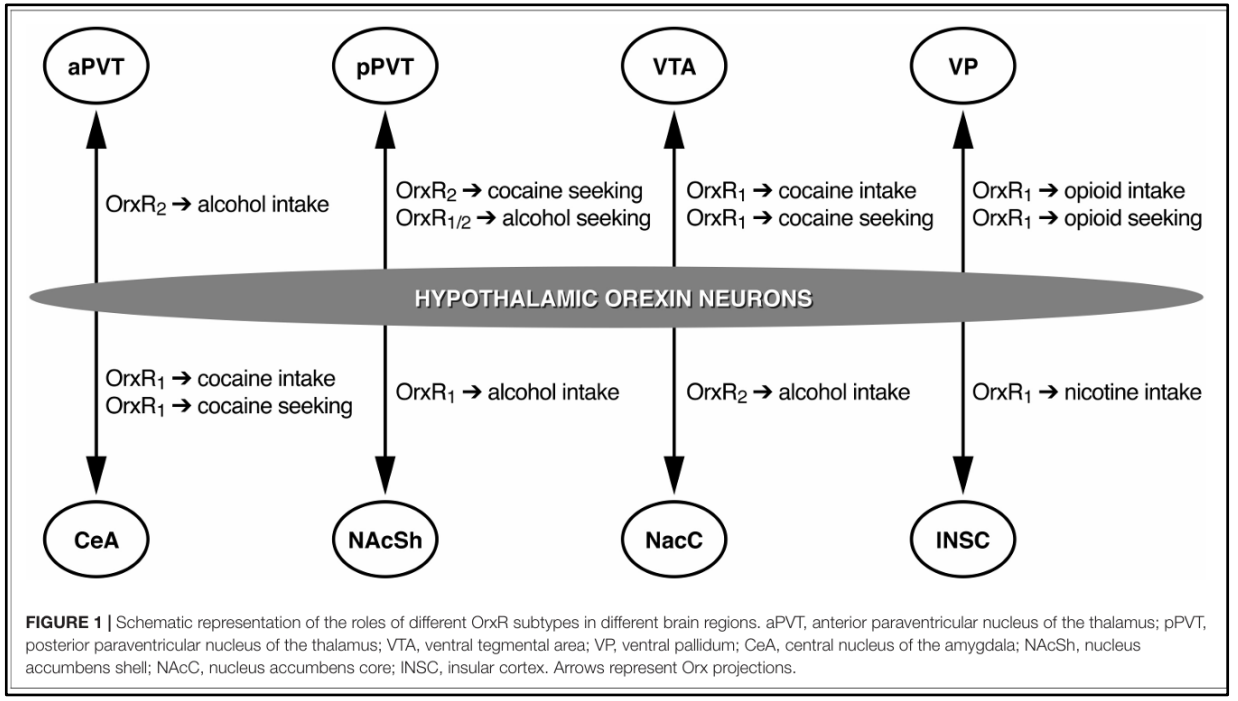


FIGURE 1 | Schematic representation of the roles of different OrxR subtypes in different brain regions. aPVT, anterior paraventricular nucleus of the thalamus; pPVT, posterior paraventricular nucleus of the thalamus; VTA, ventral tegmental area; VP, ventral pallidum; CeA, central nucleus of the amygdala; NAcSh, nucleus accumbens shell; NAcC, nucleus accumbens core; INSC, insular cortex. Arrows represent Orx projections.

aPVT = anterior paraventricular nucleus of the thalamus; pPVT = posterior paraventricular nucleus of the thalamus; VP = ventral pallidum; CeA =central nucleus of the amygdala; NAcSh = nucleus accumbens shell; NAcC = nucleus accumbens core; INSC = insular cortex.

Mahler SV, et al. *Prog Brain Res*. 2012;198:79-121. Boutrel B, et al. *Front Behav Neurosci*. 2013;7:59. Mahler SV, et al. *Nat Neurosci*. 2014;17(10):1298-1303. Mehr JB, et al. *Trends Neurosci*. 2021;44(11):852-855. Matzeu A, et al. *Front Behav Neurosci*. 2022;15:787595.

Key Learning Points

- Orexin modulation is dynamic and heterogeneous in a variety of behavioral and motivational settings. There is still much to learn about orexin interactions

- Orexin innervates with other circuitries implicated in psychiatric disorders. Selectively agonizing and antagonizing has future potential in other disease states

Psychiatric Comorbidities of Sleep-Wake Disorders

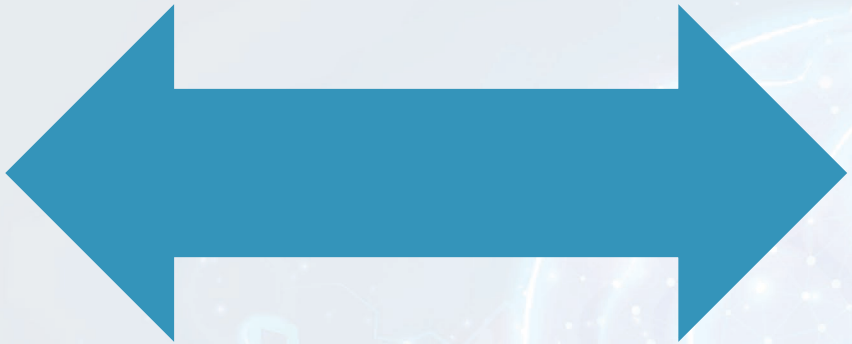
Which Type of Psychiatric Patient Struggles with Fatigue or Sleepiness?

- Major Depressive Disorder
- Bipolar Disorder
- Generalized Anxiety Disorder
- PTSD
- ADHD
- Autism
- Somatoform Disorders
- .....

PTSD = posttraumatic stress disorder; ADHD = attention-deficit hyperactivity disorder.

A Bidirectional Relationship

Excessive Daytime Sleepiness



Psychiatric D/O
Depression
Anxiety

d/o = disorder.

Excessive Daytime Sleepiness

"Irresistible sleepiness in a situation when an individual would be expected to be awake, and alert."

Definition Varies Across Specialties

EDS = symptom

Hypersomnia = specific disorders (Narcolepsy or Idiopathic Hypersomnia)

Up to 33% of US adults report excessive sleepiness during the daytime

EDS = excessive daytime sleepiness.

Ono T, et al. *Sleep Med Clin*. 2022;17(3):485-503. Gandhi KD, et al. *Mayo Clin Proc*. 2021;96(5):1288-1301.

Excessive Daytime Sleepiness and Psychiatric Disorders

Depression (MDD)	• Sleep difficulty occurs in up to 90% of those with MDD • Hypersomnia is seen in 30% of those with MDD and 50% with SAD
Bipolar Disorder	• Manic phase: Decreased need for sleep • Depressed phase: Hypersomnia
Anxiety (GAD)	• > 50% experience sleep difficulties and daytime fatigue
PTSD	• Difficulty initiating and maintaining sleep, nightmares, leading to daytime fatigue
Schizophrenia	• Shifts in circadian rhythm, 15% at risk for SDB
Alcoholism	• Poor sleep quality, EDS
ADHD	• 70%-80% individuals report sleep difficulties

MDD = major depressive disorder; GAD = generalized anxiety disorder; SAD = seasonal affective disorder; SDB = sleep-deprived breathing.

