HMP Education

Navigating Psychiatric Complexities in Sleep Medicine:

CASE-BASED STRATEGIES FOR SLEEP SPECIALISTS

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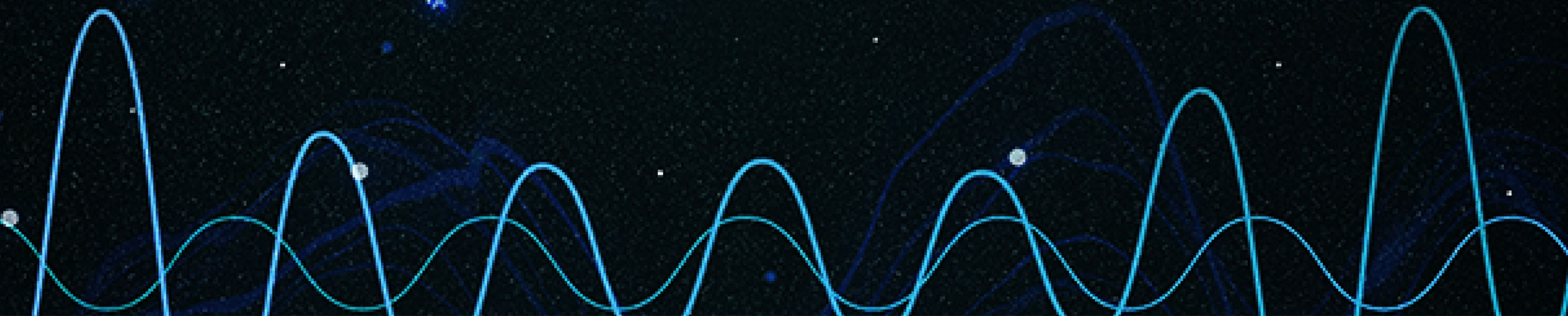

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Andrew Krystal, MD: Consulting—Axsome Therapeutics, Abbvie, Big Health, Eisai, Evecxia, Harmony Biosciences, Idorsia, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Neurocrine Biosciences, Neumora, Neurawell, Otsuka Pharmaceuticals, Sage, Takeda; Research Grants—Janssen Pharmaceuticals, Axsome Pharmaceutics, Attune, Eisai, Harmony, Neurocrine Biosciences, Reveal Biosensors, The Ray and Dagmar Dolby Family Fund, Weill Institute for Neurosciences, and the National Institutes of Health; Stock Options—Neurawell, Big-Health

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Program Information

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Learning Objectives

1. Describe the bidirectional relationship between sleep/wake and psychiatric disorders, including reciprocal neurobiological factors and functional impacts

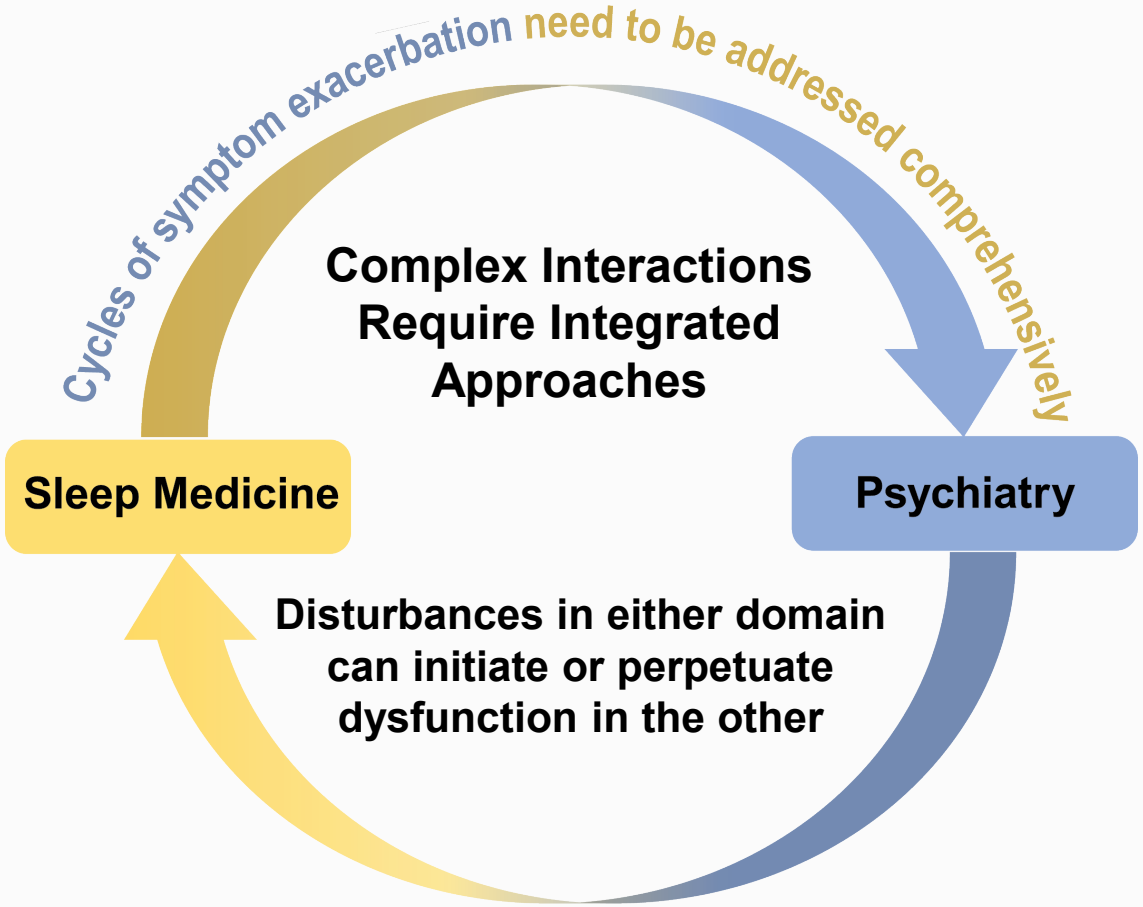
2. Evaluate the effects of medications prescribed for sleep/wake disorders on psychiatric health and the effects of medications prescribed for psychiatric disorders on sleep health

