Sleep is the Foundation of Mental Health: The Bidirectional Relationship of Sleep and Psychiatric Conditions

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Faculty Disclosures

- Advisory Board: AbbVie, Acadia, Alkermes, Axsome, Biogen, Bristol Myers Squibb, Corium, Eli Lilly, Idorsia, Intra-Cellular, Jazz, Johnson & Johnson, Lundbeck, Moderna, Neurocrine, Otsuka, Sage, Sumitomo, Takeda, Teva; Advisory Board (spouse): Bristol Myers Squibb, Otsuka; Consultant: AbbVie, Acadia, Alkermes, Axsome, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Corium, Eli Lilly, Intra-Cellular, Johnson & Johnson, Lundbeck, MedinCell, Moderna, Neurocrine, Otsuka, Sage, Sumitomo, Supernus, Takeda, Teva; Research/Grant Support: Acadia, Axsome, Harmony, Neurocrine, Teva; Speaker's Bureau: AbbVie, Acadia, Alkermes, Axsome, Boehringer Ingelheim, Bristol Myers Squibb, Corium, Intra-Cellular, Jazz, Johnson & Johnson, Lundbeck, Luye, Merck, Neurocrine, Otsuka, Sumitomo, Takeda, Teva; Stocks/Stock Options/Ownership Interest/Patents: none

Learning Objectives

- Describe the bidirectional relationship between sleep-wake cycles and psychiatric disorders
- Evaluate the uses and limitations of traditional pharmacotherapies, and consider the potential contributions of novel/investigational pharmacotherapies for sleep-wake disorders in psychiatric patients
- Identify clinical characteristics that raise suspicion for sleep-wake disorders, along with key questions to ask to improve detection and diagnosis in psychiatric patients

Significance of Sleep-Wake Disorders in Psychiatry

Why Should Psychiatric Clinicians Care About Sleep-Wake-Circadian Medicine?

Case Study: 31-year-old man seeking treatment for longstanding diagnoses of ADHD and depression

Clinical Presentation

- Careful questioning revealed he had experienced EDS since childhood
- Feeling sleepiness “beyond belief,” with only brief relief from stimulants
- Mind fog and difficulty remaining awake while driving
- Some cataplexy and some hypnagogic and hypnopompic hallucinations
- Prescribed multiple antidepressants and stimulants with little clinical benefit

Referral to sleep specialist confirmed the suspected diagnosis of **narcolepsy type 1**

Initial Treatment

Started low-sodium oxybate 2.25 g, twice nightly for 1 week, titrated to 3.75 g, twice nightly

EDS=Excessive daytime sleepiness.

Chepke C. *J Psychiatry Neurosci*. 2023;48(6):E472-E473.

Case Study: 31-year-old man seeking treatment for longstanding diagnoses of ADHD and depression

After 6 weeks of treatment:

Symptomatic Improvement	• ESS improved from 22 at diagnosis to 7 • Patient reported no napping, anxiety, depression, or cataplexy
Functional Improvement	• Significant improvements in **concentration, work performance,** and **family relationships** • Discontinued stimulant and anti-depressant use
Familial Improvement	• Based on the successful results of treatment, his father and multiple siblings subsequently received diagnoses for narcolepsy and responded well to low-sodium oxybate

EDS=Excessive daytime sleepiness; ESS=Epworth Sleepiness Scale

Chepke C. *J Psychiatry Neurosci*. 2023;48(6):E472-E473.

Sleep Is the Foundation of Mental Health…

…and without a good foundation, **your whole house will crumble**

However, a survey of psychiatry residency programs in North America found that only 34% offered an elective in sleep medicine.

Fewer than half (47%) of **chief residents** who responded were comfortable screening for SWDs outside of sleep apnea and RLS.

SWD=Sleep-Wake Disorder; RLS=Restless Leg Syndrome.

Feinstein, RE, et al. *Prim Care Companion CNS Disord*. 2017;19(4):17br02167. Khawaja, IS, et al. *Prim Care Companion CNS Disord.* 2017;19(4): 23273.

Sleep-Wake Disorders in DSM-5-TR and Their Importance to Psychiatric Clinicians

DSM-5 Sleep-Wake-Circadian Disorders/Groups

- Insomnia Disorder
- Hypersomnolence Disorder
- Narcolepsy
- Breathing-Related Sleep Disorder (eg, OSA)
- Circadian Rahythm Sleep-Wake Disorders
- Parasomnias
  - Non-REM Sleep Arousal Disorders
  - Nightmare Disorder
  - REM Sleep Behavior Disorder
- Restless Legs Syndrome
- Substance/Medication-Induced Sleep Disorder

Complaints are of dissatisfaction regarding the quality, timing, and amount of sleep.

However, resulting **daytime distress and impairment** are core features shared by all sleep-wake disorders.

Sleep disorders are often accompanied by **depression, anxiety, and cognitive changes** that must be addressed in treatment planning and management.

Furthermore, persistent sleep disturbances (both insomnia and excessive sleepiness) are established **risk factors** for the subsequent development of mental illnesses and substance use disorders.

They may also represent a **prodromal expression** of an episode of mental illness, allowing the possibility of early intervention to preempt or attenuate a full-blown episode.

OSA=obstructive sleep apnea; REM=rapid eye movement.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-Text Revision.* American Psychiatric Association Publishing; 2023.

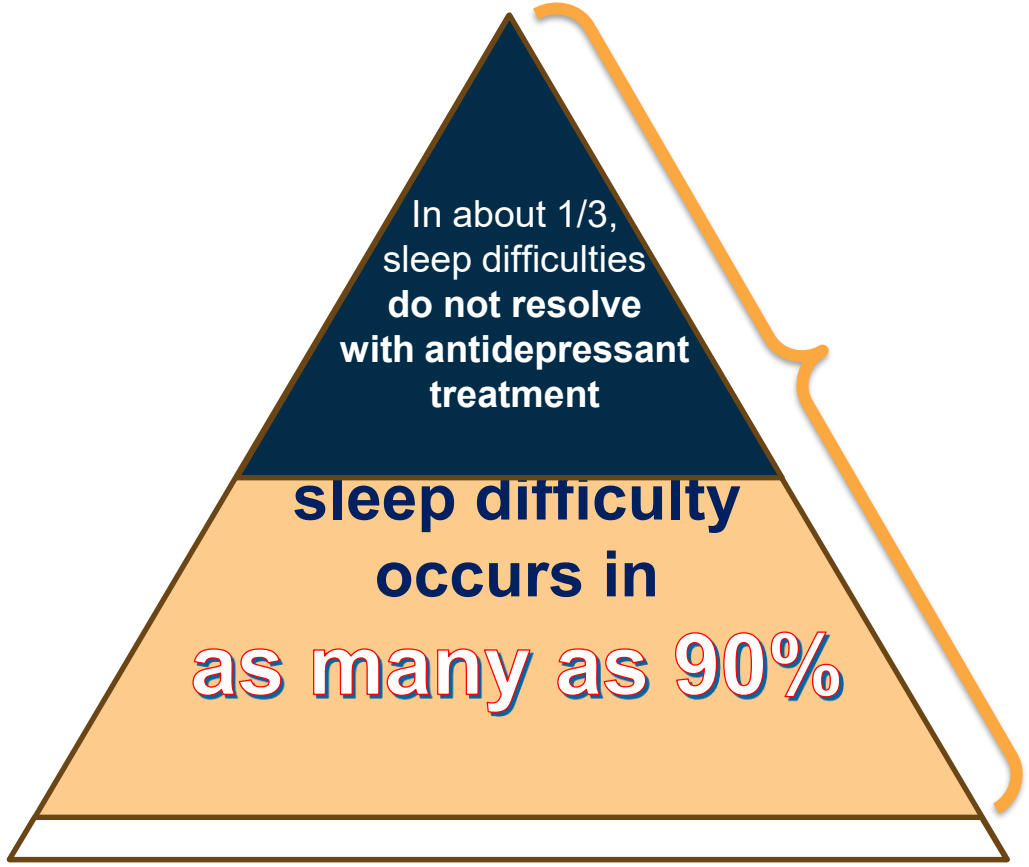
Important Changes in Sleep-Wake Disorders from DSM-IV-TR to DSM-5-TR

	DSM-IV-TR	DSM-5-TR
General	"Sleep Disorders"	"Sleep-Wake Disorders"
Insomnia	Divided into 1° and 2° Insomnia Specified as 1 month duration	No 1° vs 2° distinction → "Insomnia Disorder" Specified as ≥3 times a week, for 3 months duration
Hypersomnolence	Divided into 1° and 2° Hypersomnolence; Excessive sleepiness criterion: over past month	No 1° vs 2° distinction → "Hypersomnolence Disorder" Excessive sleepiness ≥3 times/wk over past 3 mos
Narcolepsy	Narcolepsy: irrepressible sleepiness almost daily	Irrepressible sleepiness ≥3 times/wk over past 3 mos
Circadian Rhythm		Subtypes of circadian rhythm sleep-wake disorders changed and expanded
Breathing-Related Sleep Disorders	"Breathing-related sleep disorders" was a single diagnosis	Split into Obstructive Sleep Apnea, Central Sleep Apnea, and Sleep-Related Hypoventilation
Restless Legs Syndrome	Part of "Dyssomnia Not Otherwise Specified"	Restless legs syndrome elevated to its own independent diagnostic category
Substance-Induced Sleep Disorder		Broadened to incorporate medication-induced sleep disorder, and highlighted the effects of psychotropics

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision.* American Psychiatric Association Publishing; 2000.
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-Text Revision.* American Psychiatric Association Publishing; 2023

Prevalence and Consequences of Sleep Disturbances…

In Major Depressive Disorder



Those with **poor sleep** have:

- **Lower remission rates**
- **Faster relapse**
- **Slower improvement**
- **Poorer quality of life**

Independent of depression severity

At least **32 studies** (as of 2012) have identified that sleep disturbance is **significantly linked to suicidal ideation** or **completed suicide**, even when controlling for age, gender, diagnosis, and severity of depressive symptoms.

Krystal AD. *Neurologic Clinics. 2012;*30(4):1389-1413. Ballard ED, et al. J Clin Psychiatry. 2016;77(6):825-831.

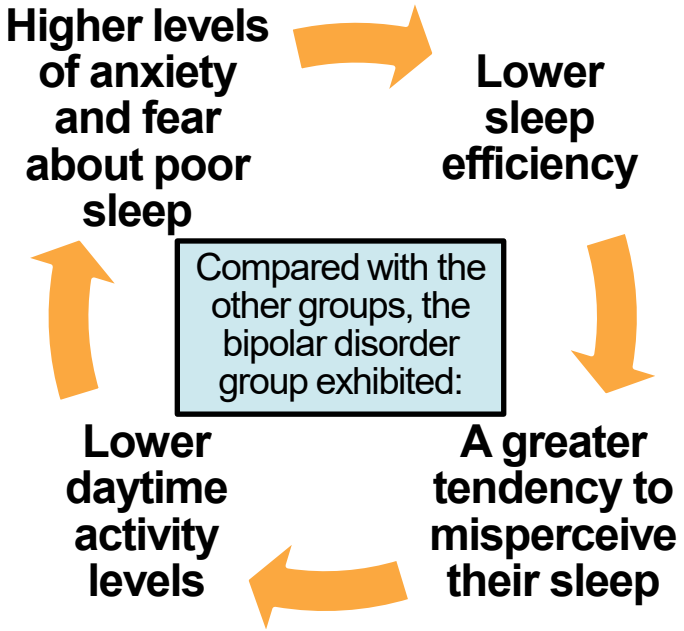
Prevalence and Consequences of Sleep Disturbances…

In Bipolar Disorder

Sleep-related functioning was assessed subjectively using data from interviews and 8 nights of sleep diaries, as well as objectively with actigraphy in individuals with:

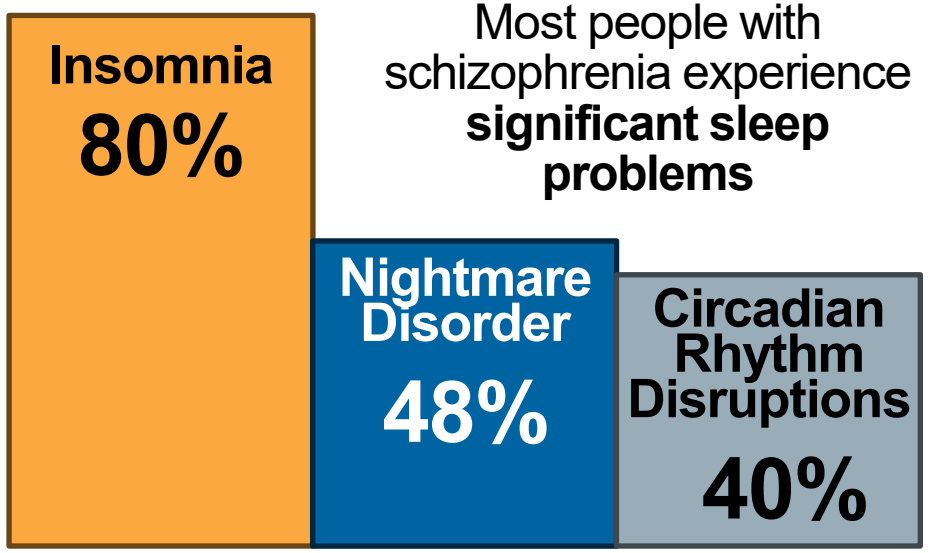
Bipolar Disorder in euthymia, Insomnia Disorder, and in healthy volunteers with good sleep (N=20 in each group)

70% of those with bipolar disorder who were **euthymic** exhibited a clinically significant sleep disturbance.



In Schizophrenia

Most people with schizophrenia experience **significant sleep problems**



Sleep disruption significantly predicts the **onset** and **persistence of psychotic experiences**, such as paranoia and hallucinations

Harvey AG, et al. Am J Psychiatry. 2005;162(1):50-57. Waite F, et al. Schizophr Res. 2020;221:44-56.

Prevalence and Consequences of Sleep Disturbances…

In Generalized Anxiety Disorder

About **60–70%** of patients with GAD and panic disorder reported prominent sleep disturbances

Up to **90%** of individuals with GAD report **insomnia symptoms**

Insomnia interacts with the **emotional**, **cognitive**, and **physiological** processes underlying anxiety

excessive worry → *can lead to* → poor sleep → *perpetuates* → excessive worry

In Post-Traumatic Stress Disorder

In the general population:

More sleep symptomology is associated with **greater PTSD symptom severity**

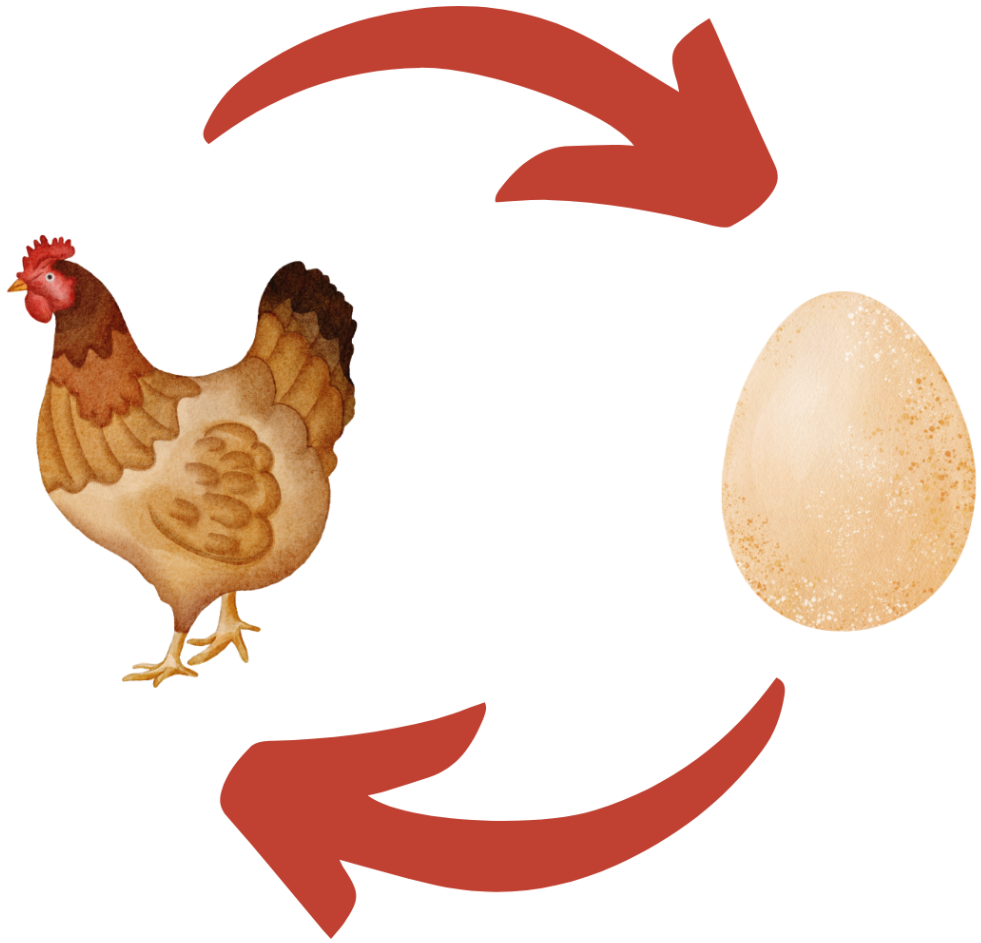
Nearly 40% of participants with PTSD had an insomnia disorder

Dangerous behaviors during sleep (punching, kicking, etc.) occur **10x more often in PTSD**

GAD=Generalized Anxiety Disorder; PTSD=Post-Traumatic Stress Disorder.