Krystal AD. *Neurol Clin*. 2012;30(4):1389-1413.

Psychiatric Comorbidity

- Strong association between EDS and Depression
- Approx. 1/3 of patients with MDD continue to experience sleep disturbance despite treatment of depression
- Symptoms are associated with worse outcomes, lower rates of remission, slower recovery, with an increased risk of relapse
- Sleep symptoms associated with increased suicidality and completed suicide, independent of MDD severity

Prevalence of EDS in Psychiatric Populations

25%

Krystal AD. *Neurol Clin*. 2012;30(4):1389-1413. Dew MA, et al. *Arch Gen Psychiatry*. 1997;54(11):1016-1024. Hawley CJ. *Int J Psychiatry Clin Pract*. 2006;10(2):117-123. Fernandez-Mendoza J, et al. *Sleep*. 2015;38(3):351-360.

Narcolepsy

Prevalence	0.02% to 0.18% in United States and Western Europe
Age of Onset	Most commonly 10–25 yr **Time to diagnosis is between 8 and 15 years after symptom onset**
Cardinal Symptom	**Excessive Daytime Sleepiness**
Other Symptoms	Disturbed nocturnal sleep REM-related phenomena • Cataplexy • Hypnagogic hallucinations • Sleep paralysis
Other Features	Severe fatigue in 50% Obesity (BMI ≥30) common Age of onset Most commonly 10–25 yr

BMI = body mass index.

American Academy of Sleep Medicine (AASM). *The International Classification of Sleep Disorders*. 3rd ed. AASM; 2014:143-161. Moturi S, et al. *Psychiatry (Edgemont)*. 2009;6(6):38-44.

Two Types of Narcolepsy

Type 1: With cataplexy – **Caused by deficiency in hypocretin/orexin signaling**

What is *cataplexy*?

A sudden loss of skeletal muscle tone that generally occurs in bilateral symmetry and is triggered by strong, typically positive emotions during arousal, such as laughter or excitement

Diagnostic Criteria: MSLT ≤8 min and ≥2 SOREMPs on MSLT, with either presence of cataplexy or CSF hypocretin-1 level is either ≤110 pg/mL

Type 2: *Without* cataplexy – Pathophysiology unclear

Diagnostic Criteria: MSLT ≤8 min and ≥2 SOREMPs on MSLT, no cataplexy present

Nishino S, Mignot E. *Handb Clin Neurol*. 2011;99:783-814.

Idiopathic Hypersomnia

Prevalence	Unclear
Pathophysiology	Unclear
Age of Onset	Age 16.6-21.2
Symptoms	Exaggerated sleep inertia (sleep drunk) – 36%-66% -Use of mult. alarms & repeated RTS - AM irritability, confusion, personality change - Automatic behavior Unrefreshing and prolonged naps (>1 hr) – 46%-78% Nocturnal sleep prolonged (12-19 hr) EDS not improved with prolonged sleep Sleep paralysis and hypnagogic hallucinations 4%-40% Cognitive impairment

Diagnostic Criteria: Absence of cataplexy, MSLT mean sleep latency ≤8 mins, <2 SOREMPS and Total 24-hr sleep time ≥660 min (typically 12–14 hr) on 24-hr polysomnogram

RTS = return to sleep; sx = symptom.

American Academy of Sleep Medicine (AASM). *The International Classification of Sleep Disorders*. 3rd ed. AASM; 2014:161-166. Kryger MH, et al. *Principles and Practice of Sleep Medicine*. 7th ed. Elsevier; 2022.

Key Learning Points

- The prevalence of excessive daytime sleepiness (EDS) among psychiatric populations is estimated to be 25%
- Narcolepsy and Idiopathic Hypersomnia are both central disorders of hypersomnolence. They share a hallmark symptom: excessive daytime sleepiness
- Narcolepsy differs from Idiopathic Hypersomnia in the following ways
  - MSLT ≤8 min and ≥2 SOREMPs on MSLT
  - Cataplexy may be present
  - Orexin deficiency

During EH, Kushida CA, eds. *Clinical Sleep Medicine: A Comprehensive Guide for Mental Health and Other Medical Professionals*. American Psychiatric Association Publishing; 2021.

Detection of Narcolepsy in Patients with Psychiatric Conditions

Symptoms of EDS and What to Pay Attention to in the Clinical Interview

- Feeling excessive sleepiness (despite treating their underlying psychiatric conditions)
- Episodes of inadvertently falling asleep
- Unrefreshing sleep
- Recurrent naps
- Sleep inertia
- Foggy mind
- Fatigue or lack of energy
- Cognitive impairment

A GOOD patient interview is vital!

- ***Verbiage matters;*** *Patients may not use the words "sleepy," but rather words such as: "tired, fatigued, lack of energy, or burnt out…"*
- ***Dig deeper;*** *Patients may minimize sleepiness in fear of workplace backlash, perception of laziness, or poor motivation by others, etc.*
- *Some patients may not recognize their sleepiness as abnormal; they have been living this way for some time and have adopted various coping strategies*

Symptoms of Narcolepsy Can Be Confused with Other Disorders

Narcolepsy Symptom	Confused with
• Cataplexy • Hypnogogic Hallucinations • Sleep paralysis • Sleep disruption • Excessive daytime sleepiness	• TIA, syncope, akinetic seizure • Dreaming, nightmares • Psychotic hallucinations • Nocturnal panic • Insomnia • ADHD • Fatigue and amotivation in depression