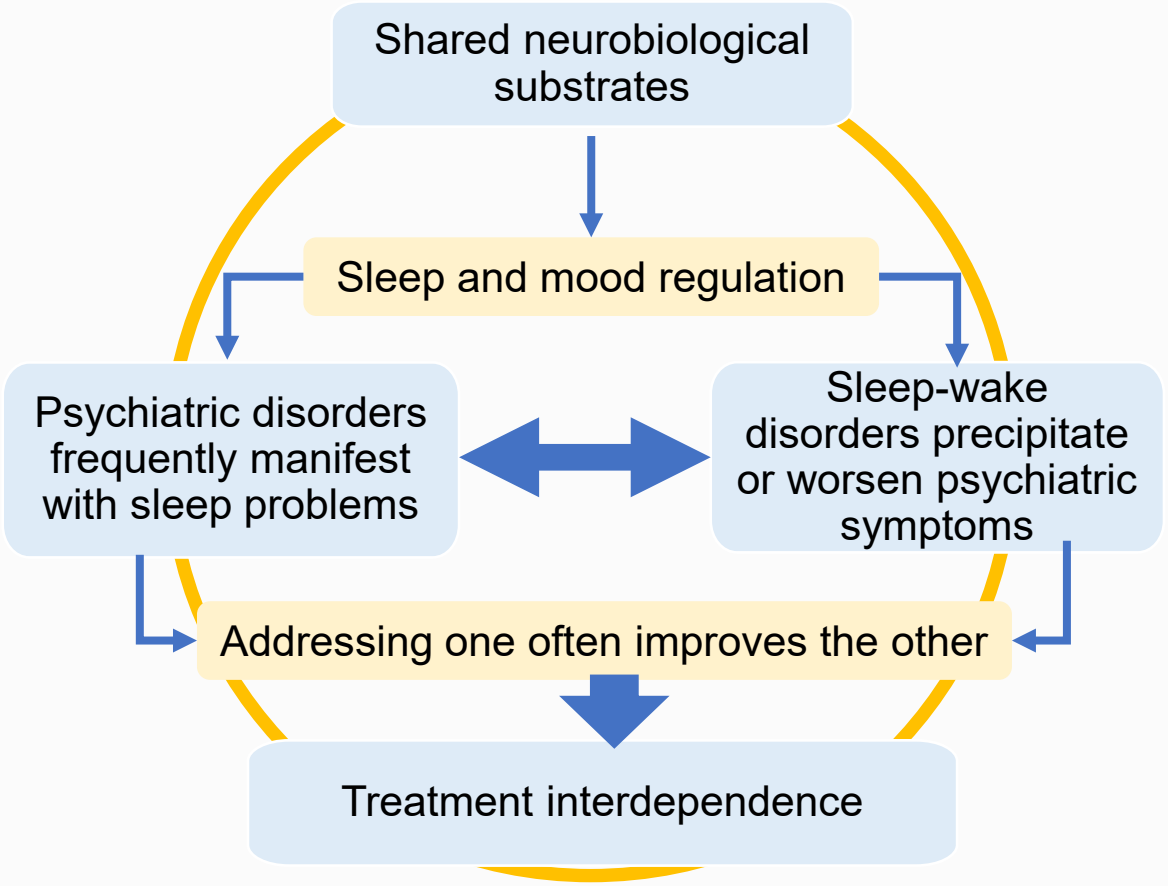
3. Implement case-based strategies to optimize sleep and psychiatric health

Significance of Mental Health in Sleep Medicine

Arwen Podesta, MD, DFAPA, DFASAM

The Bidirectional Relationship of Sleep Medicine and Psychiatry





Substance Use Disorders and Sleep

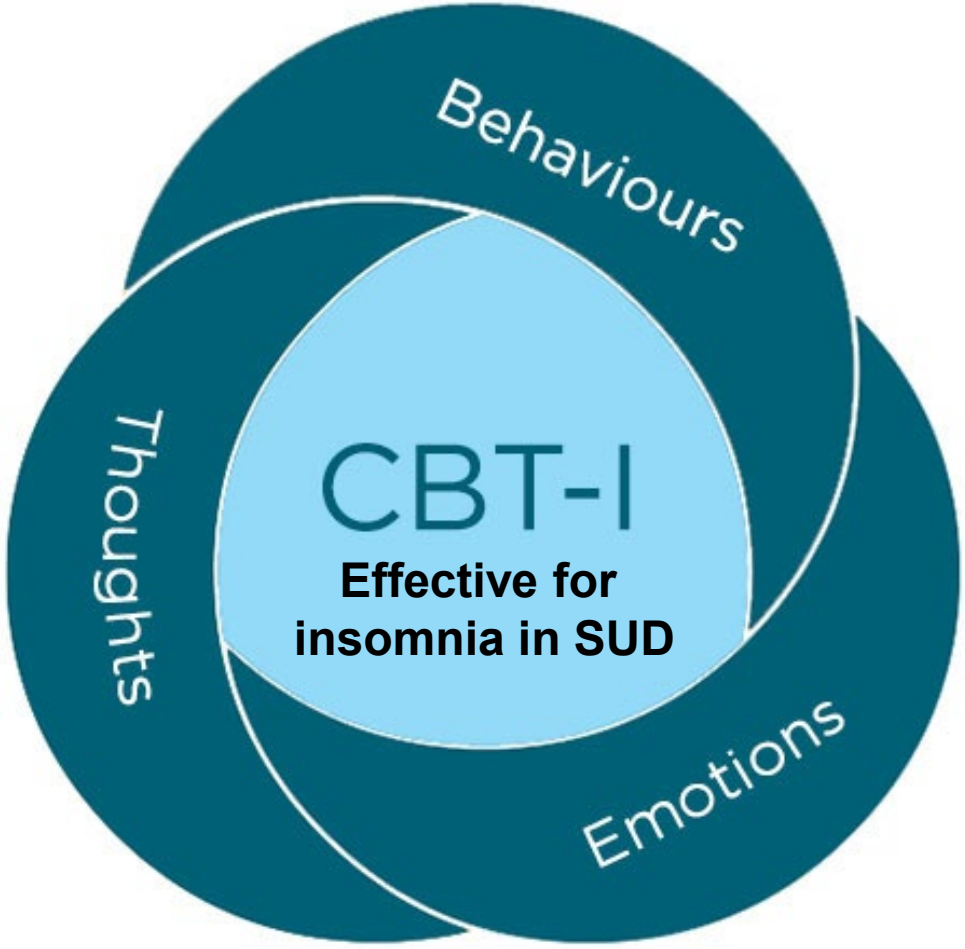
- Opioids
  - Acutely suppress REM sleep and fragments sleep architecture
  - Chronic use associated with central sleep apnea (30-75%)
  - Withdrawal causes insomnia, sleep fragmentation, and REM rebound
  - 75% to 85% of those treated with methadone report poor sleep
- Alcohol
  - Suppresses REM and fragments sleep
  - Exacerbates obstructive sleep apnea
- Cannabis
  - May improve sleep onset acutely
  - Chronic use associated with tolerance to sleep-promoting effects
- Stimulants
  - Cause profound insomnia during use
  - Hypersomnia during withdrawal
- Benzodiazepines
  - Dependence leads to rebound insomnia upon discontinuation

REM = rapid eye movement.

Roehrs T, et al. *Pharmacol Biochem Behav.* 2021;203:173153.

Sleep and Substance Use Disorders

- Clinical implications
  - Sleep-wake disorders may increase relapse risk (2-3x higher rates)
  - Sleep improvement correlates with better SUD treatment outcomes
  - Caution with hypnotic medications in SUD patients
  - Addressing sleep complaints is essential for comprehensive SUD care

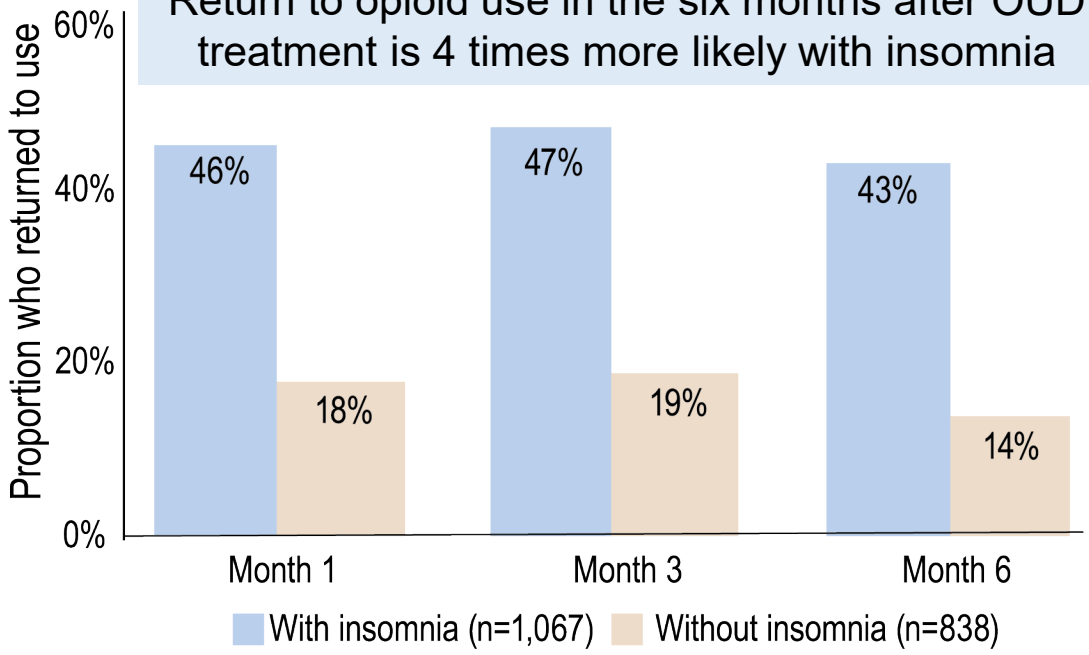


CBT-I = cognitive behavioral therapy-insomnia; SUD = substance-use disorders.