Monti JM, Monti D. Sleep Med Rev. 2000;4(3):263-276. Xue Y, et al. Sleep Med. 2025;132:106545. Slavish DC, et al. *Sleep Med*. 2023;101:269-277. Koffel E, et al. *Psychiatr Ann*. 2016;46(3):173-176. Ohayon MM, Shapiro CM. *Compr Psychiatry*. 2000;41(6):469-478.

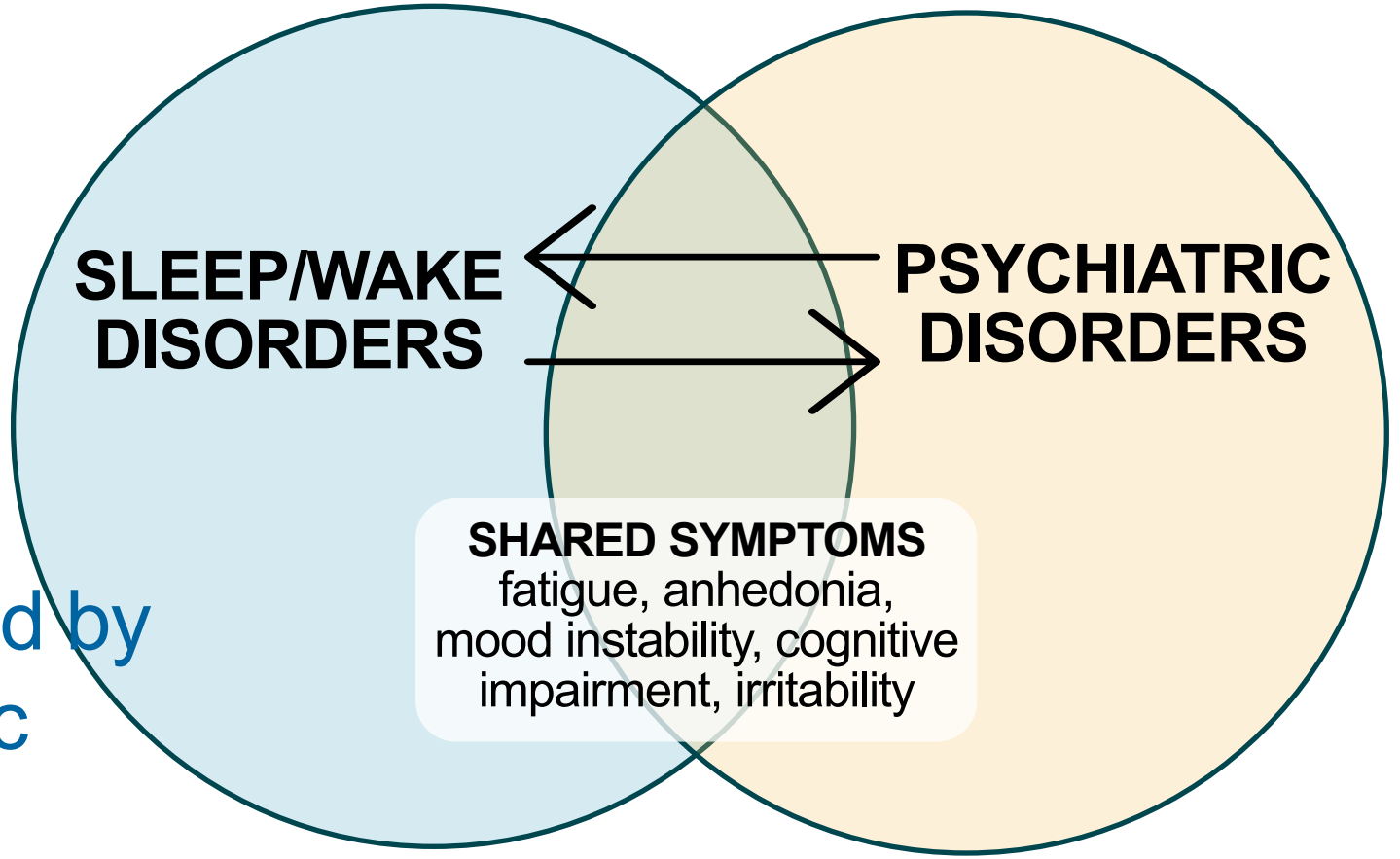
Do Psychiatric Conditions Cause Sleep Disorders? …or do Sleep Disorders Cause Psychiatric Conditions?



Sleep disturbances are both a **risk factor** and a **symptom** of psychiatric disorders

Krystal AD. *Neurologic Clinics. 2012;*30(4):1389-1413. Harvey AG, et al. *Am J Psychiatry.* 2005;162(1):50-57.

Also, Each May Exacerbate the Other



…and can be worsened by common psychiatric medications

REM= rapid eye movement; RLS=restless leg syndrome; PLMS=periodic limb movements of sleep; SSRI=selective serotonin reuptake inhibitor.

Krystal AD. *Sleep Med Clin*. 2010;5(4):571-589. Krystal AD. *Neurol Clin*. 2012;30(4):1389-1413.

Sleep/Wake Side Effects of Psychiatric Medications

Sedating Effects

- Daytime drowsiness
- Increased total sleep time
- ”Morning hangover”

- Tricyclic antidepressants
  - Amitriptyline
  - Doxepin
- Atypical antipsychotics (some)
  - Quetiapine
  - Olanzapine
- Mood stabilizers
  - Lithium
  - Valproate
- Select anxiolytics
  - Hydroxyzine
  - Pregabalin

Activating Effects

- Insomnia
- Sleep fragmentation
- Vivid dreams
- Nightmares

- SSRIs (especially early)
  - Fluoxetine
  - Sertraline
- SNRIs
  - Venlafaxine
  - Duloxetine
- Bupropion
- Select antipsychotics
  - Aripiprazole
  - Lurasidone
- Stimulant-based ADHD medications

Complex Effects

- May require polysomnography to identify and properly characterize

- Antidepressants
  - REM suppression
- Antidepressants, some antipsychotics
  - Periodic limb movements
- Psychotropics
  - Weight gain
  - Potential OSA exacerbation
- Anticholinergics
  - Can worsen sleep-disordered breathing

Ghossoub E, et al. *Sleep Sci*. 2021;14(3):236-44.

Antipsychotic Medications and Sleep

- Increase slow-wave sleep and total sleep time
- Reduce sleep latency
- Effects on REM sleep vary

Sedation profiles vary dramatically by drug and individual

- Profound sedation: clozapine
- High sedation: quetiapine and olanzapine
- Mild sedation: aripiprazole and lurasidone

Atypical antipsychotics cause weight gain

- Can worsen or unmask OSA
- Sedative effects can reduce respiratory tone
- Consider screening for OSA before initiating

Antipsychotics can induce or worsen

- Period limb movement disorder
- REM behavior disorder
- Monitor for effects on sleep and movement disorder symptoms

Low-dose quetiapine (25-100 mg) often prescribed for insomnia, despite limited evidence of favorable benefit-risk ratio

Valencia Carlo YE, et al. ***Front Psychiatry***. 2023;14:1189768.

Mood Stabilizers: Sleep/Wake Considerations

Lithium

- Increases slow-wave sleep
- Can improve sleep continuity
- May lengthen circadian period requiring schedule adjustments
- Polyuria can cause sleep disruption through nocturia
- Tremor may interfere with sleep onset

Lamotrigine

- Minimal direct effects on sleep architecture compared to other mood stabilizers
- Less likely to cause daytime sedation
- Rare reports of insomnia during dose titration
- Generally, weight-neutral, with favorable OSA risk profile

Valproate

- Moderately sedating
- Dose-dependent effects on daytime alertness
- Generally improves sleep continuity.
- Can exacerbate OSA through weight gain.
- Monitoring for excessive daytime sleepiness

Carbamazepine

- Moderate sedative properties, especially during initiation
- Autoinduction of metabolism may reduce sedation over time
- Increases slow-wave sleep with variable effects on REM
- Drug interactions can affect other sleep medications.

Legros B, Bazil CW. *Sleep Med*. 2003;4(1):51-5.

Effects of Psychiatric Medications on Sleep-Wake

Pharmacologic Mechanisms of Medication Effects on Sleep and Wake

Mechanism	Sleep Promotion	Wake Promotion	REM Suppression	Increases SWS	Promotes RLS/PLMS
H_1 antagonism	✓				
Muscarinic antagonism	✓		✓		
5-HT_2 antagonism	✓			✓	
α_1 Antagonism	✓				
D_1/D_2 antagonism	✓				✓
α_2 agonism	✓				
α_2 antagonism		✓			
β_2 antagonism		✓	✓		
5-HT reuptake inhibition		✓	✓		✓
NE reuptake inhibition		✓			
DA reuptake inhibition		✓			
MAO inhibition		✓	✓		✓
5-HT_{1A} agonism		✓	✓		

SSRIs can result in insomnia at a rate of 3x more than placebo.

REM suppression can make the sleep one does get less restorative and refreshing

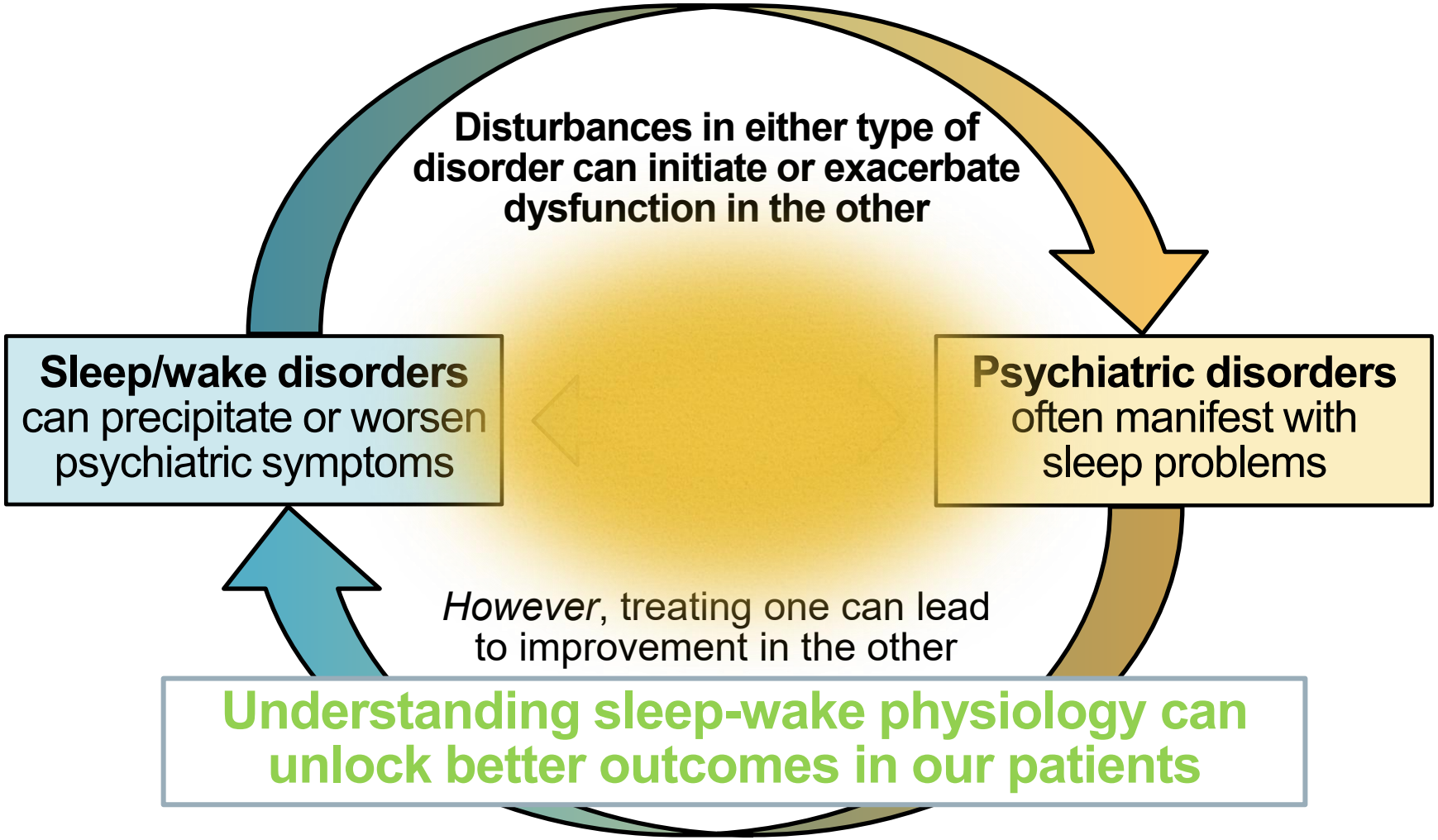
All SSRIs/SNRIs/TCAs can cause or exacerbate RLS or PLMS: more so for those with antihistamine effects

RLS can occur in up to 28% taking mirtazapine

TST=Total Sleep Time; SWS=Slow Wave Sleep; SSRI=Selective Serotonin Reuptake Inhibitor; SNRI= Serotonin-Norepinephrine Reuptake Inhibitor; TCA=Tricyclic Antidepressant; PLMS=Periodic Limb Movement Disorder.

Krystal AD. *Sleep Medicine Clinics.* 2010;5(4):571-589. Krystal AD. *Neurologic Clinics.* 2012;30(4):1389-1413. Rottach KG, et al. *J Psychiatr Res.* 2008;43(1):70-75. Hoque R, et al. *J Clin Sleep Med.* 2010;6(1):79-83.

Sleep/Wake and Psychiatric Disorders Are Bidirectional



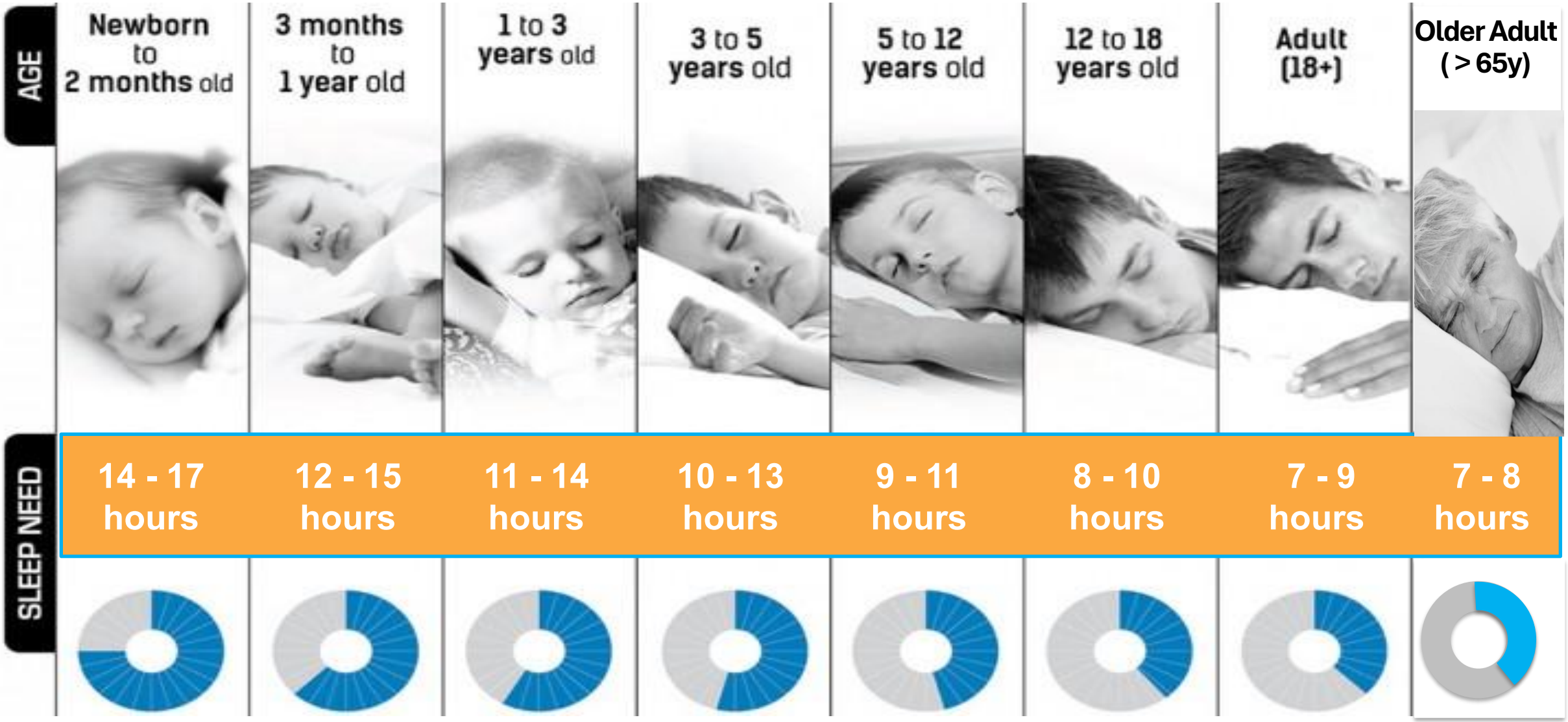
Benca RM, Buysse DJ. J Clin Psychiatry. 2018;79(1):me17008ah1c.