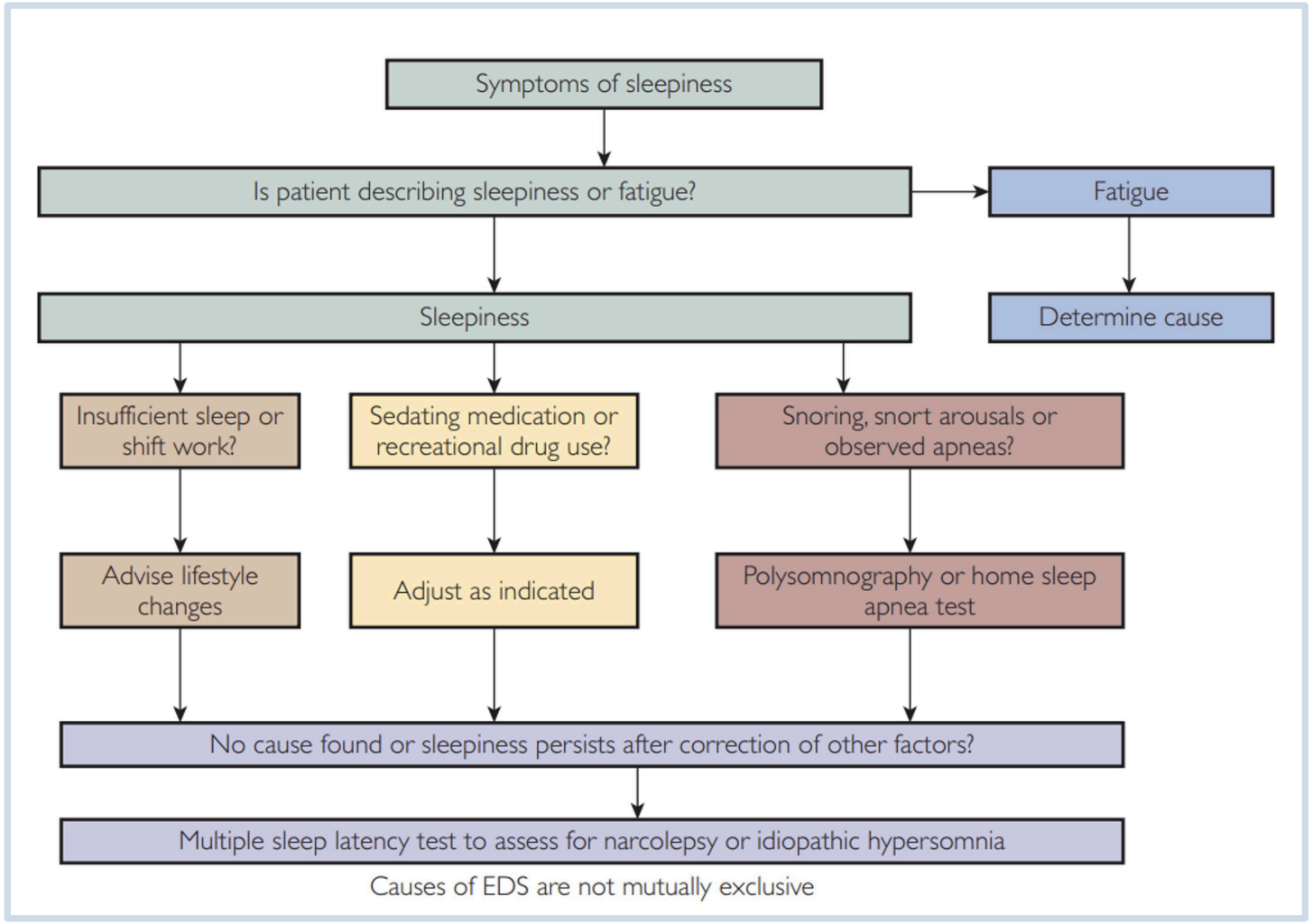
TIA = transient ischemic attack.

Kryger MH, et al. *Principles and Practice of Sleep Medicine*. 7th ed. Elsevier; 2022. American Academy of Sleep Medicine (AASM). *The International Classification of Sleep Disorders*. 3rd ed. AASM; 2014:161-162.

Suggested Algorithm for Evaluation of EDS

APA recommendation: Refer to sleep specialist upon initial evaluation if EDS is present

- PSG plus MSLT
- Actigraphy + sleep log



PSG = polysomnogram.

Gandhi KD, et al. *Mayo Clin Proc*. 2021;96(5):1288-1301. Doghramji K. American Psychiatric Association (APA). Expert Q&A: Sleep Disorders. Accessed September 2025. https://www.psychiatry.org/patients-families/sleep-disorders/expert-q-and-a. Kryger MH, et al. *Principles and Practice of Sleep Medicine*. 7th ed. Elsevier; 2022.

Screening and Assessment

- Distinguishing between EDS and fatigue can be difficult. Definitions are blurred
- Fatigue is generally characterized by
  - Lack of energy
  - Reduced ability to perform physical activities
  - Poor concentration and memory
  - Chronic medical, neurological, or psychiatric conditions, or in isolation as in chronic fatigue syndrome
- Fatigue is ***not*** generally associated with inappropriate episodes of sleep during the day

Step 1: Get a good history
- Sleep log

Step 2: Screen
- Epworth Sleepiness Scale (ESS)

Step 3: Evaluate
- R/O OSA with HST

May refer to sleep specialist

ESS = Epworth Sleepiness Scale; R/O = rule out; OSA = obstructive sleep apnea; HST = home sleep test.

Pigeon WR, et al. *J Psychosom Res*. 2003;54(1):61-69. Gandhi KD, et al. *Mayo Clin Proc*. 2021;96(5):1288-1301.

Epworth Sleepiness Scale

Epworth Sleepiness Scale (ESS)

Situation	Chance of Dozing			
Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting inactive in a public place (e.g., a theater or a meeting)	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon when circumstances permit	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after a lunch without alcohol	0	1	2	3
In a car, while stopped for a few minutes in traffic	0	1	2	3

An ESS Score >10

Suggests EDS

An ESS score ≥16 suggests a high level of EDS.

Scores within this range are generally associated with sleep disorders, including narcolepsy.

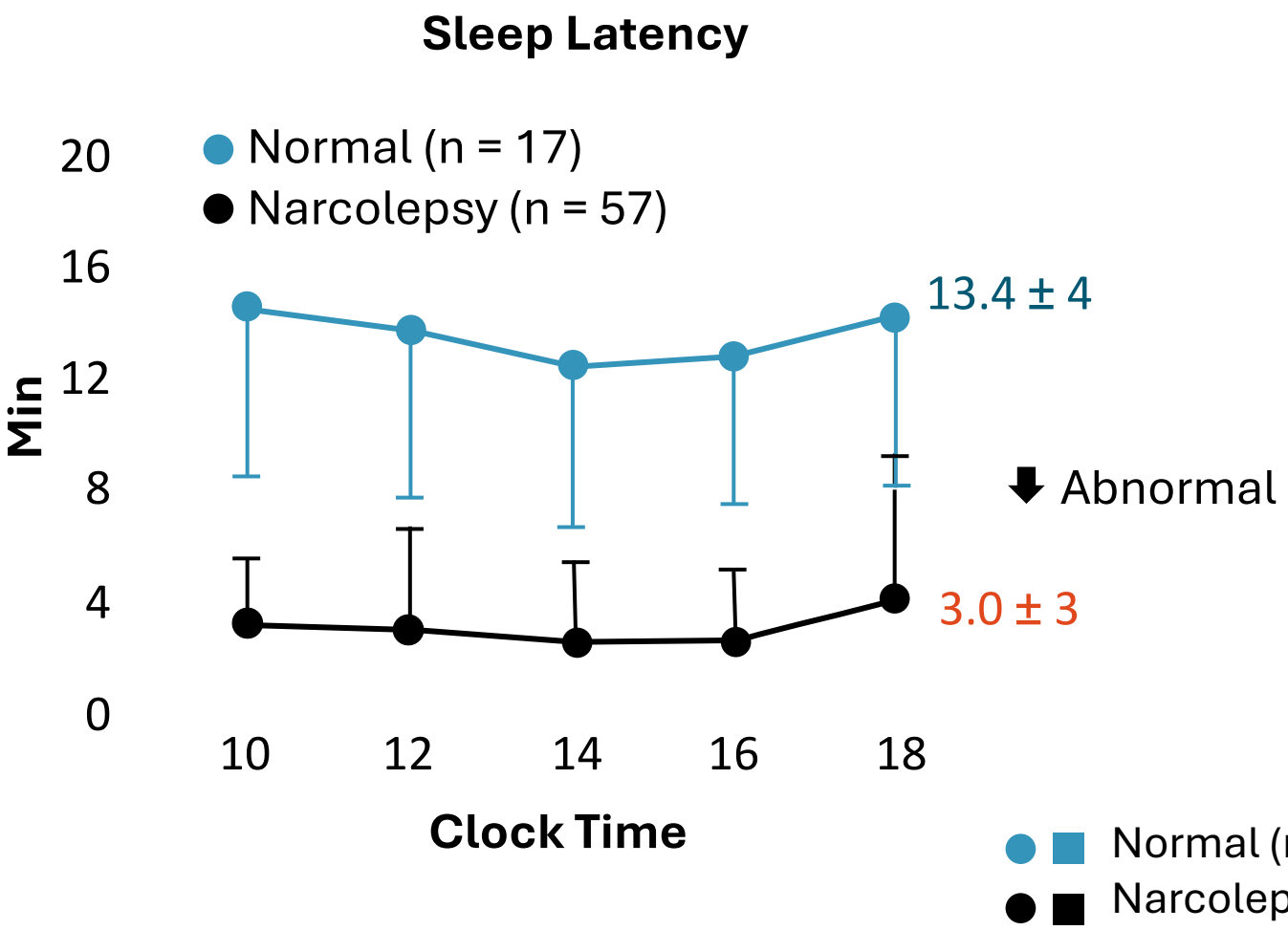
Johns MW. *Sleep*. 1991;14(6):540-545. Hoddes E, et al. *Psychophysiology*. 1972;9(1):150.