Roehrs T, et al. *Pharmacol Biochem Behav*. 2021;203:173153. Hanacek C, et al. *J Psychiatr Pract*. 2025;31(1):2-7.

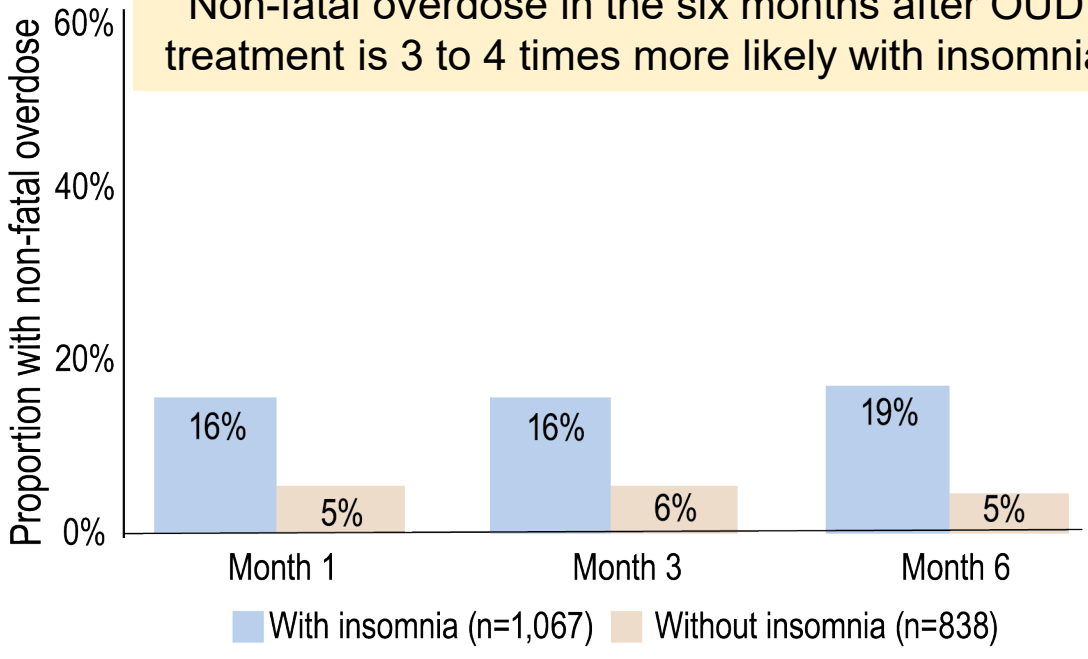
Insomnia Plays a Significant Role in Opioid Use Disorder Relapse

Return to opioid use in the six months after OUD treatment is 4 times more likely with insomnia



Month 1: aOR 3.99 (CI: 3.21 to 4.96, *P* <0.001)
Month 3: aOR = 3.71 (CI: 2.59 to 5.36, *P* <0.001)
Month 6: aOR = 3.83 (CI 2.10 to 7.09, *P*<0.001).

Non-fatal overdose in the six months after OUD treatment is 3 to 4 times more likely with insomnia



Month 1: aOR 3.31 (CI: 2.38 to 4.66, *P* <0.001)
Month 3: aOR = 2.55 (CI: 1.48 to 4.46, *P* <0.001)
Month 6: aOR = 3.92 (C: 1.62 to 10.11, *P*<0.003).

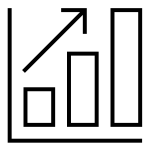
This survey study also found that insomnia at the start of treatment was significantly associated with relapse. For every 1-point increase in the ISI scale, there was an 8% increase in the odds of returning to opioid use.

aOR = adjusted odds ratio; ISI = insomnia severity index; OUD = opioid-use disorder.

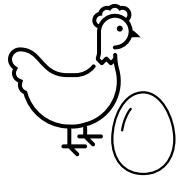
Hochheimer M, et al. *Sleep*. 2025;48(4):zsae284.

Psychiatric Disorders in Patients with Sleep/Wake Disorders

Sleep-wake disorder	Common psychiatric comorbidities	Prevalence
Insomnia	MDD, GAD, PTSD	67%-75%
Obstructive sleep apnea	MDD, GAD, cognitive Impairment	21%-53%
Narcolepsy	MDD, GAD, psychosis	15%-37%
Restless legs syndrome	MDD, GAD, ADHD	18%-45%
Circadian rhythm disorders	MDD, GAD, SUD	25%-43%



Patients with sleep-wake disorders have two to four times higher rates of psychiatric diagnoses than the general population.



Chicken or the egg?
Determining which condition preceded the other **can be challenging** but **can inform treatment sequencing.**

Overlapping symptoms (eg, fatigue, irritability, poor concentration) complicate differential diagnosis.

Treatment response may differ! Psychiatric symptoms secondary to a sleep-wake disorder often have different treatment trajectories compared with primary psychiatric conditions

ADHD = attention deficit hyperactivity disorder; MDD = major depressive disorder; GAD = generalized anxiety disorder; PTSD = post-traumatic stress disorder.

Hombali A, et al. *Psychiatry Res*. 2019;279:116-22.