Key Learning Points

- There is a bidirectional relationship between sleep-wake disorders and psychiatric disorders, so sleep symptoms can give us a glimpse into an individual's psychiatric status
- Sleep disturbances negatively impact an individual's mental health in various ways, regardless of their diagnosis.
- Most medications used to treat psychiatric conditions have an important influence on an individual's sleep and wake, which can have effects which may mimic some psychiatric symptoms.

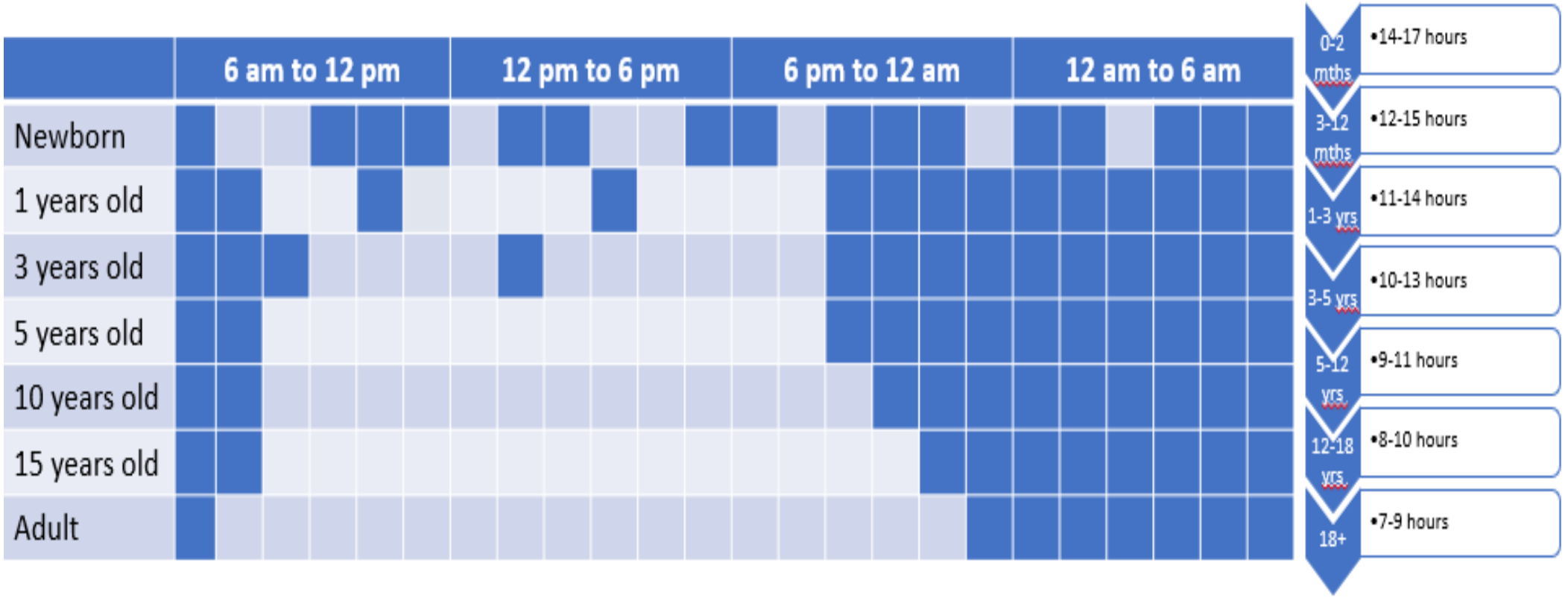
Neurophysiology of Sleep Wake and Circadian Science for Psychiatry Practice

Developmental Sleep Needs



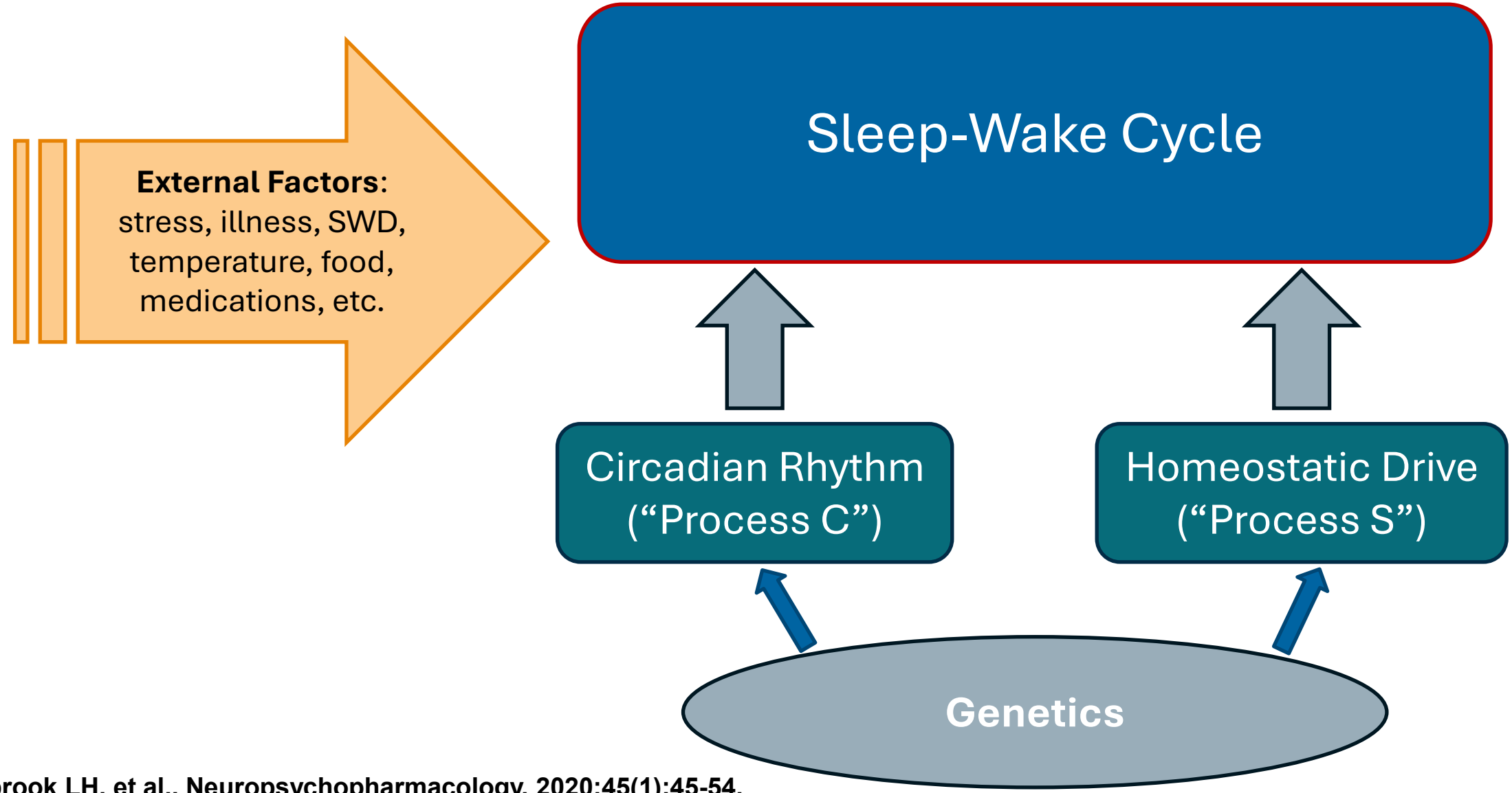
Hirshkowitz M, et al. Sleep Health. 2015;1(1):40-43.

Developmental Sleep Wake Patterns



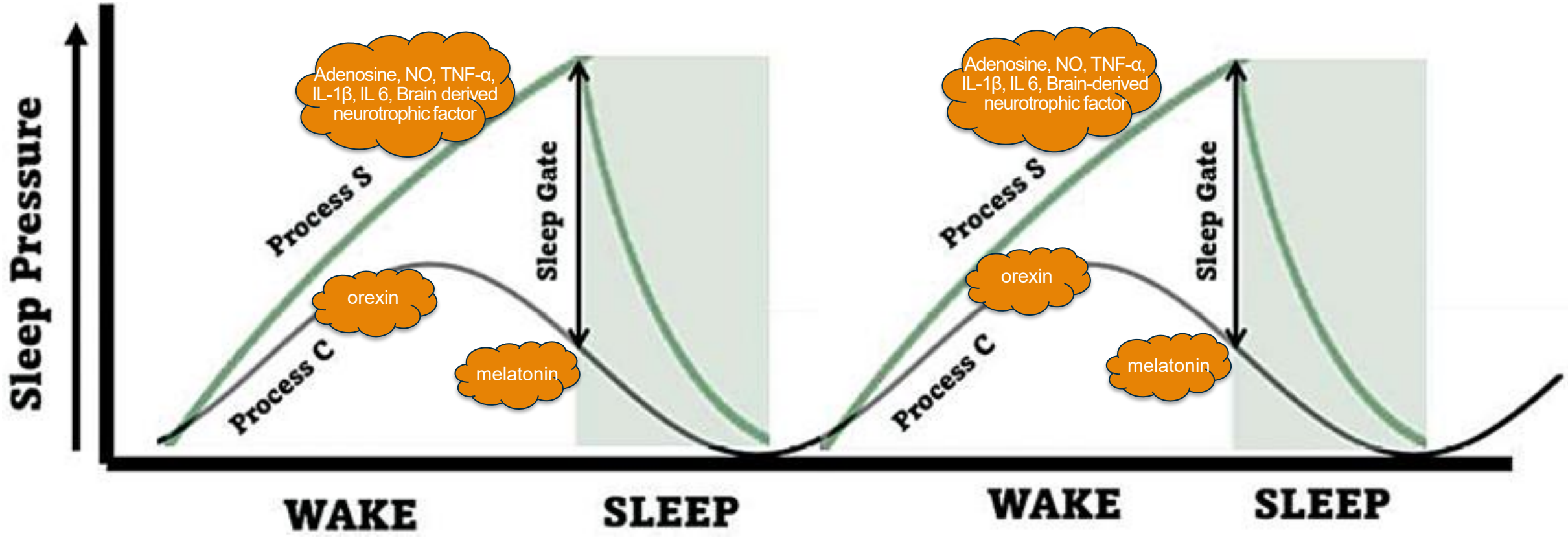
Morse & Strong, Sleep and Genetic Neurodevelopmental Disorders, Genetics of Sleep and Sleep Disorders, 2024; Adapted from Morse, Practical Neurology 2019

Sleep and Circadian Regulation



Ashbrook LH, et al., Neuropsychopharmacology. 2020;45(1):45-54.

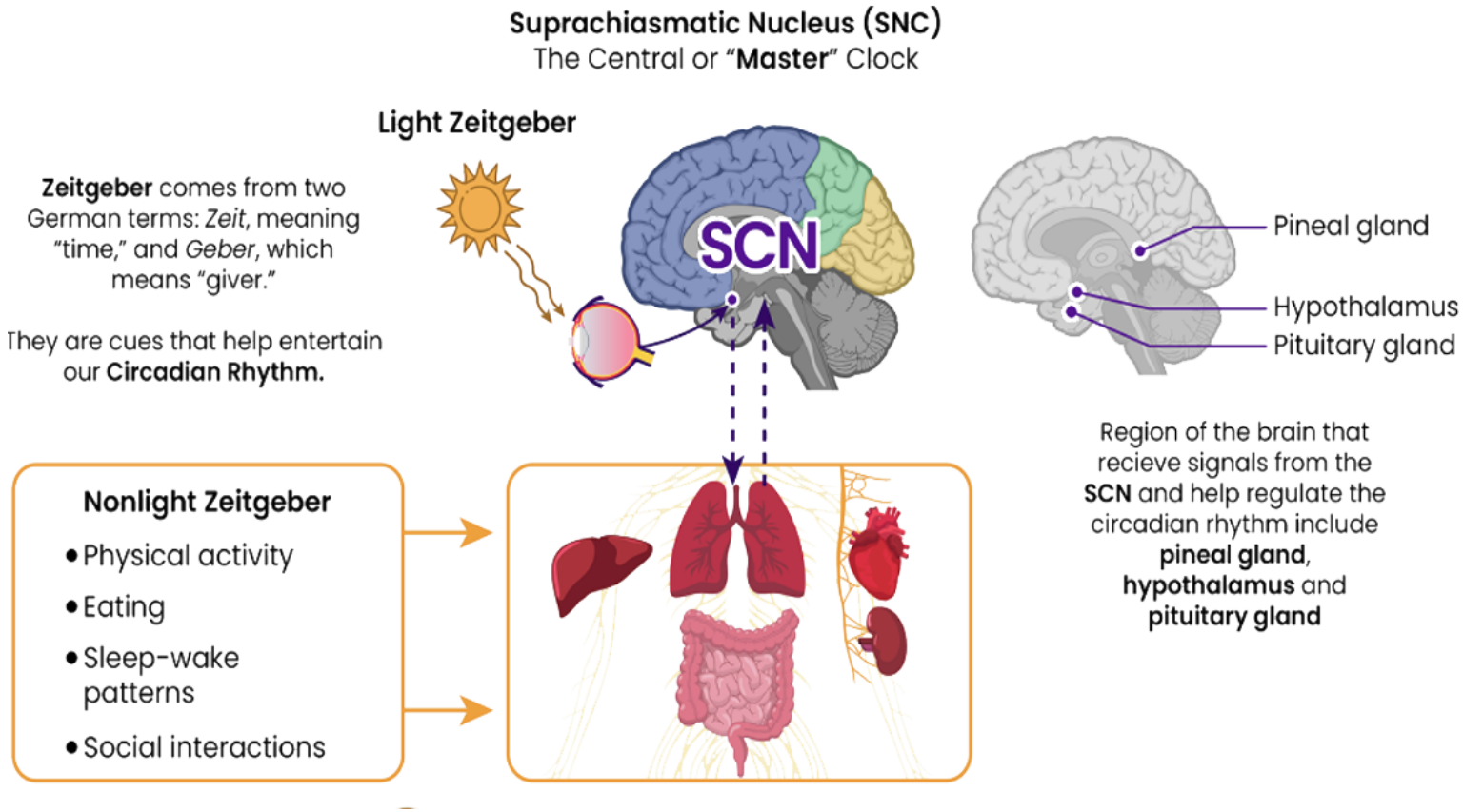
Physiology of the Sleep-Wake Cycle



NO=Nitric Oxide; **TNF-α=Tumor Necrosis Factor-Alpha; IL=Interleukin**

Adapted from Morse, A.M., 2025, May. Enhancing the management of hypersomnia: Examining the role of the orexin system. In *Seminars in Neurology*.

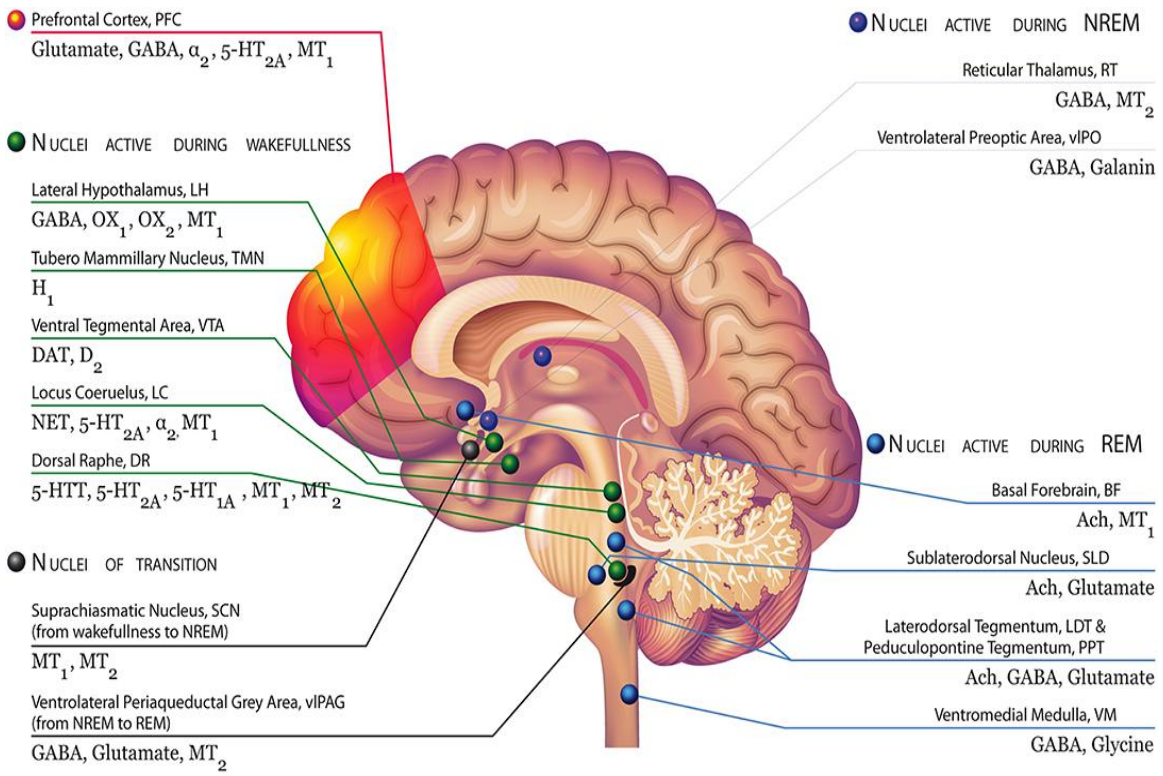
Circadian Rhythm…
More than (What) Meets the Eye?