STOP-BANG to Screen for OSA

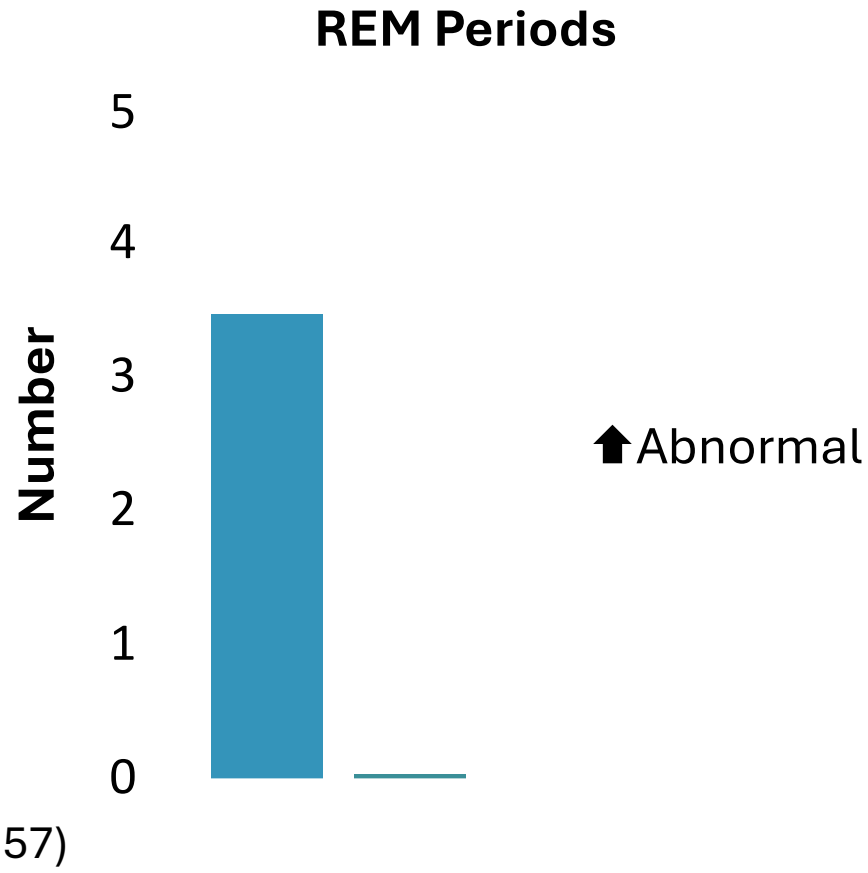
- Risk factors of OSA
  - **S**: Snoring?
  - **T**: Tired? (daytime fatigue, sleepiness)
  - **O**: Observed? (stopping breathing, choking, gasping)
  - **P**: Pressure? (high blood pressure)
  - **B**: BMI >35?
  - **A**: Age >50?
  - **N**: Neck size large? (Men >16 inches; Women >15 inches)
  - **G**: Gender = male?
- Scoring: Risk for OSA
  - **Low**: 0-2; **Intermediate**: 3-4; **High**: 5-8

Chung F, et al. *Anesthesiology*. 2008;108(5):812-821. Nagappa M, et al. *PLoS One*. 2015;10(12):e0143697.

Multiple Sleep Latency Test



Most commonly utilized procedure for the diagnosis of narcolepsy



Mitler MM, et al. *Psychiatr Clin North Am*. 1987;10(4):593-606.

Utility of Measuring CSF Orexin-1 Level in and HLA Typing in Patients with Suspected Narcolepsy

CSF Orexin 1 concentrations <110 pg/ml can be useful, **but not reliable as a standalone test,** particularly in the context of severe depression

The HLA biomarker of narcolepsy type 1 (with cataplexy), is *HLA-DQB106:02

Abstract

Objectives: The patho-aetiology of narcolepsy Type I (NT1) is the loss of hypocretin-1 secreting neurons in the hypothalamus. Diagnostic criteria for NT1 include excessive daytime sleepiness (EDS) for at least three months not explained by any other condition, cataplexy and cerebrospinal fluid (CSF) hypocretin-1 concentrations lower than 110 pg/ml. In this study we evaluated the utility of measuring CSF hypocretin-1 levels in patients with suspected narcolepsy (N).

Methods: The study included 29 consecutively recruited patients at a tertiary sleep centre presenting with EDS for exclusion of N. All patients were examined using an extensive clinical interview followed by two weeks of actigraphy and sleep diary recordings, polysomnography (PSG) and multiple sleep latency testing (MSLT). Additionally, HLA-typing, urinary screening for substances of abuse and a lumbar puncture to measure CSF hypocretin-1 expression using radioimmunoassay were carried out.

Results: In sum, 19 patients (66%) had a CSF hypocretin-1 level <110 pg/ml, of whom two had current severe depression without any features of narcolepsy except EDS. The predictive potential of hypocretin-1 measurement in diagnosing narcolepsy revealed a positive predictive value (PPV) of 89%, a specificity of 83%, with both negative predictive value (NPV) and sensitivity equal to 100%.