Parasomnias in Patients with Psychiatric Disorders

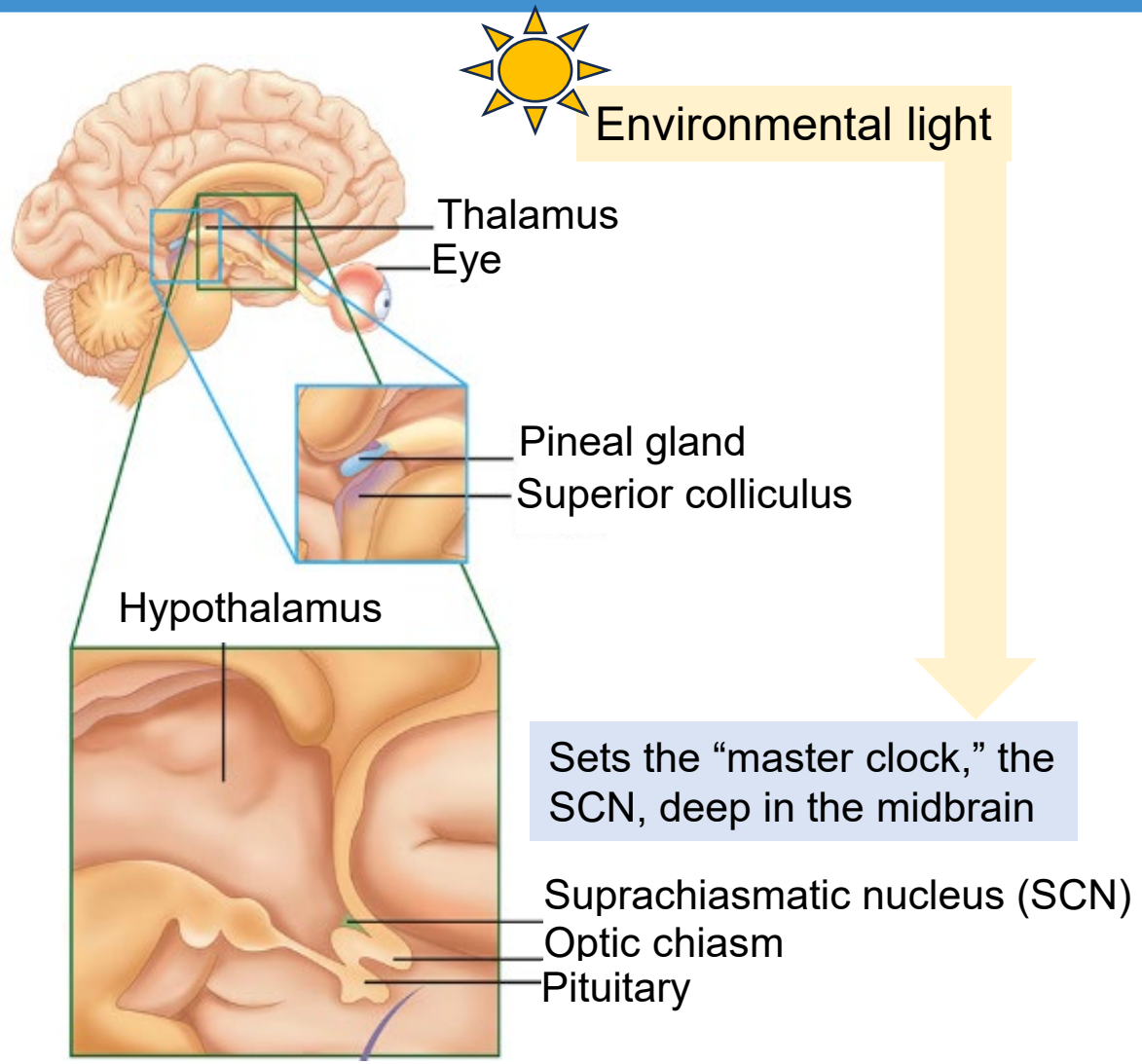
- **REM Sleep Behavior Disorder**
  - Often precedes neurodegenerative disorders with psychiatric features (eg, cognitive problems, depression, apathy, agitation, and hallucinations)
    - Parkinson's disease/Parkinson’s dementia
    - Lewy body dementia
    - Multiple system atrophy
  - Early psychiatric symptoms may include depression, anxiety, and apathy

- **Non-REM Sleep Parasomnias**
  - Frequently coexist with psychiatric conditions
  - Sleep terrors strongly associated with PTSD, anxiety disorders
  - Sleepwalking more common in patients with dissociative disorders
  - Confusional arousals may mimic psychotic episodes

- **Nightmare Disorder**
  - Strongly associated with trauma-related conditions
  - 70-90% of PTSD patients experience recurrent nightmares
  - Content often reflects psychological conflicts in personality disorders

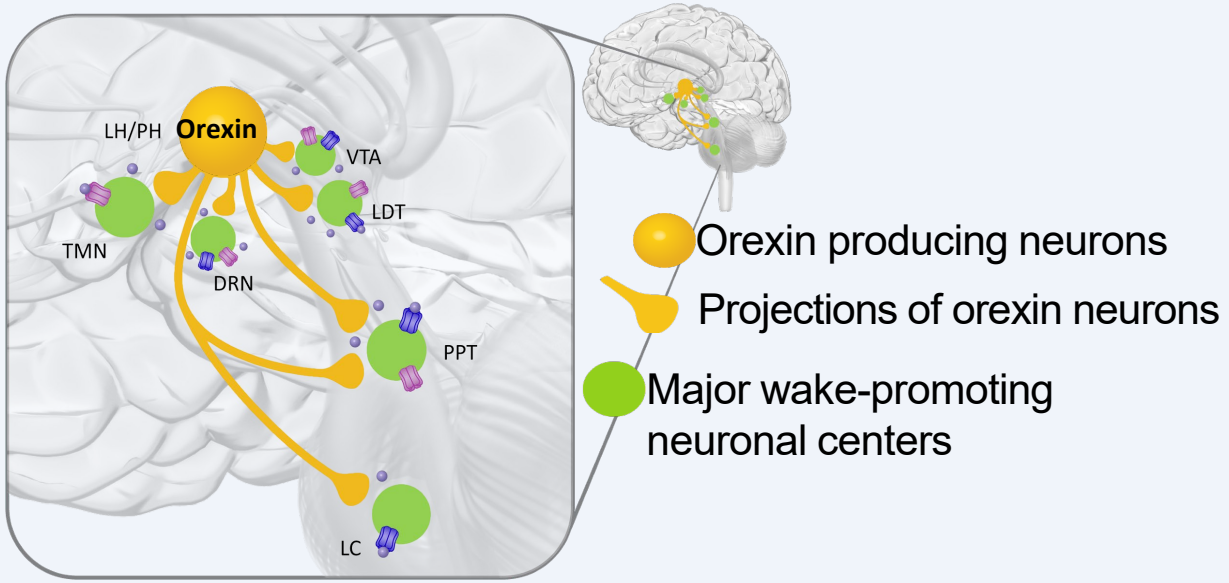
Singh S, et al. *Cureus*. 2018;10(12):e3807.

Circadian Systems Regulate Sleep and Affect Mood



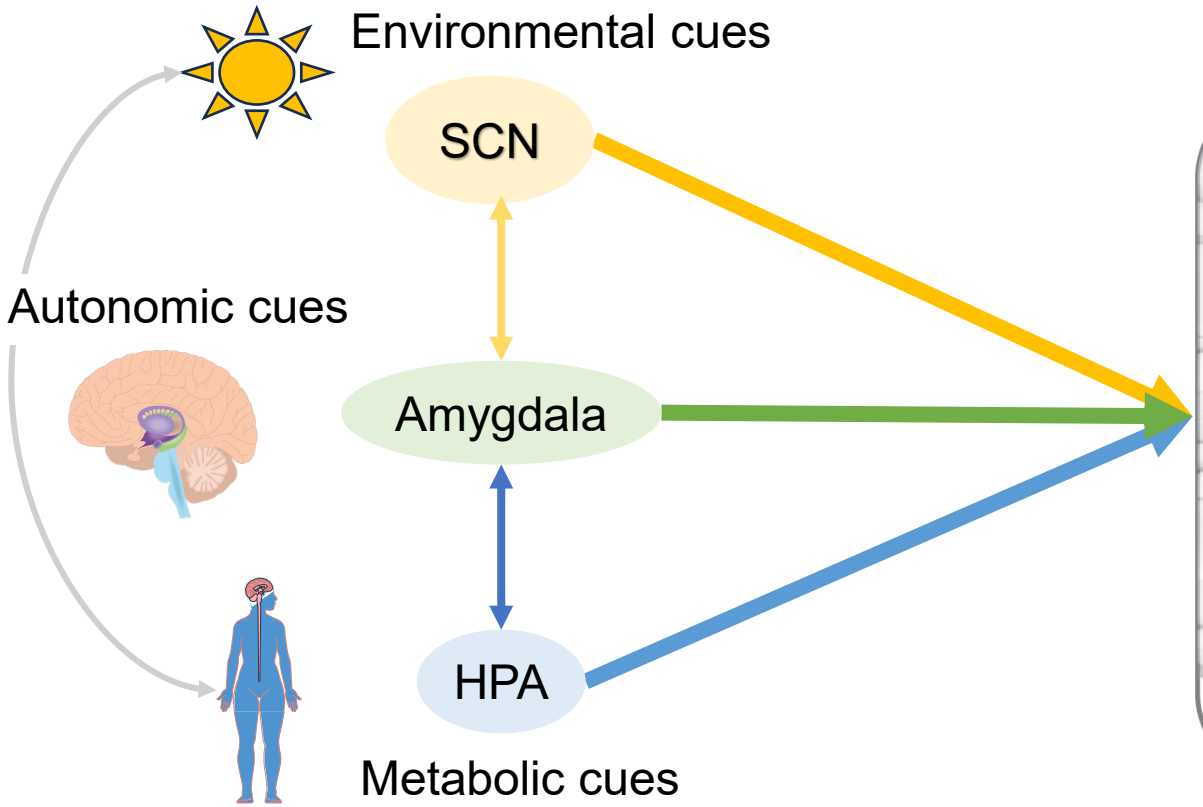
The SCN regulates

- Neuroendocrine, pre-autonomic, and intermediate neurons
- Hormone production
- Orexin release
- Neurotransmitter production
- Sleep-wake cycle