The circadian rhythm is part of the body's internal clock. It follows a 24-hour schedule that regulates the sleep-wake cycle, hormone production, and other bodily functions, as well as our behaviors.

Sleep & Circadian Basics. SleepHealth.org. Accessed September 10, 2025. https://www.sleephealth.org/sleep-circadian-basics/

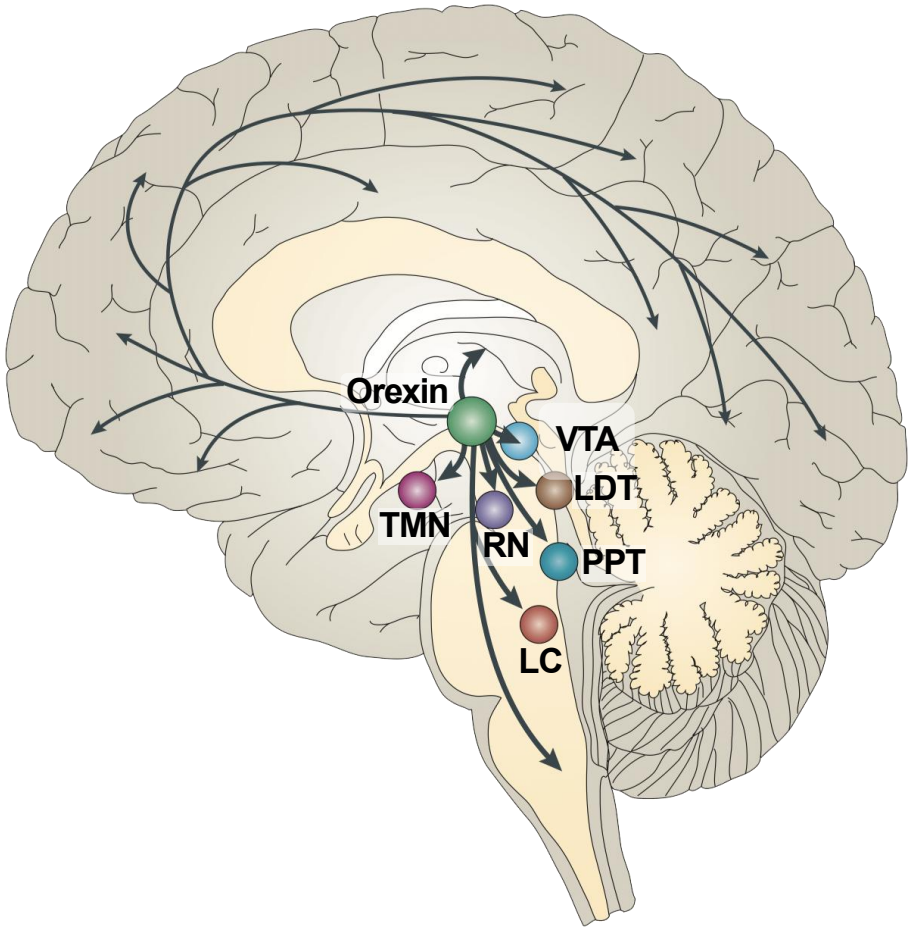
Areas of the Brain in Which Wake- and Sleep-Promoting Neurotransmitters are Produced

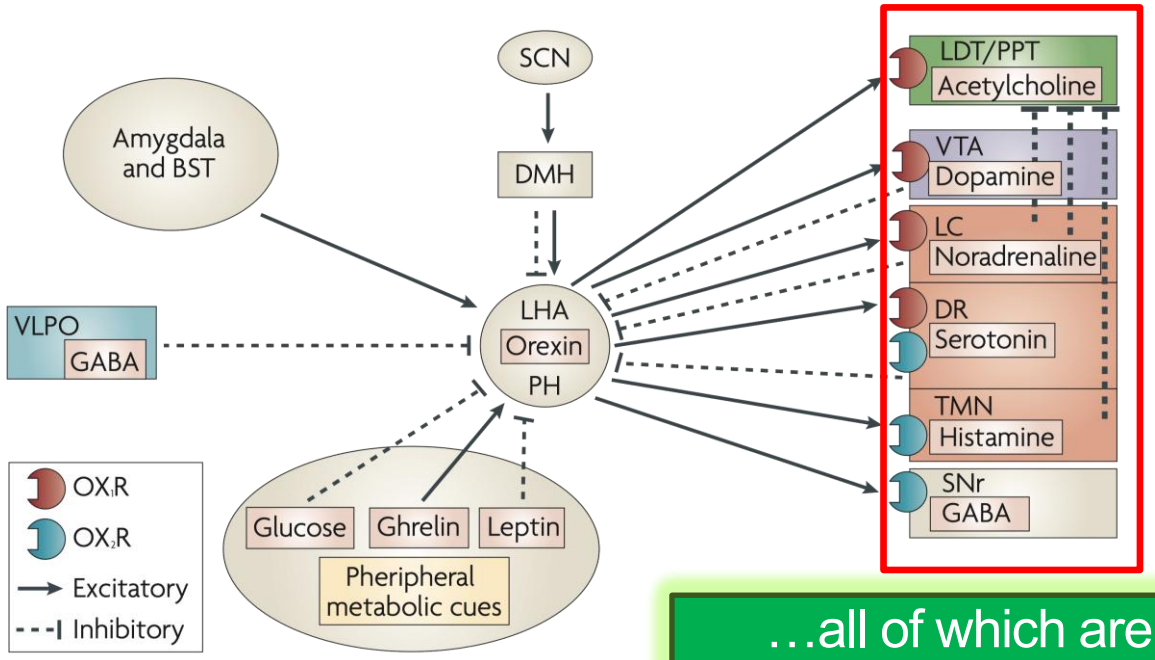


Area of the Brain	Neurotransmitter	Side of the Sleep Switch
Ventrolateral Preoptic Nucleus	GABA Galanin	Sleep
Locus Coeruleus	Norepinephrine	Wake
Substantia Nigra	Dopamine	Wake
Dorsal Medial Nucleus	Serotonin	Wake
Tuberomammillary Nuclei	Histamine	Wake

Atkin T, Comai S, Gobbi G. Drugs for insomnia beyond benzodiazepines: pharmacology, clinical applications, and discovery. *Pharmacol Rev*. 2018;70(2):197–245. Sleep & Circadian Basics. SleepHealth.org. Accessed September 10, 2025. https://www.sleephealth.org/sleep-circadian-basics/

Orexin Neurons Project to All Major Sleep-Wake Centers…



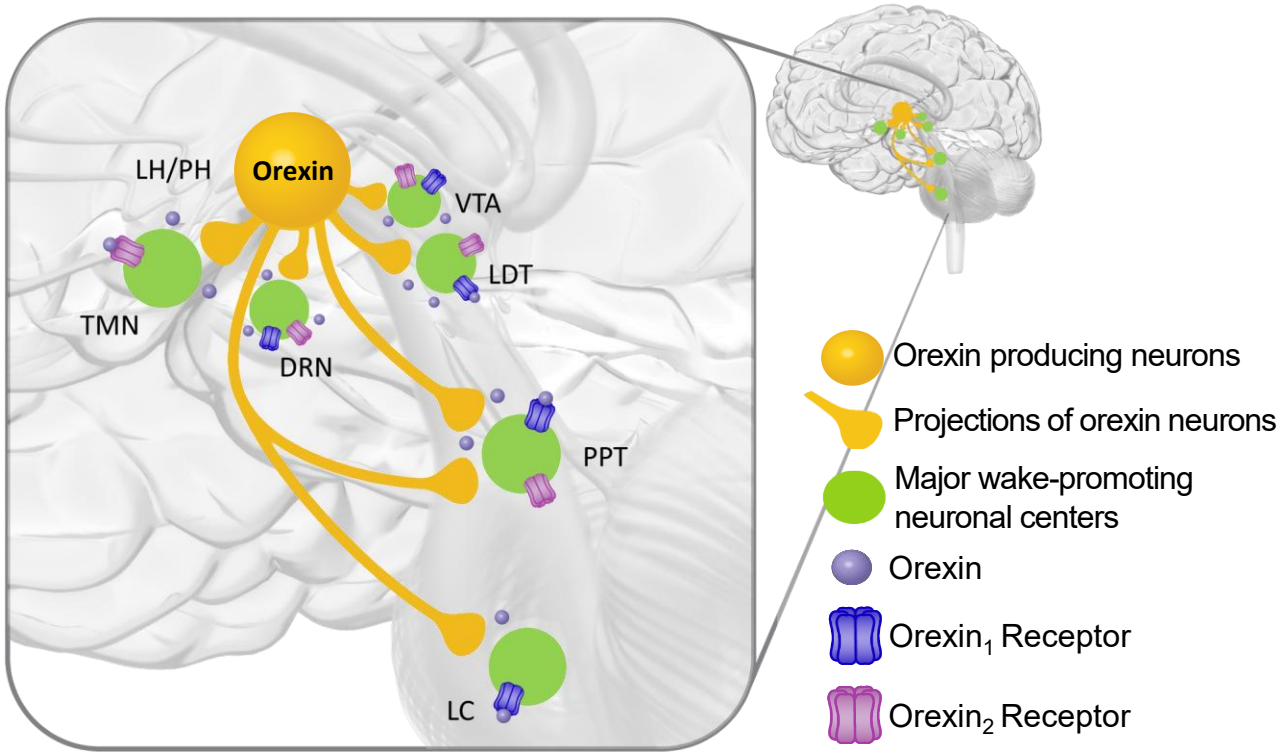


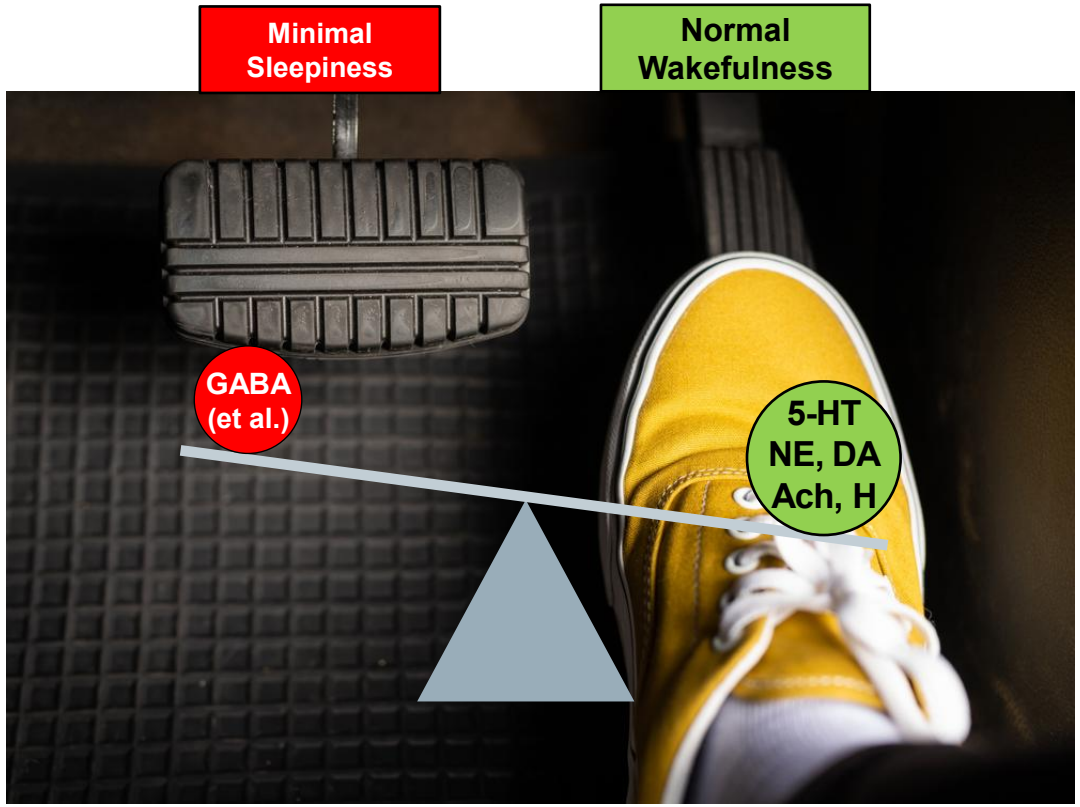
…all of which are also centers of neurotransmitters implicated in psychiatric conditions

VTA=Ventral Tegmental Area, LDT=Laterodorsal Tegmental; PPT=Pedunculopontine; LC=Locus Coeruleus; RN=Raphe Nuclei; TMN=Tuberomammillary Nucleus.

Sakurai T. *Nature Reviews Neuroscience* 2007;8(3):171-181.

The Normal Orexin System



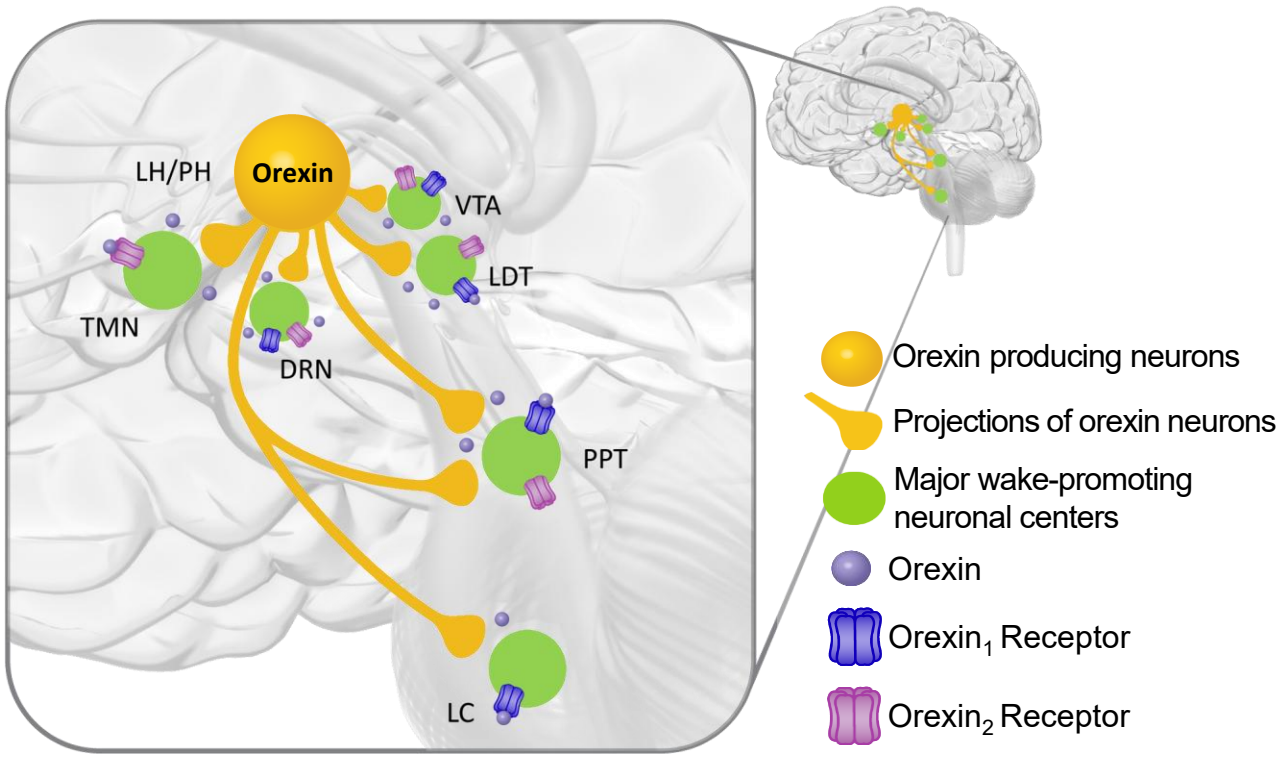


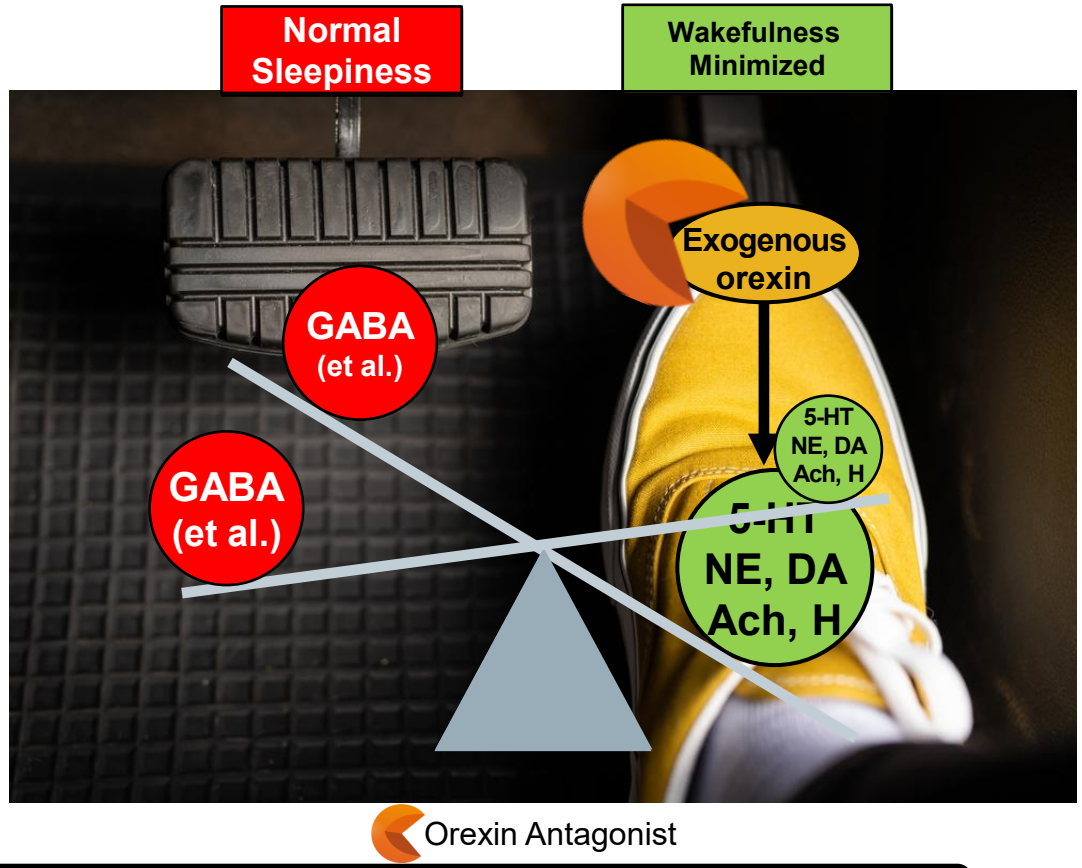
Orexin stabilizes the wake-promoting neurotransmitter centers of the brain to produce wakefulness

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.