N = narcoclepsy; NT1 = narcolepsy type 1; HLA = human leukocyte antigen; PPV = positive predictive value; NPV = negative predictive value.

Gabryelska A, et al. *Sleep Med*. 2020;71:48-51.

Key Learning Points

Our role as psychiatric clinicians is to

- Embrace sleep
- Dig deeper in the clinical interview. Know how to differentiate between fatigue and excessive daytime sleepiness
- SCREEN!
- Be suspicious and advocate for evaluation and referral to sleep specialist

Current Challenges in Treatment of Narcolepsy

Pharmacological Options

Narcolepsy – Goals of Treatment

- Reduce daytime sleepiness
- Control ancillary symptoms
  - Cataplexy
  - Nightmares and hallucinations
  - Sleep paralysis
  - Disturbed nocturnal sleep
- Improve psychosocial and work functioning
- Improve safety of patient and public

Wake Promoting Agents

- Modafinil/armodafinil
- Solriamfetol
- Pitolisant
- Traditional Psychostimulants
  - Methylphenidate
  - Mixed amphetamine salts
  - Dextroamphetamine

Modafinil/Armodafinil

- FDA indicated for narcolepsy, residual sleepiness in OSA, shift-work sleep disorder
- Mechanism of action
  - Binds to dopamine transporter (DAT), increasing dopamine in synaptic cleft
  - May indirectly increase NE and 5HT
  - May stimulate with hypothalamic orexin and histamine activity
  - May also have glutamatergic effects
- Risk of severe dermatologic reactions (eg, Stevens-Johnson Syndrome)
- Drug-drug interaction with estrogen-containing compounds (enhances metabolism)
- Modafinil $t_{1/2}$=9-14 hrs; armodafinil (*r*-enantiomer of modafinil) = 15 hours
- Schedule IV
- Typical doses: modafinil 100-400 mg daily; 150-250 mg armodafinil

DAT = dopamine transporter.

Pitolisant (Wakix)

- Histamine 3 receptor agonist/inverse agonist
- Approved to treat excessive daytime sleepiness and cataplexy in narcolepsy
- Can affect QTc
- Non-scheduled
- Drug-drug interactions
  - CYP2D6 inhibitors can increase exposure by ~2-fold (have to reduce dose by 50%)
  - CYP3A4 inducers can reduce exposure by 50%
- Typical adult dose 17.8-35.6 mg

Solriamfetol (Sunosi)

- Norepinephrine-dopamine reuptake inhibitor
- Approved to treat excessive daytime sleepiness in narcolepsy and obstructive sleep apnea
- Typical adult dose 75-150 mg
- Potent wake-promoting effects measured by maintenance of wakefulness test (~9.8 minutes in narcolepsy at 150mg dose)
- Dose-dependent increase in blood pressure and heart rate

Thorpy MJ, et al. *Ann Neurol*. 2019;85(3):359-370.

Traditional Psychostimulants

- Increase monoamine concentrations (DA, NE, 5HT) in synaptic cleft by
  - Blocking presynaptic transporters
  - Increasing monoamine release
- Side effects: psychomotor agitation, xerostomia, arrhythmias, hypertension, insomnia, racing thoughts, euphoria, anxiety, paranoia/psychosis, tics
- Schedule II

Oxybates

- Salts of γ-hydroxybutyrate (GHB)
  - Sodium oxybate (generic; Xyrem®)
  - Low-sodium oxybate (Xywav®)
- Rapid absorption, $t_{1/2}$=0.5-1.25 hrs
- Approved for EDS and cataplexy in narcolepsy and low sodium oxybate for idiopathic hypersomnia
- Often requires split dosing
  - Once nightly sodium oxybate (Lumryz™)
- ↑SWS and growth hormone
- Stabilizes NREM/REM cycling

GHB = gamma-hydroxybutyrate.

Oxybates

- Schedule III (dispensed from central pharmacy and has REMS program)
  - History of use as a “date rape” and recreational drug, bodybuilding
- Common adverse effects
  - Somnolence, enuresis, nausea/appetite reduction, confusion, psychiatric effects
- Avoid with EtOH (respiratory depression)
- Should not be used with other CNS depressants

EtOH = ethanol/ethyl alcohol; CNS = central nervous system.