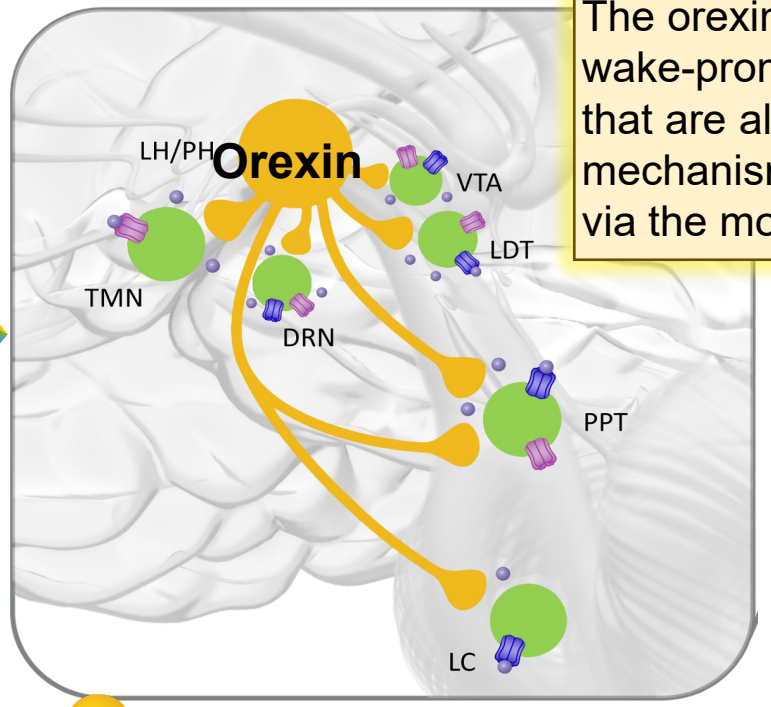


Challet E, Pevet P. *Front Biosci*. 2003;8:s246-57. Date Y, et al. *Proc Natl Acad Sci USA*. 1999; 96:748-53. Vadnie CA, McClung CA. *Neural Plast*. 2017;2017:1504507. Sakurai T. *Nat Rev Neurosci*. 2007;8(3):171-81. Sakurai T, et al. *Front Neurol Neurosci*. 2021;45:11-21.

The Orexin System



Environmental cues are not all sunny; trauma and chronic illness act here too!



The orexin system projects to wake-promoting neural centers that are all also implicated in mechanisms of mood disorders via the monoaminergic system

Orexin producing neurons

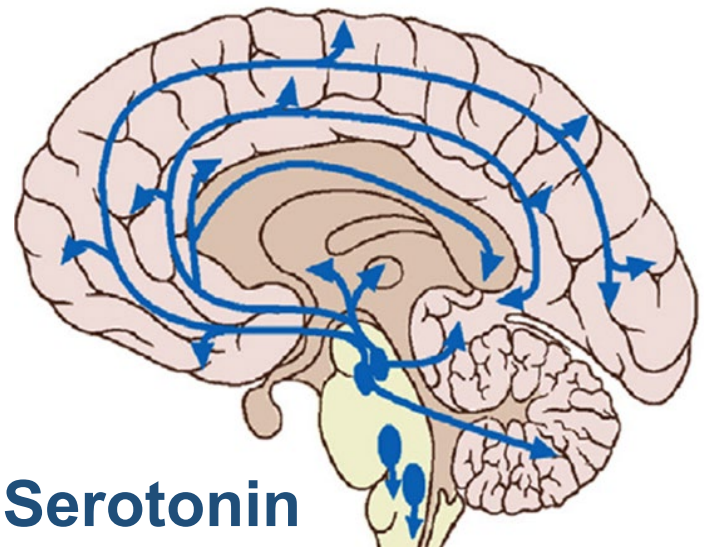
Projections of orexin neurons

Major wake-promoting neuronal centers

HPA = hypothalamic-pituitary axis; LDT = laterodorsal tegmental area; PPT = pedunculopontine; LC = locus coeruleus; RN = raphe nuclei; TMN = tuberomammillary nucleus.

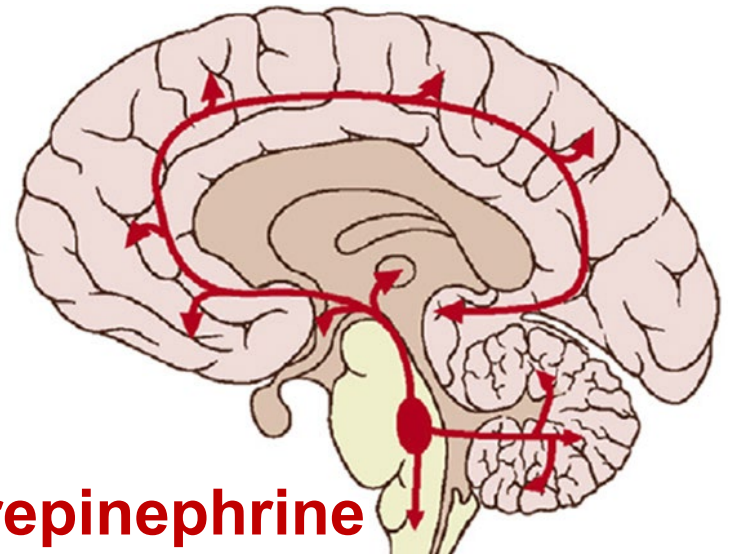
Challet E, Pevet P. *Front Biosci*. 2003;8:s246-57. Date Y, et al. *Proc Natl Acad Sci USA*. 1999; 96:748-53. Vadnie CA, McClung CA. *Neural Plast*. 2017;2017:1504507. Sakurai T. *Nat Rev Neurosci*. 2007;8(3):171-81. Sakurai T, et al. *Front Neurol Neurosci*. 2021;45:11-21.