Insomnia Disorder



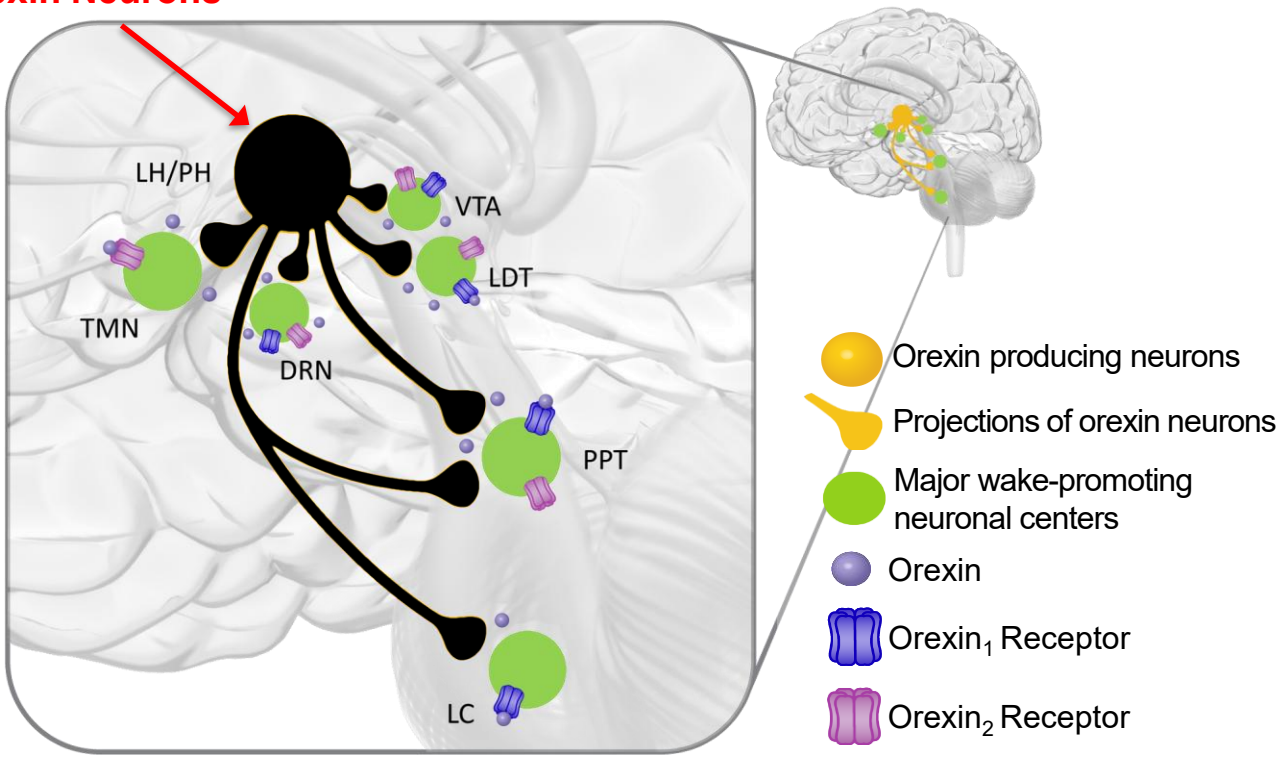


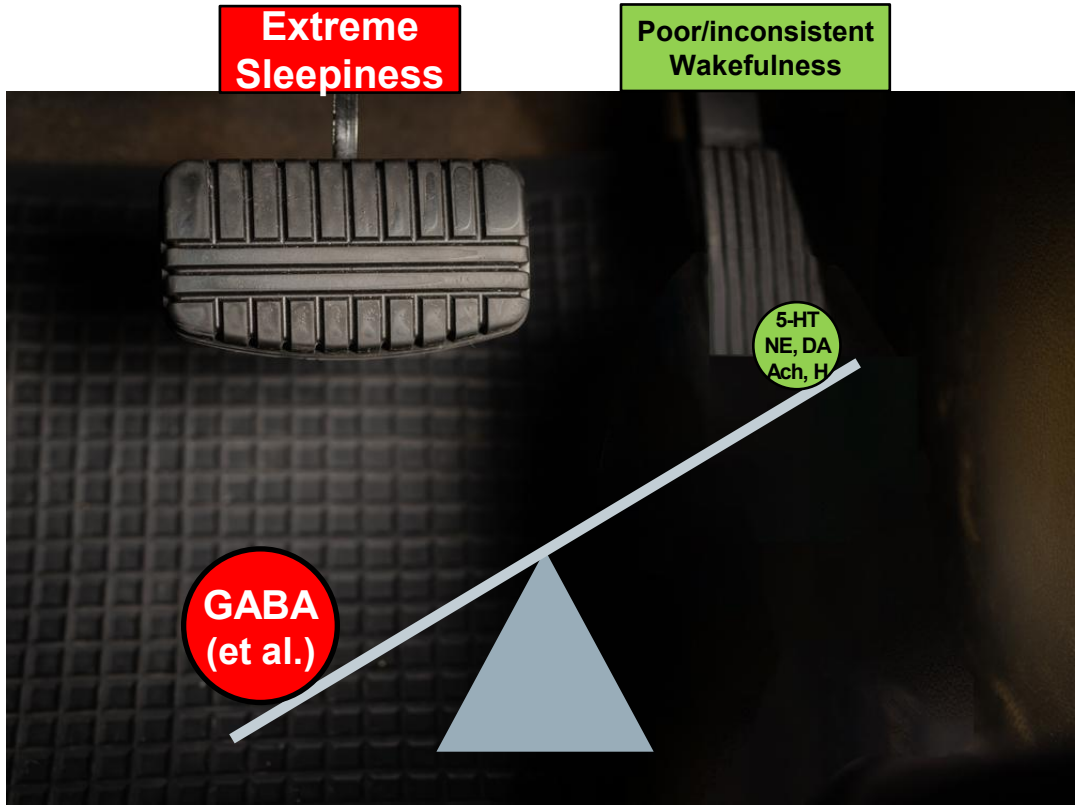
Orexin antagonists enable sleep by reducing excessive wakefulness

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.

Narcolepsy Type 1

Deficiency of Orexin Neurons

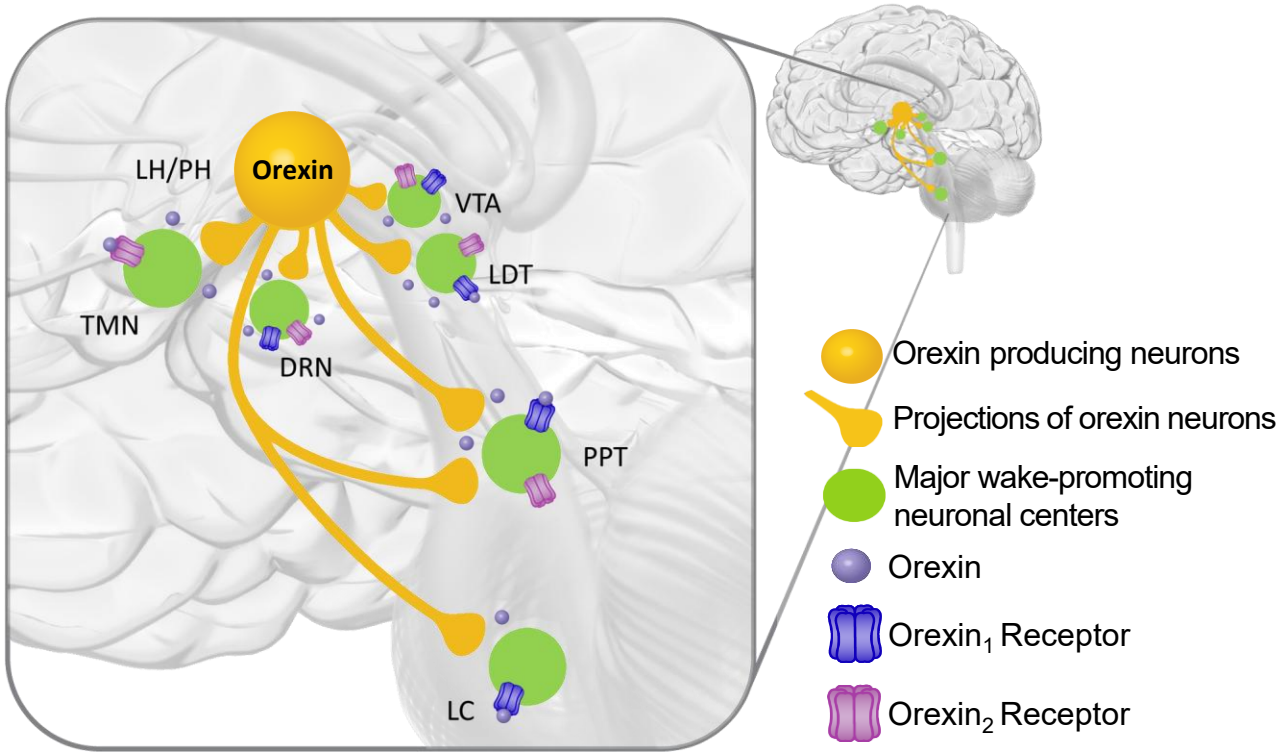


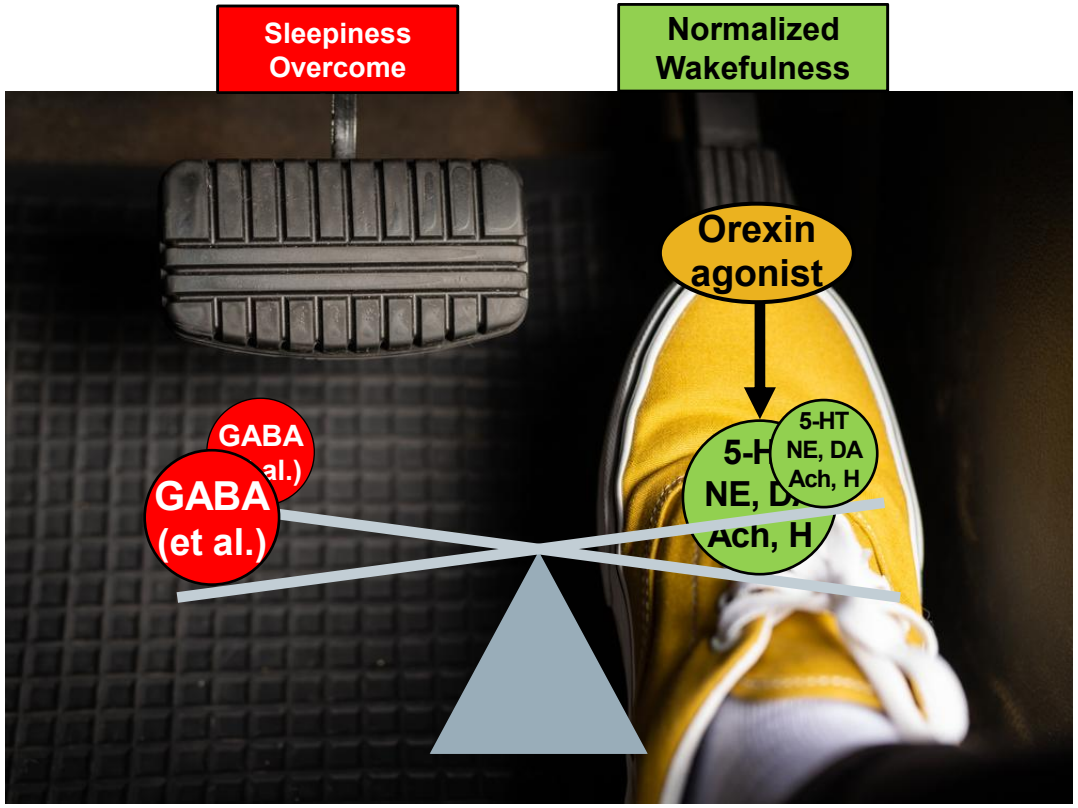


Deficiency of orexin neurons produces unrelenting sleepiness and intermittent cateplexy

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.

Potential for Orexin Agonists in OSA?