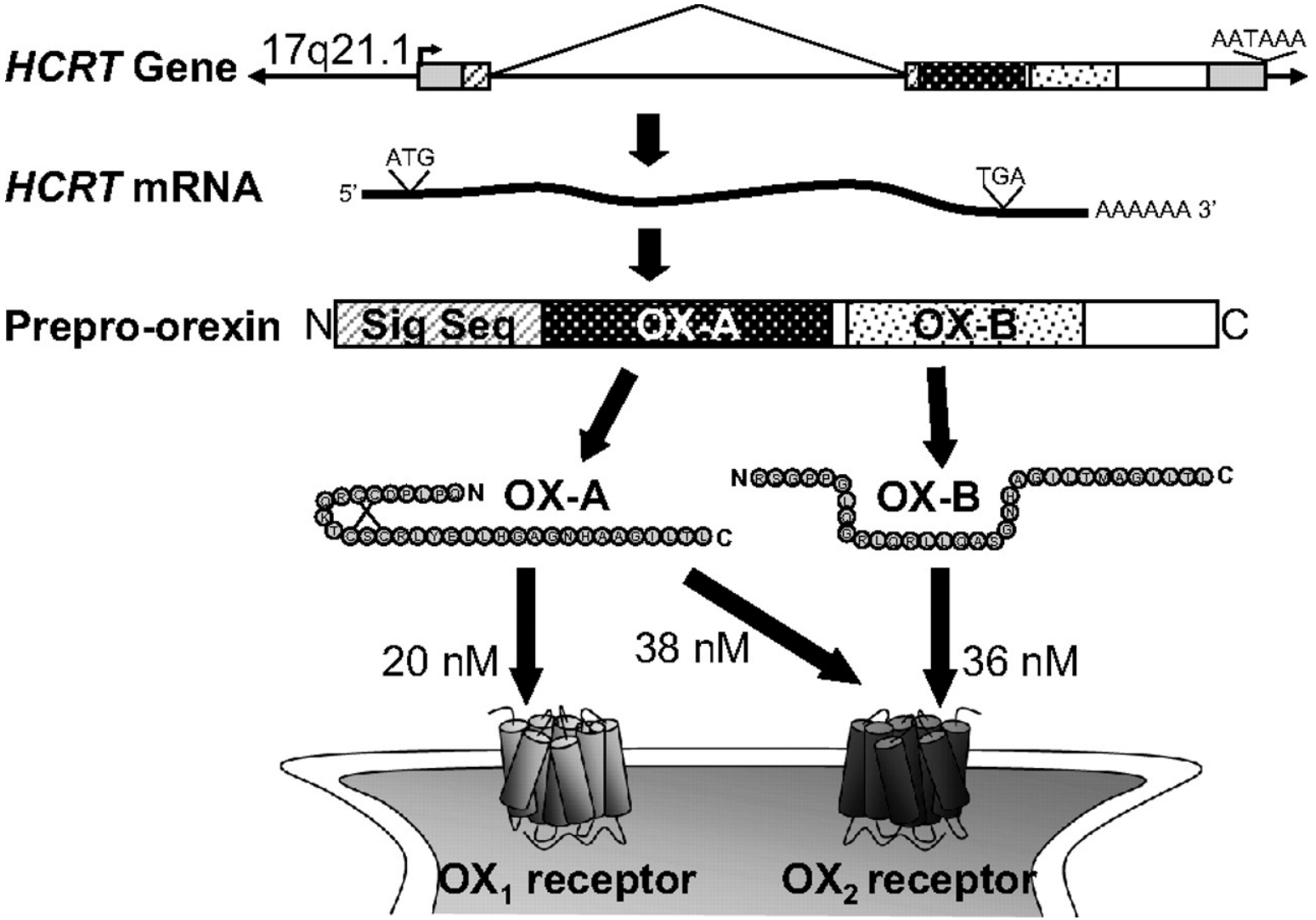
Key Learning Points

- Several compounds available for the management of narcolepsy
- Majority target monoaminergic aspects of the arousal mechanism
- Side effects can make use of specific compounds challenging
  - Co-occurring psychiatric conditions
  - Co-occurring cardiometabolic disease

Orexin 2 Receptor Agonists

Emerging Therapeutics for CNS Hypersomnias

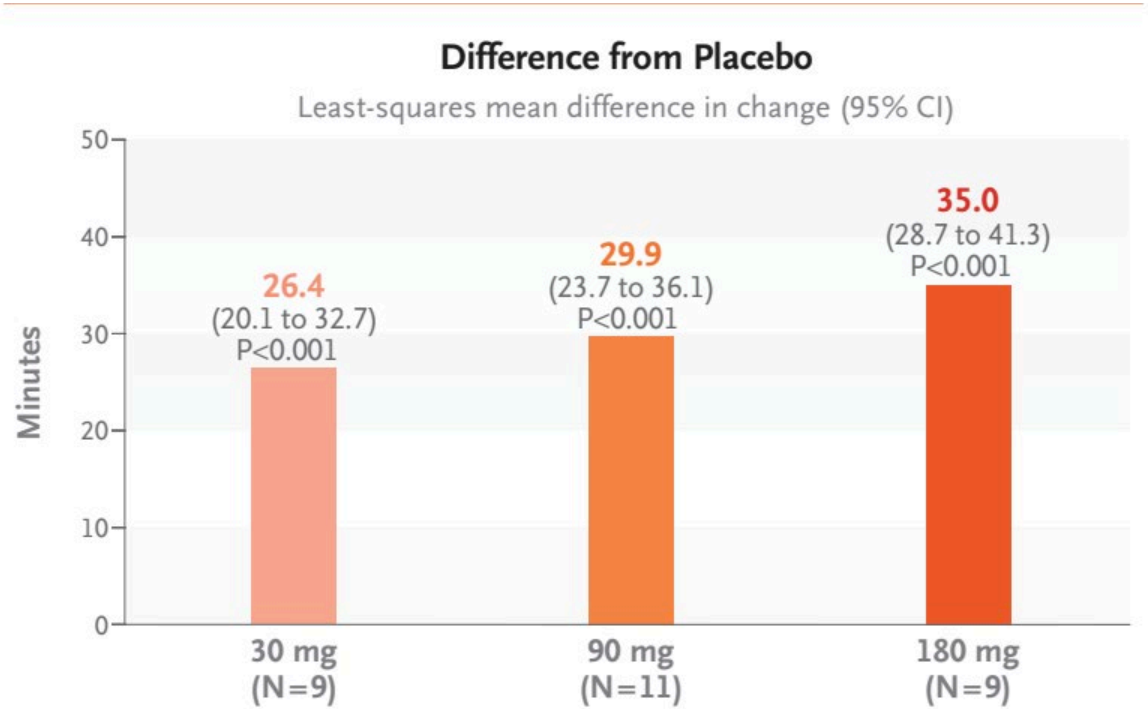
Basics of Orexin



Gotter AL, et al. *Pharmacol Rev*. 2012;64(3):389-420.

Climbing the Orexin Agonist Mountain

- JZP441 (DSP-0187)
  - Development stopped due to "visual disturbances" and cardiovascular effects
- TAK-994
  - High degree of clinical efficacy in Phase 2 study
  - Development stopped due to idiosyncratic drug-induced hepatotoxicity

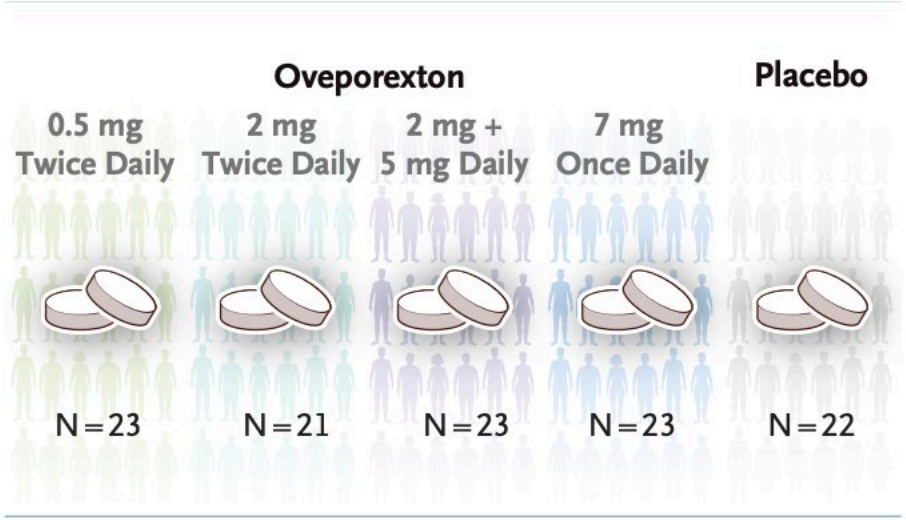


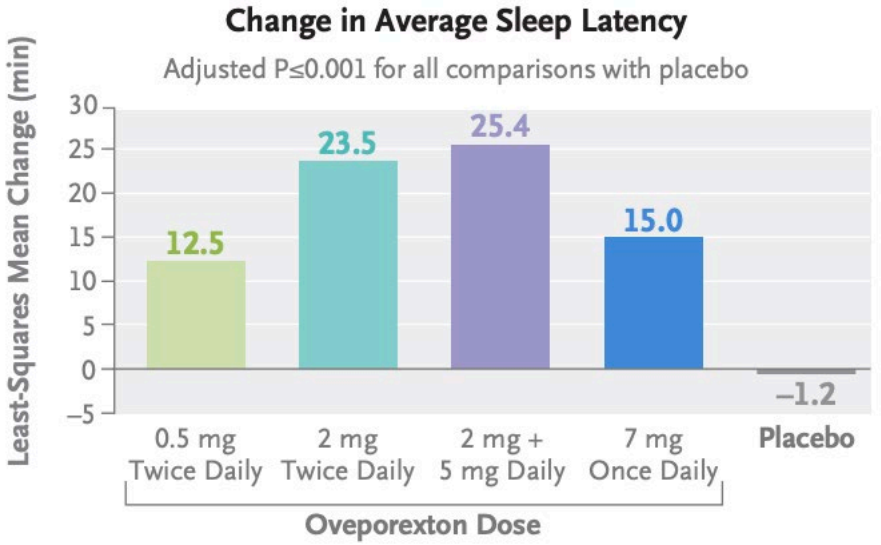
CI = confidence interval.