Monoaminergic System Receives Orexin Inputs



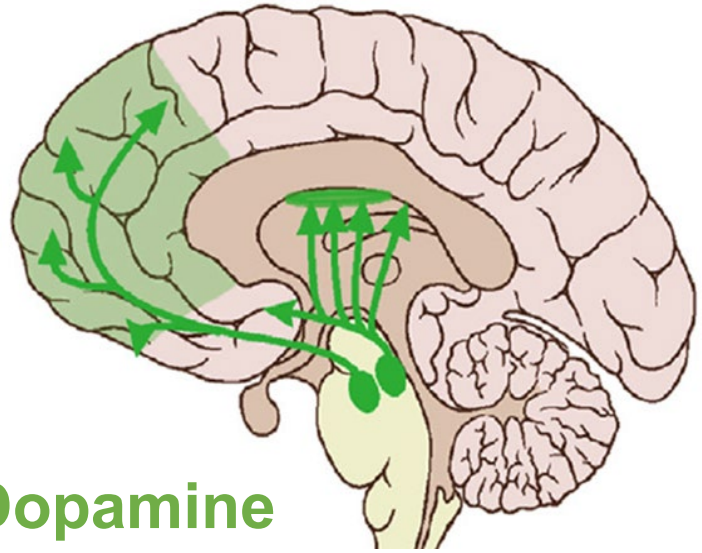
Serotonin

- Projects from raphe nuclei of brainstem
- Regulates both non-REM sleep architecture and mood
  - highlighted by SSRIs that suppress REM sleep and treat depression



Norepinephrine

- Projects from the locus coeruleus
- Regulates emotional responsivity
- Maintains arousal in wakefulness
- High norepinephrine activity contributes to insomnia and anxiety



Dopamine

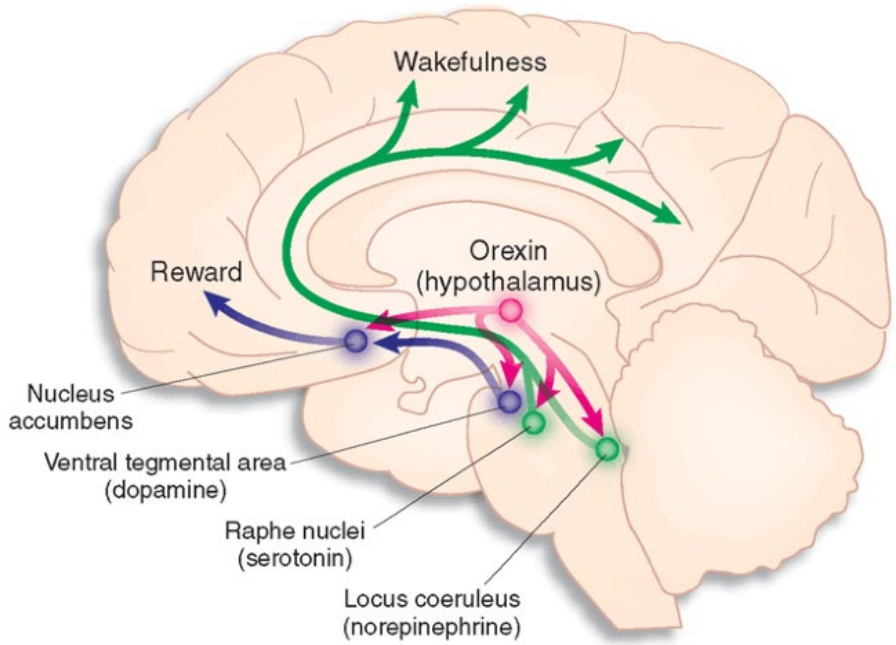
- Projects from ventral tegmental area and substantia nigra
- Regulates
  - reward processing motivation
  - wakefulness
- Implicated in parasomnia, hypersomnia, and anhedonic depression

Holst SC, Landolt HP. *Sleep Med Clin*. 2022;17(2):151-160.

Orexins and Monoamines Are Another Bidirectional Interaction

Orexin

- Deficiency causes narcolepsy
- Hyperactivity is implicated in anxiety, SUD, and insomnia
- Hypoactivity is implicated in hypersomnia, depression



Monoamines

- Deficiency (serotonin, norepinephrine) causes depression, anxiety
- Hyperactivity (dopamine) causes psychotic symptoms
- Implicated in sleep disorders

- Orexin antagonists treat insomnia
- Orexin agonists increase wakefulness, reduce cataplexy
- SSRIs/SNRIs improve mood but cause insomnia
- Dopamine D_2 receptor antagonists treat psychosis but reduce REM sleep

SNRIs = selective norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

Challet E, Pevet P. *Front Biosci*. 2003;8:s246-57. Date Y, et al. *Proc Natl Acad Sci USA*. 1999; 96:748-53. Vadnie CA, McClung CA. *Neural Plast*. 2017;2017:1504507. Sakurai T. *Nat Rev Neurosci*. 2007;8(3):171-81. Sakurai T, et al. *Front Neurol Neurosci*. 2021;45:11-21.

Key Learning Points

- The **bidirectional relationship** of sleep-wake disorders and psychiatric conditions involve **overlapping symptoms** and **shared mechanisms** that benefit from **collaborative, integrated treatment**

- When **sleep-wake disorders** and **psychiatric conditions** coexist, **addressing one often improves the other**

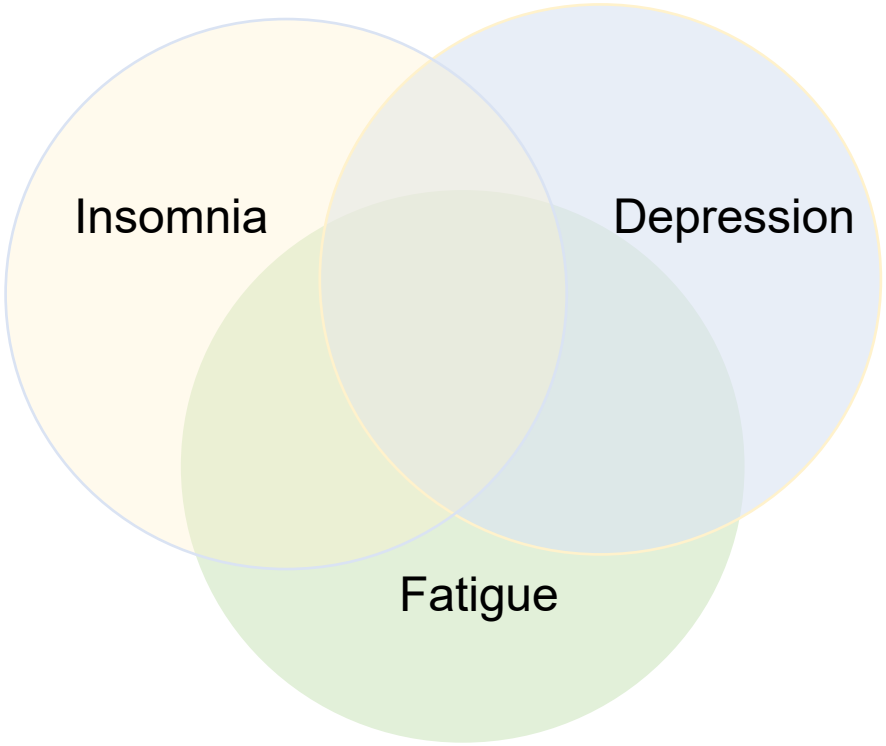
- **Orexin receptors** are involved in sleep/wake cycles localized to the lateral hypothalamus and have extensive projections throughout the brain, **including areas implicated in psychiatric disorders**.