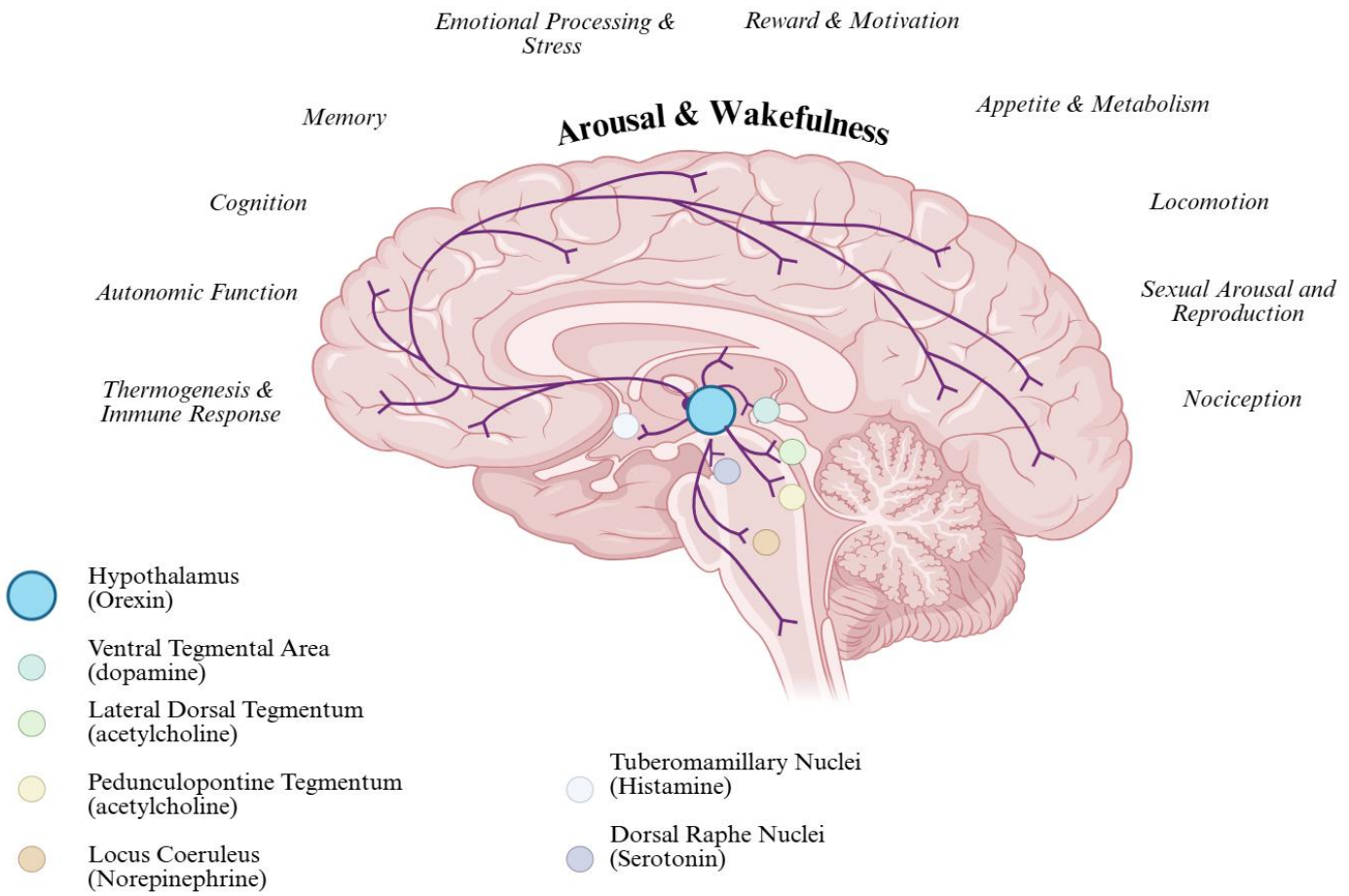


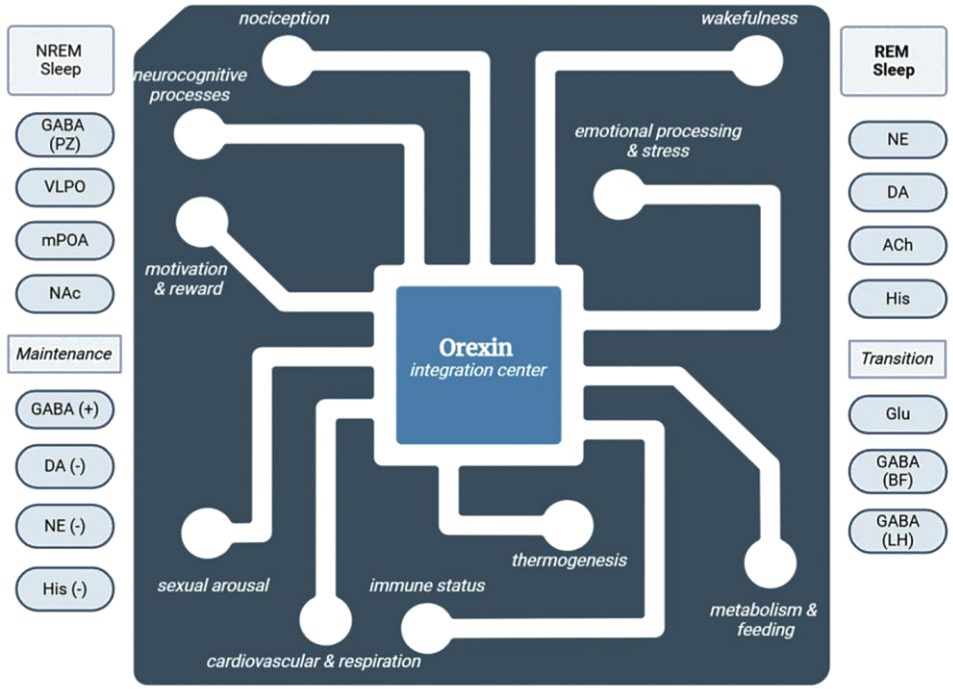


An orexin agonist could restore normal wakefulness in EDS of OSA (or narcolepsy)

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.

The Orexin System: An Integrator of Sleep, Circadian, and Overall Health and Wellness





Morse, AM (2025, May). Enhancing the management of hypersomnia: Examining the role of the orexin system. In Seminars in Neurology. Thieme Med.

Key Learning Points

- Sleep and Circadian Health are key factors in Mental Health, necessitating a 24-hour approach in management considerations

- The Natural Ontogeny of Sleep provides insight into evolving brain development and brain health

- The Orexin system serves as an essential integrator of sleep, circadian, and overall health and wellness, including mental health

Strategies to Improve Assessment of Sleep-Wake Disorders in Psychiatry

Optimal Use of Available Assessment Tools: Sleep Diaries

Today's Date	10/15			
In total, how long did you nap or doze yesterday?	1:30-2:45 pm			
1. What time did you get into bed?	11:00 pm			
2. What time did you try to go to sleep?	11:30 pm			
3. How long did it take you to fall asleep?	40 min			
4. How many times did you wake up, not counting your final awakening?	2			
5. In total, how long did these awakenings last	1 hour, 5 min			
6a. What time was your final awakening? 6b. Did you wake up earlier than you planned/desired? 6c. If yes, how many minutes earlier?	6:30 am ☑ Yes ☐ No 30 min	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
7. What time did you get out of bed for the day?	7:15 am			
8. How would you rate the quality of your sleep?	Poor			
9. Comments (if applicable):	I have a cold			

Optimal Use of Available Assessment Tools:
Self-Report Scales

Epworth Sleepiness Scale (ESS)	• 8 self-reported items rating the likelihood to doze off or fall asleep in situations such as watching tv, as a passenger in a car, or sitting and talking to someone • 8-9 is average EDS, 10-15 situational EDS, 16-24 strongly indicates EDS
Insomnia Severity Index (ISI)	• 5 self-reported Likert ratings of questions related to severity, noticeability, and interference of insomnia in daily functioning • 8-14=subthreshold insomnia, 15-21=moderate insomnia, 22-28=severe insomnia
PROMIS-SD	• 27 Likert scale questions, available in short form and computerized adaptive test • Any score above 50 indicates a higher clinical significance

PROMIS-SD= Patient-Reported Outcomes Measurement Information System-Sleep Disturbance;

Buysse DJ, et al. *Psychiatry Research.* 1989;28:193-213. Johns MW. *Sleep.* 1991;14(6):540-545. Bastien CH, et al. *Sleep Medicine.* 2001;2:297-307. Yu, Lan, et al. Behavioral sleep medicine 10.1 (2012): 6-24.

Utility and Limitations of Consumer Actigraphy

- Actigraphy: devices that measure movement (and heart rate, skin temp, etc) to estimate sleep/wake patterns
- Pros: objective, can collect data over long periods of time
- Cons: unknown validity, less accurate with worse sleep

Differentiating Hypersomnolence Disorders from ADHD and Difficult-to-Treat MDD

Overlap of Psychiatric Diagnoses and Hypersomnolence Disorders

Overlap of MDD and Hypersomnolence

- Patients may say they feel “fatigued”, “low energy”/ “low motivation”, or even “depressed” when they mean ”sleepy”.
- Depression may make people *feel* sleepy **w/o** increased sleep propensity

Overlap of ADHD & Hypersomnolence

- The cognitive fog and under-arousal in narcolepsy can look like inattention
- Hyperactivity in ADHD can be a *compensatory* response to sleepiness
- Stimulant response creates the perception of an ADHD diagnosis

Clues that Favor Hypersomnolence Disorders

- When depression/anxiety seems unusually refractory despite good treatment.
- Irresistible dozing in passive situations or massive over-caffeination
- Habitual total sleep ≥10 -11h (**Long sleep time in IH)**
- Prolonged confusion, irritability, strong pull to return to sleep on awakening (**Sleep inertia/“drunkenness” in IH)**
- Emotion-triggered brief weakness: knee buckling, jaw slackening, dysarthria, grip loss **(Cataplexy in NT1)**

Quick Questions to Surface Red Flags

- Do you fight sleep most days? When you say tired, do you mean nodding off or just exhausted? (**EDS**)
- When you laugh or feel excited/angry, does your jaw get slack, words get slurred, do your knees buckle, or do you drop objects? **(Cataplexy)**
- How long until you can think or function after waking? **(Sleep Inertia)**
- Ever “zone out “or “go on autopilot” and then realize you kept doing something (working, cooking, driving) but don’t remember doing it? (**Automatic Behaviors)**
- Have you ever woken up unable to move or speak, even though you’re fully aware? (**Sleep Paralysis)**
- As you’re drifting off or waking up, do you ever see vivid images, hear voices/sounds, or feel a presence in the room? (**Hypnagogic/Hypnopompic events**)

ADHD=Attention Deficit Hyperactivity Disorder; MDD=Major Depressive Disorder; EDS=Excessive Daytime Sleepiness

Chepke C, et al. J Clin Psychiatry 86.3 (2025): 24nr15718. Morse AM & K Sanjeev. Med. Sci 6.1 (2018): 16. Dunne L, et al. Sleep and Breathing 20.4 (2016): 1277-1284. Thorpy M and AM Morse. Sleep Medicine Clinics 12.1 (2017): 61-71. Morse AM, et al. CNS drugs (2025): 1-14. Moderie C, and DB Boivin. Sleep Medicine 124 (2024): 462-470. Chepke C. J Psychiatry Neurosci. 2023;48(6):E472-E473

When to Refer to a Sleep Specialist

- If you suspect sleep disorders that require specializes diagnostic assessment or non-mental health treatment (sleep apnea, narcolepsy, etc.)
- If a sleep disorder seems to be driving the psychiatric symptoms
- If treatment of the psychiatric disorder(s) does not lead to improvement in sleep

Further tests that may be conducted by sleep specialists

- Polysomnography (PSG) – i.e., a “sleep study”
- Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT) – repeated opportunities to fall asleep or stay awake across the day
- Orexin-A CSF test – for diagnosis of narcolepsy

Developing Competence in Assessing SWDs

- Education in SWDs, and sleep more generally, is usually minimal in psychiatric/mental health education training curricula

- Consider connecting with relevant organizations
  - Sleep Research Society
  - American Academy of Sleep Medicine

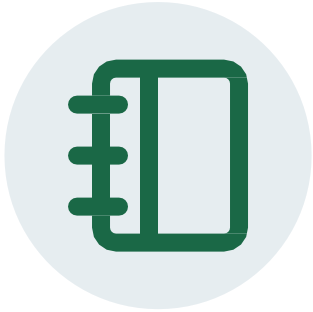
- Develop connections with local sleep medicine providers
  - Most sleep providers have no idea how to manage patients with psychiatric conditions and have no mental health providers on staff

Key Learning Points

- SWDs, especially insomnia and hypersomnia, are common in patients with psychiatric disorders but they often go under-recognized and under-treated
- Basic information about SWDs can be gathered in the clinical history and using self-report measures
- Integrating sleep-focused assessment and treatment into your practice can improve outcomes
- Refer to a sleep specialist for additional diagnostic testing, e.g. Polysomnography

Brief Review of Selected Sleep-Wake Disorders

Prevalence of Insomnia Symptoms and Disorder



Acute Insomnia

Acute insomnia is a short-term condition that lasts for a few days to a few weeks.

Insomnia Disorder

Chronic insomnia occurs at least three times a week for three months or longer.

Onset Insomnia

Onset insomnia refers to difficulty falling asleep at the beginning of the night.

Maintenance Insomnia

Maintenance insomnia involves trouble staying asleep throughout the night.

- Insomnia symptoms (U.S. adults):
  - ~30–40% report insomnia symptoms (difficulty falling or staying asleep) in a given year.
  - In 2020 NHIS:
    14.5% had trouble falling asleep most/every day;
    17.8% had trouble staying asleep most/every day.
- Insomnia disorder:
  - ~5–10% of adults meet criteria for insomnia disorder at any given time.
- Chronic/diagnosed insomnia:
  - ~12% of Americans report a clinician diagnosis of chronic insomnia (AASM survey).

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-Text Revision.* American Psychiatric Association Publishing; 2023. CDC. QuickStats: Trouble Falling Asleep and Staying Asleep Among Adults — United States, 2020. NHIS. Bhaskar S et al. Chronic insomnia and its association with health conditions. Sleep Med Rev. 2016. Ohayon MM. Epidemiology of insomnia: what we know and still need to learn. Sleep Med Rev. 2002. AASM. Insomnia Awareness and Chronic Insomnia Survey, 2024.

CBT-I and Other Behavioral Therapies

- Cognitive-Behavioral Therapy for Insomnia (CBT-I)
  - Gold standard for behavioral treatment of insomnia
  - 6 to 8 in-person visits over 8 weeks
- Unguided CBT-I via smartphone
  - Somryst™ (a/k/a "SHUTi")
  - Validated, with durability for 18 months
  - Cleared by FDA as a prescription digital therapeutic March 2020, access currently limited
- Brief Behavioral Therapy for Insomnia (BBTI)
  - Created in 2011 to increase access to behavioral treatments for insomnia
  - Initial efficacy study performed by an NP with no prior experience in sleep medicine or behavioral interventions for insomnia
  - 2 in-person visits, 2 telephone sessions over 4 weeks
  - Currently ongoing trial of BBTI delivered entirely via telehealth

SHUTi = Sleep Healthy Using the Internet.

Vedaa Ø, et al. *J Clin Sleep Med*. 2019;15(1):101-110. Levenson JC, et al. *Trials*. 2017;18(1):256. Gunn HE, et al. *Sleep Med Clin*. 2019;14(2):235-243.

Don’t Forget Exercise for Insomnia!

- Meta-analysis of 14 studies (6 RCTs) assessing effects of exercise on sleep outcomes in adults 60+ years
  - Moderate intensity exercise 3×/week produced the highest number of significant improvements
  - Session duration range 20–70 minutes
  - Examples: Qi Gong, Tai chi, Silver Yoga
- Significant effects in:
  - Subjective sleep quantity, difficulty falling back to sleep (100% of studies)
  - Sleep latency, wake after sleep onset, total sleep time (50% of studies)
  - Reduction in sleep medication use (40% of studies)
- Large standardized effect size (Cohen’s d≥0.8) in 40% of studies

Vanderlinden J, et al. *Int J Behav Nutr Phys Act*. 2020;17(1):11.

Approved Pharmacotherapies for Insomnia Disorder

- Benzodiazepine Receptor Agonists (BzRA)
  - Estazolam, flurazepam, quazepam, temazepam, triazolam
- Nonbenzodiazepine BzRA ("Z-drugs")
  - Eszopiclone, zaleplon, zolpidem
- Melatonin Agonist
  - Ramelteon
- Selective H_1 Antagonist
  - Doxepin low dose
- Dual Orexin Receptor Antagonists (DORAs)
  - Daridorexant, lemborexant, suvorexant

Neubauer DN. In: Dringenberg H. (Ed.) *Handbook of Sleep Research*. Volume 30. Academic Press; 2019:639-648. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

2017 AASM Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults

Recommendations

- Difficulties with sleep onset
  - Ramelteon, triazolam, zaleplon
- Difficulties with sleep maintenance
  - Doxepin low dose, suvorexant
- Difficulties with onset and maintenance
  - Eszopiclone, temazepam, zolpidem

NOT Recommended

- Diphenhydramine
- Tiagabine
- Melatonin, tryptophan, valerian
- Suvorexant for sleep-onset insomnia
- Trazodone

Evaluated but no formal statement

- Quetiapine

AASM = American Academy of Sleep Medicine.

Sateia MJ, et al. *J Clin Sleep Med*. 2017;13(2):307-349.

Limitations of Off-Label Therapies

Trazodone

- Insufficient evidence of efficacy
- Retrospective study of 348,449 Veterans: Suicide attempt hazard 61% higher with trazodone (< 200 mg) than zolpidem
  - Boxed warning for suicidality < 25 years
- The primary metabolite of trazodone (mCPP) is anxiogenic, pro-migraine
  - Metabolized by CYP450 2D6
  - Genetic polymorphism or those on 2D6 inhibitors (eg, fluoxetine, paroxetine, bupropion) may have adverse effects

Melatonin

- Insufficient evidence of efficacy
- Physiologic dose is 0.1–0.3 mg
  - Unclear effect of chronic supraphysiologic dosing
- May impair glucose tolerance

Quetiapine

- Insufficient evidence of efficacy
- Anticholinergic, risk of weight gain, metabolic syndrome, tardive dyskinesia

These agents are not FDA approved for insomnia.

mCPP = m-Chlorophenylpiperazine.

Rubio-Sastre P, et al. *Sleep*. 2014;37(10):1715-1719. Lavigne JE, et al. *J Gen Intern Med*. 2019;34(8):1554-1563. Rotzinger S, et al. *Biol Psychiatry*. 1998;44(11):1185-1191. Leone M, et al. *Neurology*. 2000;55(1):136-139.

Using Patient and Disease Characteristics to Inform Treatment Decisions in Insomnia

- Patient age
  - Some therapies are better studied than others in aging populations
- Onset-predominant?
  - Consider ramelteon, zolpidem, zaleplon
- Maintenance-predominant?
  - Most nights: doxepin low dose
  - Infrequent: zolpidem low dose SL PRN MOTN awakening
- Onset and Maintenance?
  - Consider daridorexant, eszopiclone, lemborexant, suvorexant, zolpidem ER
- Need to awaken to auditory stimulus? (eg, parent with baby or job requiring overnight call)
  - Consider doxepin low dose, lemborexant, suvorexant
- Comorbid mild-to-moderate OSA/COPD?
  - Consider ramelteon, daridorexant, lemborexant, suvorexant
- Need for the lowest abuse potential?
  - Consider ramelteon, doxepin
- Patient preference
  - May refuse controlled agents or have other choices we must consider

OSA=Obstructive Sleep Apnea; COPD=Chronic Obstructive Pulmonary Disease

Krystal AD. *Psychiatr Clin North Am*. 2015;38(4):843-860. Sun H, et al. *J Clin Sleep Med*. 2016;12(1):9-17. Cheng JY, et al. *J Sleep Res*. 2020:e13021. Sateia MJ, et al. *J Clin Sleep Med*. 2017;13(2):307-349.