Dauvilliers Y, et al. *N Engl J Med*. 2023;389(4):309-321.

Oveporexton (TAK-861)

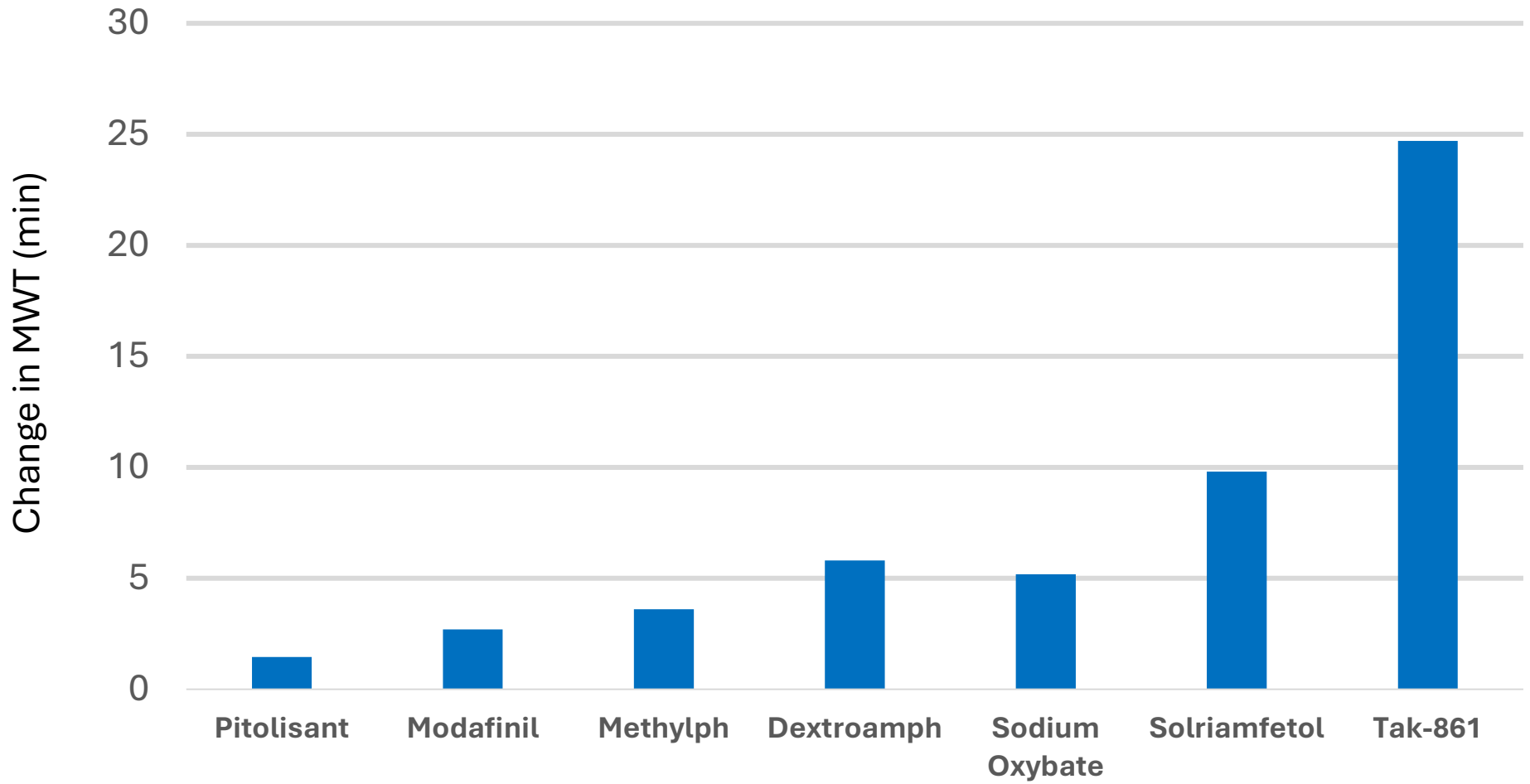
- Highly selective Orexin 2 agonist furthest along the developmental pipeline
- Published positive phase 2 study
- Reductions in daytime sleepiness and cataplexy
- Most common side effects included insomnia, urinary urgency/frequency, salivary hypersecretion, headache, nasopharyngitis
- No hepatotoxicity





Dauvilliers Y, et al. *N Engl J Med*. 2025;392:1905-16.

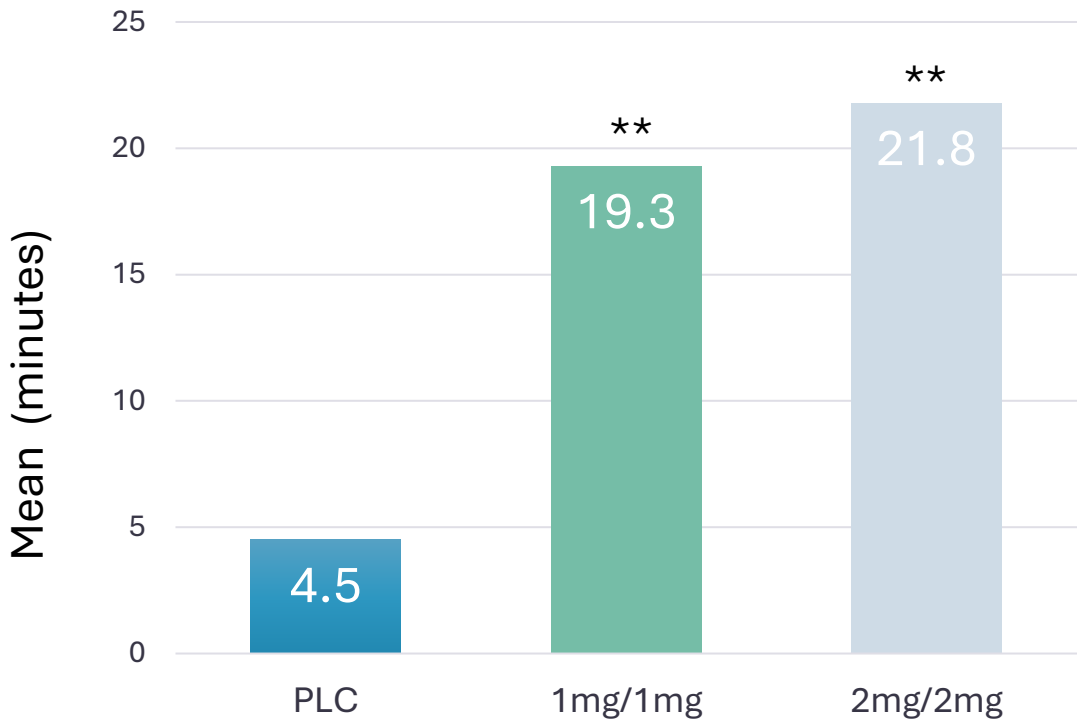
Orexin Agonists Set New Standards in Wake Promotion for Narcolepsy