Evaluation of Mental Health in Sleep Medicine

Andrew Krystal, MD

Symptom Overlap

- Many sleep-wake disorders share symptoms with psychiatric conditions
- Sometimes people with sleep-wake disorders have these symptoms without a comorbid psychiatric condition
  - Can be challenging to determine when this is the case
  - Is essential to determine as it dictates treatment targets
- Sometimes a co-morbid psychiatric condition is causing the symptoms rather than the sleep-wake disorder
  - Merits consideration for specific treatment of psychiatric conditions
  - More likely when the sleep-wake disorder is one commonly co-morbid with the psychiatric disorder
  - Treatment for both conditions is generally indicated



Symptoms of Sleep-Wake Disorders Overlap with Symptoms of Psychiatric Disorders

Sleep-Wake Disorder	Frequently Co-Morbid Psychiatric Disorder	Symptom	Psychiatric Conditions Sharing Symptom
Insomnia	MDD, GAD, PTSD, alcohol use disorder, stimulant use disorder	Daytime fatigue	MDD, BPD, PTSD
		Irritability	BPD mixed or manic state
		Cognitive impairment	Depression, BPD, schizophrenia, alcohol use disorder
Obstructive sleep apnea	MDD, PTSD, schizophrenia	Daytime sleepiness	MDD, BPD, PTSD
		Cognitive impairment	Depression, BPD, schizophrenia, alcohol use disorder
Narcolepsy	MDD	Daytime sleepiness	MDD, BPD, PTSD
		Disturbed sleep	MDD, BPD, GAD, PTSD, alcohol use disorder, stimulant use disorder, schizophrenia
Idiopathic hypersomnia	MDD	Daytime sleepiness	MDD, BPD, PTSD
		Non-refreshing sleep	MDD, BPD
Periodic limb movement disorder	N/A	Sleep disturbance	MDD, BPD, GAD, PTSD, alcohol use disorder, stimulant use disorder, schizophrenia
		Daytime sleepiness	MDD, BPD, PTSD
Delayed sleep-wake phase disorder	PTSD, MDD	Daytime sleepiness	MDD, BPD, PTSD
		Delay in sleep phase	MDD, PTSD
Irregular sleep-wake rhythm disorder	N/A	Irregular sleep phase	Schizophrenia, alcohol use disorder
Nightmare disorder	N/A	Nightmares	PTSD

BPD = bipolar depression. Xiao L, et al. *Neuropsychol Rev*. 2021;31(1):89-102. Krystal AD, et al. *JAMA*. 2021;326(23):2444. McCall WV, et al. *J Psychiatr Res*. 2019;116:147-150. Krystal AD, et al. *Ann Clin Psychiatry*. 2008;20(1):39-46. Morin CM, et al. *Nat Rev Dis Primers*. 2015;1:15026. Benca RM, et al. *J Clin Psychiatry*. 2023;84(2):22r14521. McCall CA, Watson NF. *Clin Med*. 2022;11(2):415. Geldenhuys C, et al. *CNS Drugs*. 2022;36(7):721-737. Zou H, et al. *Front Neurosci*. 2022;16:811771. Ashton A, Jagannath A. *Front Neurosci*. 2020;14:636.

Differentiating Depression and Sleep-Wake Disorders

Major Depressive Episode

Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observations made by others (eg, appears tearful).
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
3.
4. Insomnia or hypersomnia nearly every day.
5.
6. Fatigue or loss of energy nearly every day.
7.
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
9.

Useful, but may reflect sleep disorder

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

Best Differentiators

3. Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day.

9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Differentiating Bipolar Mania and Sleep-Wake Disorders

Mania in Bipolar Disorder

A distinct period of abnormally and persistently elevated, expansive, or an abnormally and persistently increased goal-directed activity, **irritable mood** or energy, lasting at least one week and present most of the day, nearly every day.

During the period of mood disturbance and increased energy or activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior.

1.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3.
4.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), reported or observed.
6.
7.

Useful, but may reflect sleep disorder

Best Differentiators

1. Inflated sense of grandiosity.
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
6. Increase in goal-directed activity (socially, at work or school, or sexually) or psychomotor agitation (ie, purposeless, non-goal-directed activity).
7. Excessive involvement in activities with high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

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Differentiating Bipolar Disorder With Mixed Features From Sleep-Wake Disorders

Bipolar Disorder With Mixed Features

At least 3 of the symptoms during the majority of the days of the current or most recent episode of mania/hypomania.

1. Prominent dysphoria or depressed mood as indicated by either subjective report (eg, feels sad or empty) or observation made by others (eg, appears tearful).
2. Diminished interest or pleasure in all, or almost all, activities (as indicated by either subjective account or observation made by others).
3.
4. Fatigue or loss of energy.
5.
6.

Useful, but may reflect sleep disorder

Best Differentiators

3. Psychomotor retardation nearly every day (observable by others, not merely subjective feelings of being slowed down).

5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

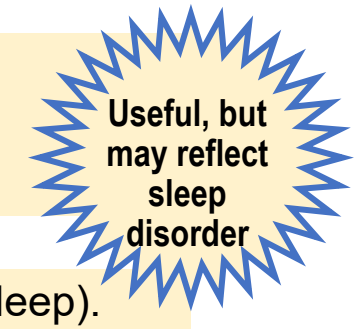
6. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

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

Differentiating GAD and Sleep-Wake Disorders

Generalized Anxiety Disorder

- **Excessive anxiety and worry** (apprehensive expectation), occurring more days than not for at least six months, **about a number of events or activities**.
- The individual finds it difficult to control the worry.
- The anxiety and worry are associated with 3 (or more) of the following 6 symptoms (with at least some symptoms having been present for more days than not for the past six months):
  1. Restlessness or feeling keyed up or on edge.
  2. Being easily fatigued.
  3. Difficulty concentrating or mind going blank.
  4. Irritability.
  5. Muscle tension
  6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
- The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.



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Differentiating PTSD and Sleep-Wake Disorders Part 1

Post-Traumatic Stress Disorder

- Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following:
  1. Directly experiencing the traumatic event(s).
  2. Witnessing, in person, the event(s) as it occurred to others.
  3. Learning that the traumatic event(s) occurred to a close family member or close friend.
  4. Experiencing repeated or extreme exposure to aversive details of event(s)
- Presence of one (or more) of the following intrusion symptoms associated with the event(s):
  1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).
  2.
  3. Dissociative reactions in which the individual feels or acts as if the traumatic event(s) were recurring.
  4. Intense or prolonged psychological distress at exposure to cues that symbolize or resemble aspect of the event(s).
  5. Marked physiological reactions to internal/external cues that symbolize/resemble an aspect of the traumatic event(s)

Useful, but may reflect sleep disorder

2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).

- Persistent avoidance of stimuli associated with the traumatic event as evidenced by one or both of the following:
  1. Avoidance of distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
  2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

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Differentiating PTSD and Sleep-Wake Disorders Part 2

Post-Traumatic Stress Disorder

- Negative alterations in cognitions/mood associated with the event(s), evidenced by **2 or more of the following**:
  1.
  2.
  3.
  4.
  5. Markedly diminished interest or participation in significant activities.
  6.
  7. Persistent inability to experience positive emotions
- Duration of the disturbance is more than 1 month.

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Best Differentiators

1. Inability to remember an important aspect of the traumatic event(s).
2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world.
3. Persistent, distorted cognitions about cause or consequences of the event(s) that lead to blame self or others.
4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
6. Feelings of detachment or estrangement from others.

Differentiating PTSD and Sleep-Wake Disorders Part 3

- Marked alterations in arousal and reactivity evidenced by two (or more) of the following:
  1. Reckless or self-destructive behavior.
  2. Exaggerated startle response.
  3.
  4.
  5.
  6.
- Duration of the disturbance is more than 1 month.