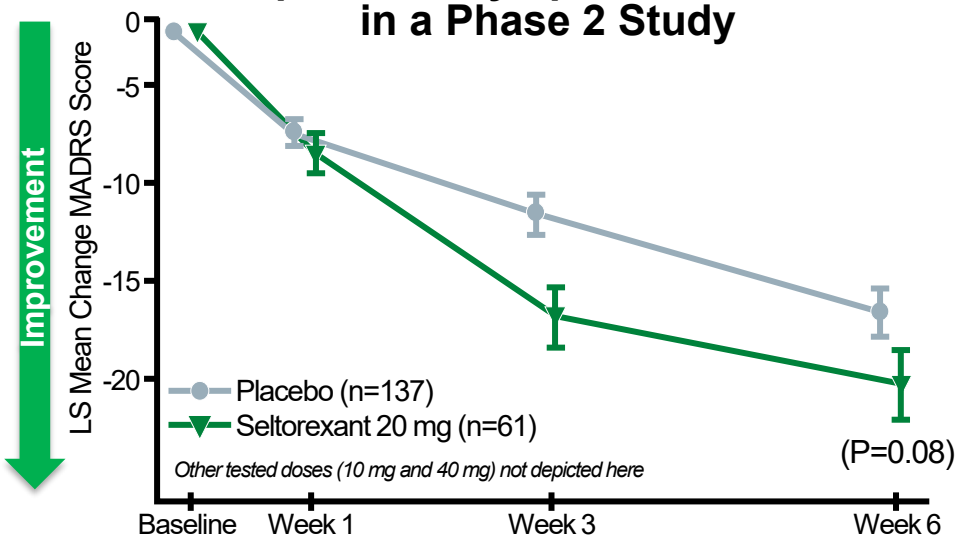
Seltorexant: Orexin-2 Receptor Antagonist for Adjunctive MDD with Insomnia Symptoms

Insomnia is an independent risk factor of suicidality, and the orexin system has deep ties to both sleep and affective regulation systems

Seltorexant is a selective orexin-2 receptor antagonist with no appreciable binding to other receptors and a 2-hour half-life

Adverse Events ≥ 5% in either arm	Seltorexant 20 mg + SSRI/SNRI	Placebo + SSRI/SNRI
Somnolence	6 (9.8%)	7 (5.1%)
Nausea	4 (6.6%)	4 (2.9%)
Headache	1 (1.6%)	9 (6.6%)
Diarrhea	0	7 (5.1%)
D/C due to AE	1 (1.6%)	2 (1.5%)
No weight/metabolic changes or sexual AEs		

Depressive Symptom Reduction in a Phase 2 Study



Secondary Endpoints

Core symptoms of depression on MADRS-6 (did not include sleep item) were significantly improved

Results by Insomnia Severity

ISI ≥15: **−4.9** (−8.98, −0.80)

ISI <15: **−0.7** (−5.16, 3.76)

Adjunctive seltorexant is promising for depressive symptoms in MDD with inadequate response, with greater benefit for those with more severe insomnia

LS = least squares; ISI = Insomnia Severity Index; D/C = discontinuation.

Savitz A, et al. *Int J Neuropsychopharm*. 2021;24:965. Ziemichód W, et al. *Molecules*. 2023;28(8):3575. NIH. Accessed May 14, 2023. clinicaltrials.gov/ct2/show/results/NCT03321526. McCall,WV, et al. *Sleep Medicine*. 2010;11(9):822-827. Shariq AS, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;92:1-7.

Every Psychiatric Clinician Has Individuals With Hypersomnolence in Their Practice

And Obstructive Sleep Apnea is the Most Likely Condition Causing Hypersomnolence in Psychiatric Practices

Pooled Prevalence of OSA by Meta-Analysis:

- Schizophrenia **15%**
- Bipolar Disorder **25%**
- General Population (30-70yo) **26%**
- Major Depressive Disorder **36%**
- Post-Traumatic Stress Disorder **55%**

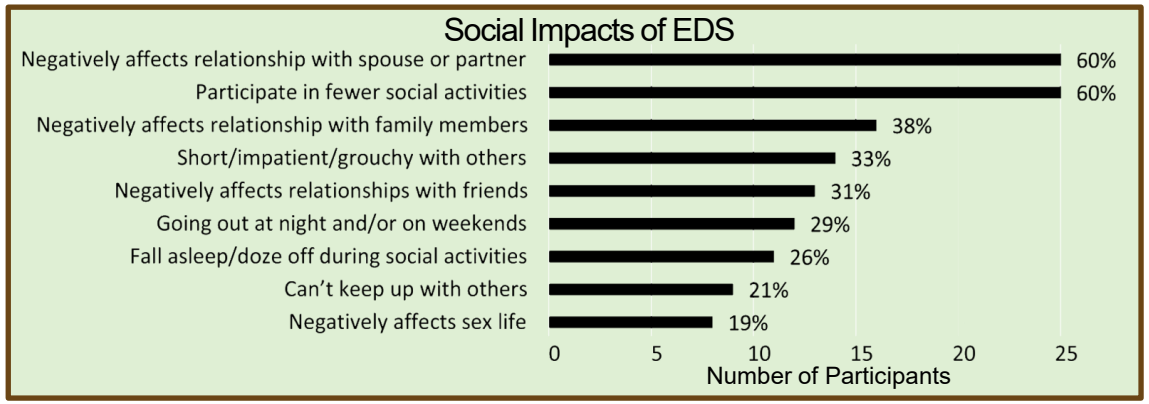
A trial of outpatients with MDD who had **insomnia** and were **acutely suicidal** excluded anyone with a known history of OSA or other respiratory conditions

14% were found to have unsuspected OSA (AHI≥10) on routine sleep studies for trial participants

60% of those with unsuspected OSA were women, and **35%** were ***women with BMI <30.***

OSA with EDS is associated with reduced Health-Related **Quality of Life** and greater impairment in **productivity** compared to OSA without ES or to non-OSA controls.

Individuals with EDS have a **40%** higher likelihood of **disability** and a **43%** increased **mortality risk**.



AHI=Apnea-Hypoxia Index.

Benca RM, et al. *J Clin Psychiatry.* 2023;84(2):45191. Peppard PE, et al. *Am J. Epidemiol.* 2013;177(9):1006-1014. Stubbs B, et al. *J Affect Disord.* 2016;197:259-267. Zhang Y, et al. *Sleep Med.* 2017;36:125-132. Gupta MA, et al. *J Clin Sleep Med.* 2015;11(2):165-175. McCall WV, et al. *J Psychiatr Res.* 2019;116:147-150. Waldman LT, et al. *Health and Quality of Life Outcomes.* 2020;18:1-14.

Hypersomnolence Disorders Run in the Same Circles as Psychiatric Conditions

While narcolepsy and IH are considered rare disorders, there are high rates of psychiatric comorbidities, and therefore, these individuals may concentrate in our clinics

Compared with matched controls, people with narcolepsy in a survey study were:

2.7x more likely to have MDD;
3.3x more likely to have GAD;
4.6x more likely to have bipolar disorder

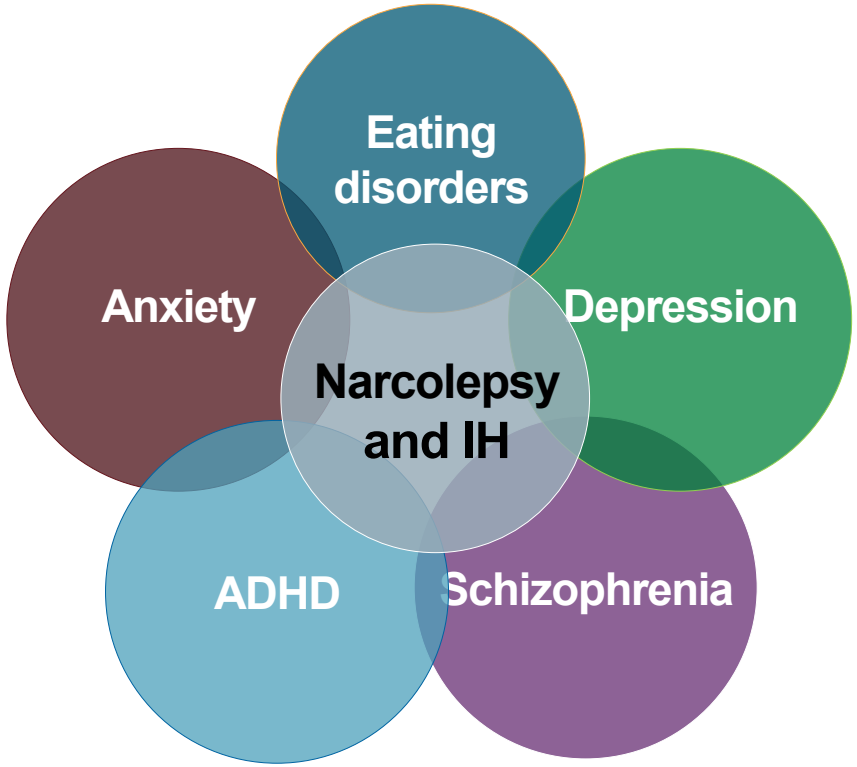
While no studies have evaluated IH prevalence *in individuals with psychiatric disorders,*

Subjective EDS (ESS>10) is common in retrospective & cross-sectional studies:

50.8% of people with MDD;
40% of people with bipolar disorder;
47% of adults with ADHD

Hypersomnolence is often unrecognized and underdiagnosed; Narcolepsy is often diagnosed **10-15 years after symptom onset**

60% of people with narcolepsy were initially misdiagnosed, 31% of them with depression, in an HCP survey and retrospective chart review (n=252)



EDS=Excessive Daytime Sleepiness; ESS=Epworth Sleepiness Scale;
IH=Idiopathic Hypersomnia; ADHD=Attnetion Deficit Hyperactivity Disorder; MDD=Major Depressive Disorder; GAD=Generalized Anxiety Disorder

Chepke C, et al. J Clin Psychiatry 86.3 (2025): 24nr15718. Morse AM & K Sanjeev. Med. Sci 6.1 (2018): 16. Saad R, et al. Nat. Sci. Sleep (2025): 1809-1823. Thorpy MJ & AC Krieger. *Sleep Med.* 2014;15(5):502-507. Carter, LP, et al. Postgrad Med 126.3 (2014): 216-224. Ohayon MM. Sleep Med 14.6 (2013): 488-492.

Differential Diagnosis of Hypersomnolence

Obstructive Sleep Apnea

Disruptive snoring

Waking up gasping for air, choking, or holding one's breath

Excessive daytime sleepiness

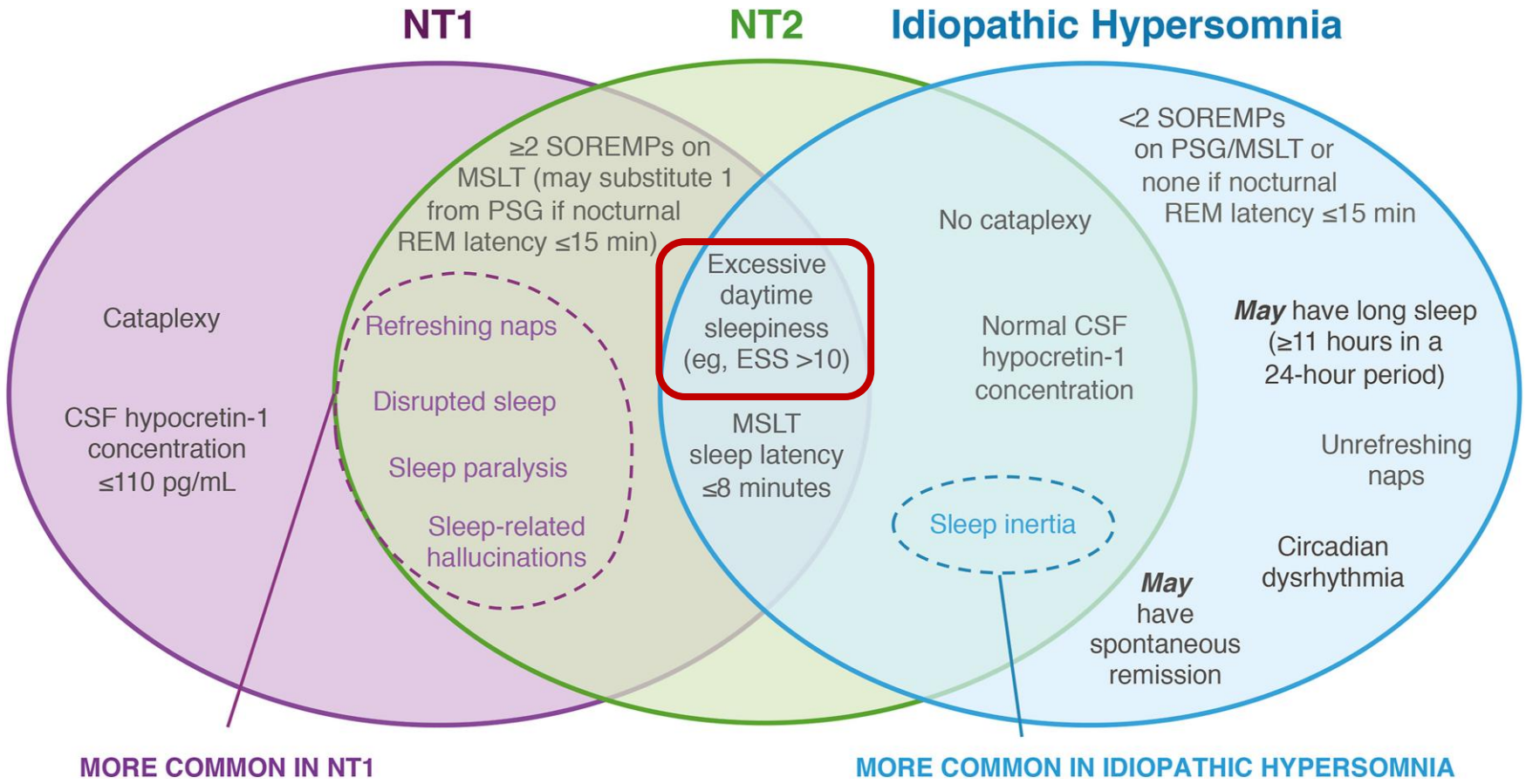
Fragmented and nonrestorative sleep

Cognitive impairment

Medication-Induced Sleep Disorder

Circadian Rhythm Disorder

Kleine–Levin Syndrome



OSA may be the most common primary hypersomnolence disorder in psychiatric clinics, but IH and Narcolepsy are important for us to understand as well!

OSA=Obstructive Sleep Apnea; NT1=Narcolepsy Type 1; NT2=Narcolepsy Type 2; IH=Idiopathic Hypersomnia

Dauvilliers Y, et al. *Sleep Med Rev*. 2022;66:101709. Chepke C, et al. J Clin Psychiatry 86.3 (2025): 24nr15718.

Traditional Pharmacotherapy Options for Excessive Daytime Sleepiness in OSA

Medication	Schedule	Mechanism of Action	FDA Indications
Modafinil/Armodafinil	IV	Dopamine reuptake inhibitors	**EDS in OSA**, Narcolepsy, and SWSD
Methylphenidate	II	Inhibits reuptake of dopamine and norepinephrine	ADHD, Narcolepsy (some)
Amphetamines	II	Inhibits reuptake of and causes release of dopamine, norepinephrine	ADHD, Narcolepsy (some)
Caffeine	None	Adenosine receptor antagonist	Off-Label (Over the Counter)

SWSD = shift work sleep disorder.

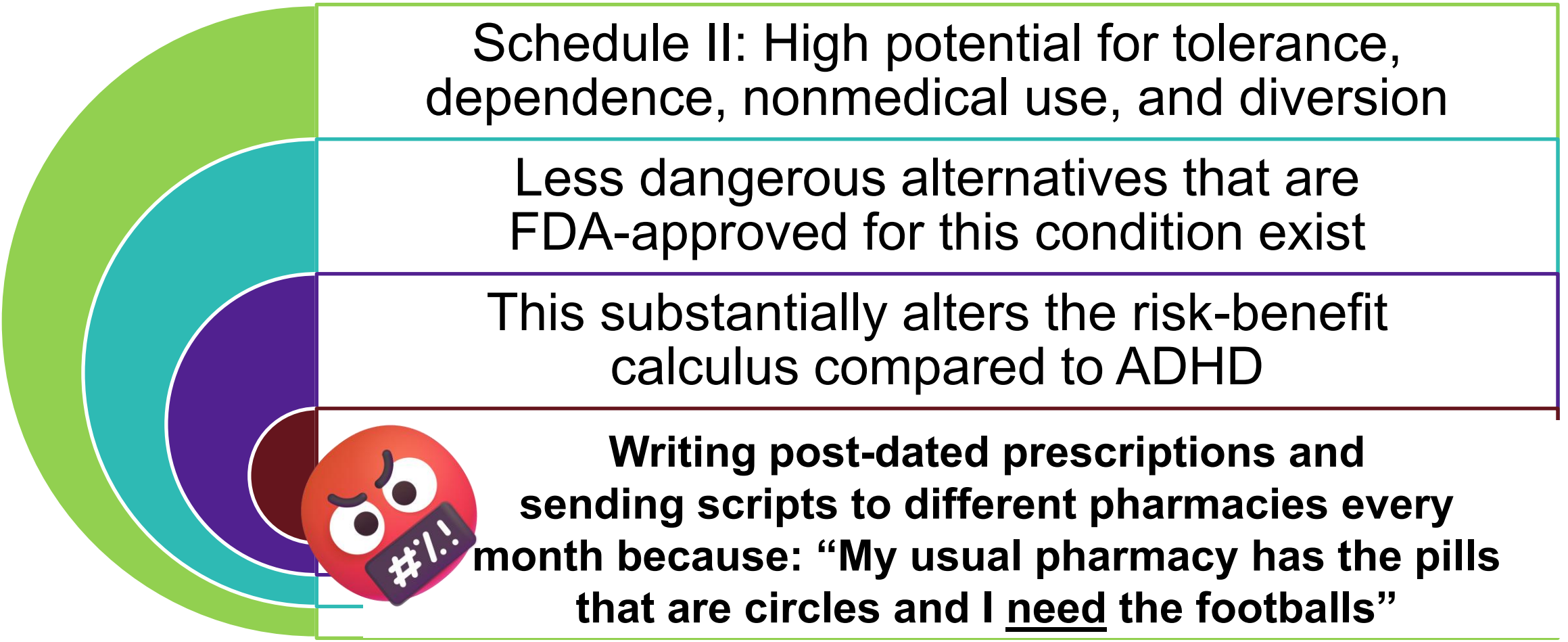
Rosenberg R, et al. Postgraduate medicine. 2021;133(7): 772-783. Aldosari MS, et al. *Sleep Breath*. 2020;24(4):1675-1684.