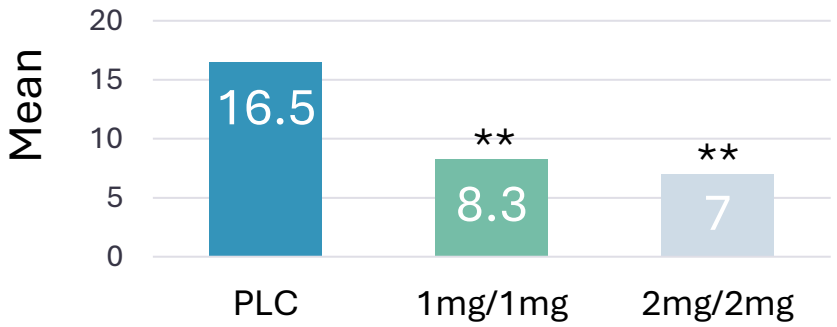
Mitler MM, Hajdukovic R. *Sleep*. 1991;14(3):218-220. Thorpy MJ, et al. *Ann Neurol*. 2019;85(3):359-370. Alshaikh MK, et al. *J Clin Sleep Med*. 2012;8(4):451-458. Dauvilliers Y, et al. *N Engl J Med*. 2023;389(4):309-321. NIH. 2023. Accessed September 2025. https://www.ncbi.nlm.nih.gov/books/NBK601765/.

FirstLight (Phase 3): Oveporexton (TAK-861)

MWT



ESS



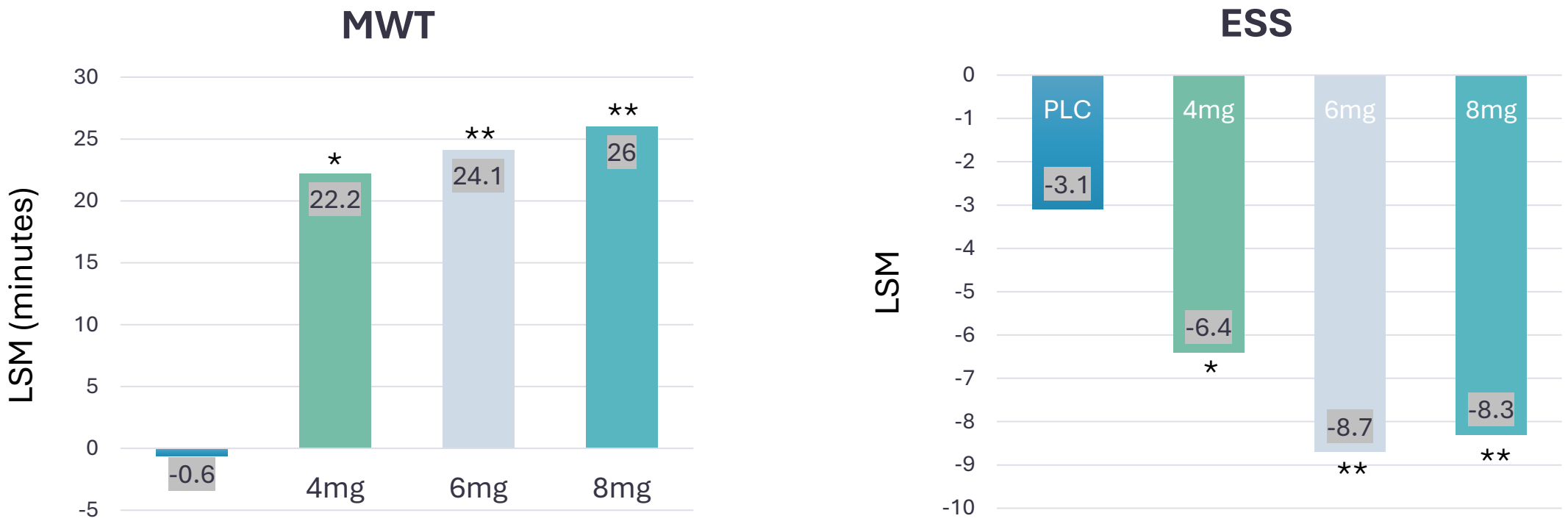
**p<0.001

Cataplexy

Treatment	IRR (95%CI)
1mg/1mg	0.34 (0.20, 0.57)**
2mg/2mg	0.38 (0.23, 0.61)**

Mignot E, et al. **The First Light: Efficacy and Safety of a Multi-Dose Study of Oveporexton (TAK-861), an Oral Orexin Receptor 2 Agonist, for the treatment of narcolepsy type 1.** Presented at: World Sleep Congress 2025; Sept 5-10, 2025; Singapore. **https://vimeo.com/showcase/11870602. Accessed September 15, 2025**

Vibrance-1 (Phase 2): Alixorexton (ALKS-2680)



*p=0.01; **p<0.0001

Press Release. Alkermes. https://investor.alkermes.com/news-releases/news-release-details/alkermes-presents-detailed-positive-results-vibrance-1-phase-2. Accessed September 15, 2025.

Other Orexin 2 Agonists in the Pipeline

- ORX-750
  - Currently in Phase 2 randomized, double-blind, placebo-controlled, cross-over basket study with separate cohorts for NT1, NT2, and IH
- TAK-360
  - Currently Phase 2 studies in NT2 and IH
- Others on the horizon

Key Learning Points

- Orexin 2 agonists show immense promise in improving core symptoms and features of type 1 narcolepsy
- Orexin 2 agonists are also being studied as therapies for other disorders associated with excessive daytime sleepiness (NT2 and IH)
- Potential for a new class of medications that could ultimately have broad implications for treatment of many neuropsychiatric conditions

Faculty Panel Discussion

Role of Psychiatry Clinicians in the Care of Patients with Narcolepsy

Optimal Collaboration with Sleep Specialists
(eg, Obtaining Sleep Studies)

Primacy of Orexin in Many Sleep-Wake Disorders

Potential of Orexin Beyond Narcolepsy
(eg, EDS in OSA, ADHD)

Further Consultation & Education Resources

Sleep Research Society and American Academy of Sleep Medicine

Practical Take-Aways

- Embrace sleep and begin looking for excessive daytime sleepiness in your patients
- Know when to refer to sleep specialist and advocate for your patient's journey to diagnosis of narcolepsy
- Watch for orexin agonists and their implications in narcolepsy, as well as orexinergic MOAs to treat other psychiatric comorbidities

MOA = mechanism of action.

Q&A