The Most Common Pharmacotherapy for EDS in OSA?

In one study, patients with OSA consumed ~3x as much caffeine as controls

Bardwell WA, et al. *Journal of Sleep Research*. 2000;9(3):269-272.

Stimulants for EDS in OSA: 100% Off-Label, 100% Unnecessary



Gruner JA, et al. *Sleep*. 2009;32(11)1425-1438. Rosenberg R, et al. *Postgraduate Medicine*. 2021;133(7):772-783.

Introduction to Solriamfetol

Approved as a dopamine-norepinephrine reuptake inhibitor indicated for adults with EDS associated with OSA or narcolepsy

Limitation of use: Ensure that the underlying airway obstruction is treated (e.g., with CPAP) for at least one month prior to initiating *(ie, adjunctive use)*

Approved doses:
37.5, 75, or 150 mg
once daily *in the morning*

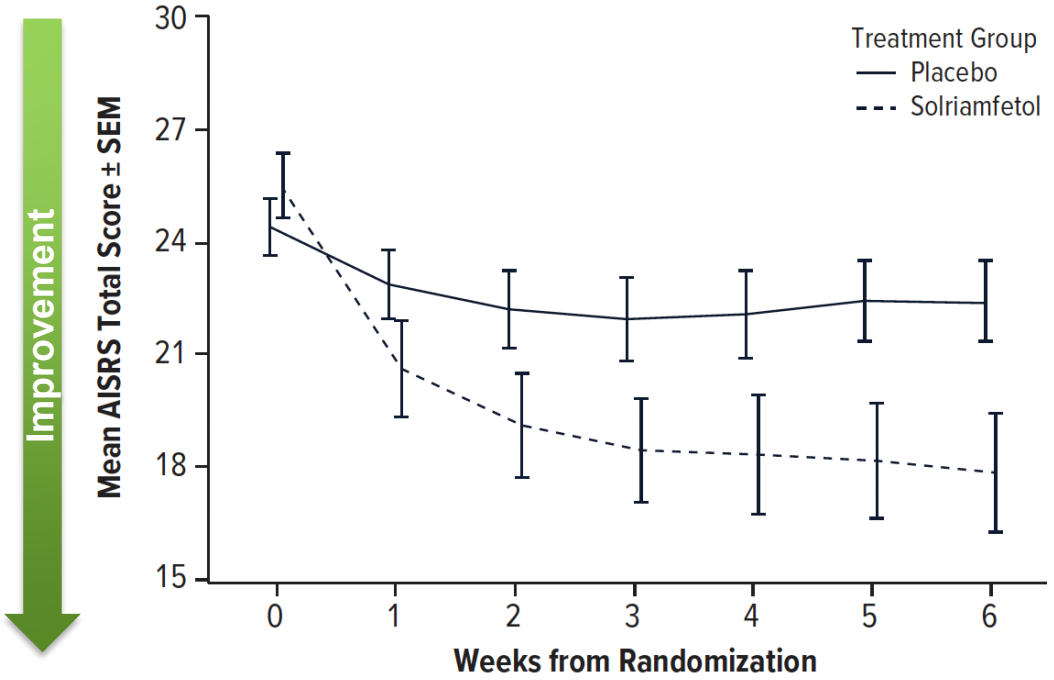
Not a stimulant:
a schedule IV medication with
no evidence of tolerance, withdrawal,
or dependence in clinical trials

EDS = excessive daytime sleepiness; OSA = Obstructive Sleep Apnea; CYP = cytochrome P450; CPAP = continuous positive airway pressure.

Solriamfetol Prescribing Information. Drugs@FDA: Accessed 8.20.25. www.accessdata.fda.gov/scripts/cder/daf/. Carter, LP, et al. *J. Psychopharmacol.* 2018;32(12): 1351-1361.

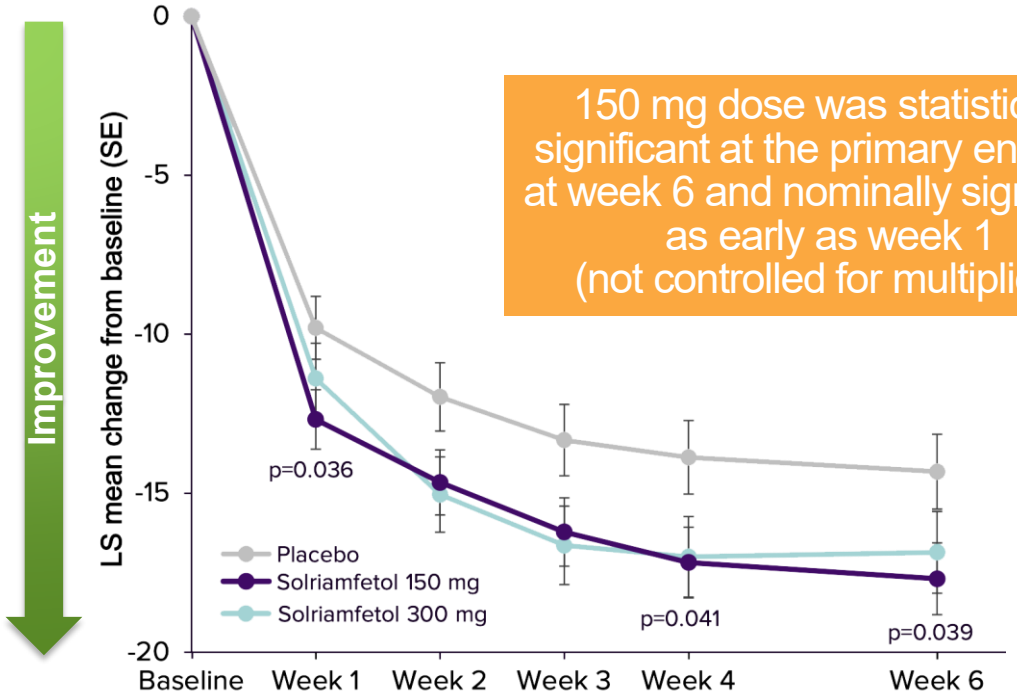
Solriamfetol Improved ADHD in Adults in Two Trials

Mean AISRS Total Score in a Pilot Study



6-week randomized, double-blind trial in 60 adults with ADHD. Significant improvement vs placebo for those taking solriamfetol 150 mg from weeks 3-6; effect size=1.09

Mean AISRS Total Score in a Phase 3 Trial



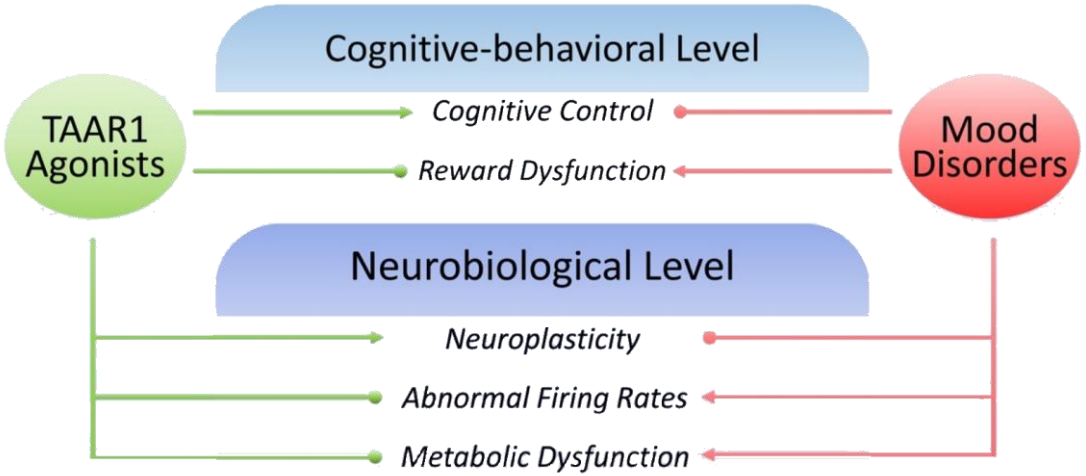
150 mg dose was statistically significant at the primary endpoint at week 6 and nominally significant as early as week 1 (not controlled for multiplicity)

Adverse event profile of both trials consistent with the established safety profile of solriamfetol

AISRS = Adult ADHD Investigator Symptom Rating Scale; SEM = standard error of the mean.

Surman CBH, et al. *J Clin Psychiatry.* 2023;84(6):49350. Frontiers in Brain Health R&D Day. https://axsometherapeuticsinc.gcs-web.com/static-files/c9a3a0a7-cd82-4e73-8a2b-ccb6a41c8214. Accessed 8.20.25.

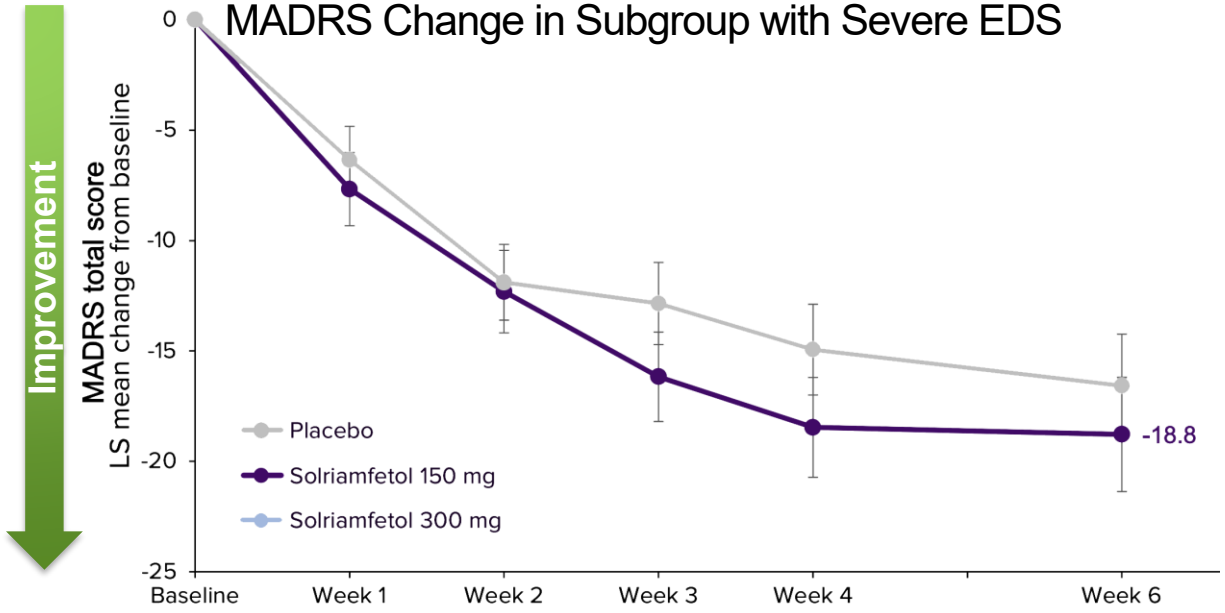
Solriamfetol May Also Have Benefits in MDD



In addition to dopamine and norepinephrine reuptake inhibition, TAAR1 agonism may have downstream effects leading to increased neuroplasticity and reward signaling

A recent phase 3 study of solriamfetol as monotherapy of MDD did not separate from placebo on the primary endpoint

However, a prespecified analysis in those with severe EDS did show a nominally significant benefit vs. placebo



Further studies are planned in a population of MDD with EDS

MADRS = Montgomery-Åsberg Depression Rating Scale

Alnefeesi, Y, et al. *Neuroscience & Biobehavioral Reviews*. 2021;131:192-210. Frontiers in Brain Health R&D Day. https://axsometherapeuticsinc.gcs-web.com/static-files/c9a3a0a7-cd82-4e73-8a2b-ccb6a41c8214. Accessed 8.20.25.

Orexin-2 Receptor Agonists May Hold the Keys to the Future of Hypersomnolence Disorders

Danavorexton (TAK-925): IV orexin-2 receptor agonist

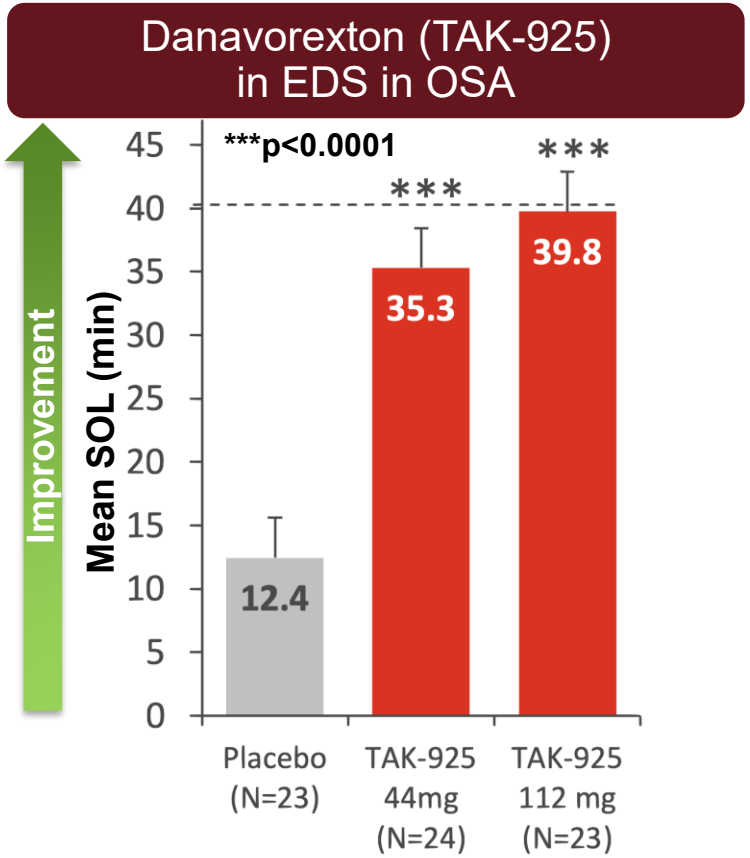
- Positive Phase Ib study in EDS in OSA
- No serious TEAEs or discontinuations due to TEAEs occurred

Oveporexton (TAK-861): **oral** orexin-2 receptor agonist for Narcolepsy Type I

- Positive Phase 2 study with no discontinuations due to adverse events
- Two phase 3 studies met all primary and secondary endpoints, including functioning and quality of life; most common AEs: insomnia, urinary urgency and frequency
- Another agent, TAK-360 being studied for Narcolepsy Type 2 and IH

Other **oral** orexin-2 receptor agonists being studied for narcolepsy and/or IH

- ALKS 2680: Positive phase 2 results in NT1; underway
- ORX750: Phase 1 complete; phase 2 trial in NT1/2+IH expected to complete 12-2025
- JZP-441: currently in phase 1 trial for NT1



SOL = sleep onset latency; RA = receptor agonist; TEAE = treatment-emergent adverse event.

Bogan RK, et al. *Sleep Medicine.* 2023;107:229-235. Dauvilliers Y, et al. *N Engl J Med.* 2025;392(19):1905-1916. https://investor.alkermes.com/news-releases/news-release-details/alkermes-announces-positive-topline-results-vibrance-1-phase-2. Acccessed 8-20-25. https://clinicaltrials.gov/study/NCT06752668. Accessed 8-20-25. https://clinicaltrials.gov/study/NCT06961266. Accessed 8-20-25.

Summary

- Current guidelines for Insomnia Disorder do not recommend most popular off-label treatments
- Dual Orexin Receptor Antagonists may play a crucial role for patients with insomnia disorder
- Seltorexant (Selective Orexin-2 Receptor Antagonist) may treat the core symptoms of depression in addition to insomnia symptoms
- Finding hypersomnolence disorders can massively benefit the lives of people in your practice, especially if medications other than stimulants are used!
- Solriamfetol (DNRI and TAAR1 Agonist) can treat EDS due to OSA or narcolepsy, and has potential for ADHD and MDD with EDS
- Above all, take the time to listen to what your patient's goals are, solicit their preferences, and fully educate them so you can share the decision-making and create a personalized treatment plan for their needs

Practical Take-Aways

- Sleep/Wake Disorders are common in individuals with psychiatric conditions, and each may worsen the other
- The neurobiology of sleep and wake is complex, and the Orexin system is a key integrator of sleep, wake, circadian, and overall health and wellness
- Integrating sleep-focused assessment into your practice can improve outcomes; this can be done with a variety of screening tools, or a simple sleep diary

Q&A