Useful, but may reflect sleep disorder

1. Irritable behavior and angry outbursts, typically expressed as verbal or physical aggression toward people or objects.
2.
3. Hypervigilance.
4.
5. Problems with concentration.
6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

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

Differentiating Schizophrenia and Sleep-Wake Disorders

Schizophrenia

- Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be delusions, hallucinations or disorganized speech:
  1. Delusions
  2. Hallucinations
  3. Disorganized speech (eg, frequent derailment or incoherence)
  4. Grossly disorganized or catatonic behavior
  5. Negative symptoms (ie, diminished emotional expression or avolition)
- Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms that meet the above criteria
- For a significant portion of time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or selfcare is markedly below the level achieved prior to the onset

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

Differentiating SUD and Sleep-Wake Disorders

Substance-Use Disorders

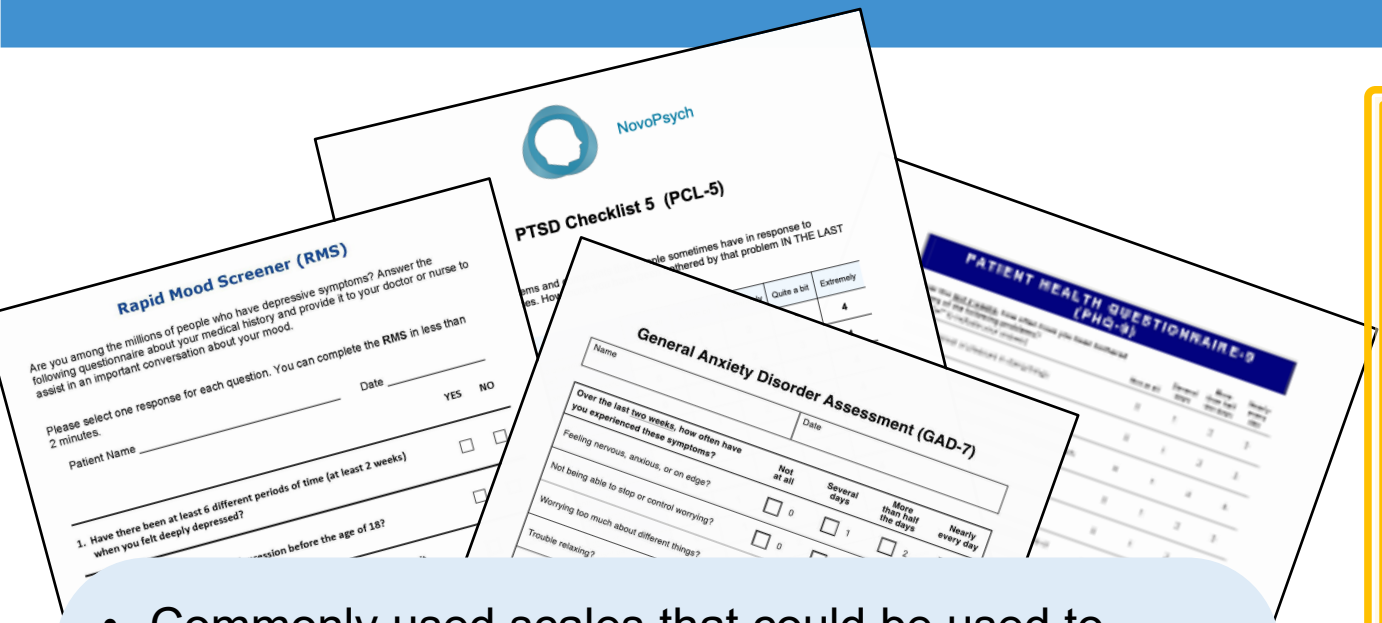
- Patterns of symptoms caused by using a substance that an individual continues taking despite its negative effects
  - Using more of substance than intended or using it for longer than you're meant to.
  - Trying to cut down or stop using the substance but being unable to.
  - Experiencing intense cravings or urges to use the substance.
  - Needing more of the substance to get the desired effect — also called tolerance.
  - Developing withdrawal symptoms when not using the substance.
  - Spending more time getting and using drugs and recovering from substance use.
  - Neglecting responsibilities at home, work or school because of substance use.
  - Continuing to use even when it causes relationship problems.
  - Giving up important or desirable social and recreational activities due to use.
  - Using substances in risky settings that put you in danger.
  - Continuing use despite substance causing problems to physical and mental health.

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

Appropriate and Effective Questions to Ask

- Which came first, depression or insomnia?
- When unable to sleep, do you lie in bed worrying (rumination)?
- Has lack of energy from poor sleep contributed to lower activity levels during the day?
- Does your mood/symptoms change (improve) after a relatively good night's sleep?
- If you were in a good mood during the day, do you sleep better at night?
- Is severity of the two symptom sets linked?

Use of Scales to Detect Psychiatric Conditions



- Commonly used scales that could be used to assess a patient with sleep-wake disorder for psychiatric conditions include:
  - PHQ-9 (MDD)
  - GAD-7 (GAD)
  - RMS (BPD)
  - PCL-5 (PTSD)
- **But symptom overlap can create false positives**

Case example

- ✓ 45-year-old man with sleep onset and maintenance insomnia
  - ✓ Daytime fatigue
  - ✓ Irritability
  - ✓ Trouble concentrating
  - ✓ Low energy that prevents activities
- ✓ Patient reports all are consequences of his insomnia.
  - ✓ Feels fine on those rare nights when he gets a good night's sleep.
  - ✓ Has no sadness, guilt, hopelessness, suicidal ideation
  - ✓ Denies depression.

Use of Scales May Result in False Positives

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(use"✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly everyday
1. Little interest or pleasure in doing things	0	1	2	(3)
2. Feeling down, depressed, irritable, or hopeless	0	1	2	(3)
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	(3)
4. Feeling tired or having little energy	0	1	2	(3)
5. Poor appetite, weight loss, or overeating	(0)	1	2	3
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	(0)	1	2	3
7. Trouble concentrating on things, such as school work, reading, or watching television	0	1	2	(3)
8. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	(0)	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	(0)	1	2	3

Insomnia Patient Score = 15

0-4	None to minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

FALSE POSITIVE

for moderately severe depression
based on established cutoffs above

How to Treat Patients with Co-Morbid Sleep and Psychiatric Disorders

Andrew Krystal, MD

Single-Agent Approaches for Treating Insomnia

The Single-Agent Approach Targets Both Conditions With One Medication

All single-agent options are off-label

None are FDA-approved for treating insomnia and a psychiatric disorder at the same dose

- Advantages
  - Cost
  - Adherence to treatment
- Disadvantages
  - Limitations in choice of agent, particular to the adverse effects profile

Treatments for Insomnia with Specific Co-Existing Psychiatric Condition

Co-existing psychiatric disorder	Off-label treatment options	Notes
Generalized anxiety disorder	Pregabalin	Shown to improve sleep in GAD
	Gabapentin	Shown to improve pre-operative anxiety; improved sleep in healthy controls
Major depressive disorder	Mirtazapine	FDA-approved for MDD at 15 mg S-isomer effective for insomnia at 3-4 mg
Alcohol-use disorder	Gabapentin	Shown to improve sleep in alcohol-use disorder
Bipolar disorder	Lurasidone	FDA-approved for BPD; found to have some benefit for insomnia in healthy controls
Schizophrenia	Lurasidone	FDA-approved for schizophrenia; found to have some benefit for insomnia in healthy controls

Holsboer-Trachsler E, et al. *Int J Neuropsychopharmacol*. 2013;16(4):925-36. Hoffman M, et al. *J Addict Med*. 2024;18(5):520-5. Furey SA, et al. *J Clin Sleep Med*. 2014;10(10):1101-9. Ivgy-May N, et al. *Sleep Med*. 2015;16(7):838-44. Krystal AD. *Hum Psychopharmacol*. 2016;31(3):206-16.

Dual-Agent Approaches for Treating Sleep-Wake Disorders and Co-Existing Psychiatric Conditions

The Dual-Agent Approach Targets Each Condition With a Separate Medication

Dual-agent options to treat psychiatric conditions in patients with co-existing sleep-wake disorders include

- Hypnotics
- Sedating antidepressants
- Activating antidepressants
- Stimulants
- Atypical antipsychotics
- Antiepileptic drugs
- Lithium

Insomnia Special Case

Eszopiclone 3 mg improved sleep

AND AUGMENTED

Antidepressant response beyond SSRI

Antianxiety response beyond SSRI

Low back pain response beyond naproxen

Goforth HW, et al. *Sleep*. 2014;37(6):1053-60; Pollack M, et al. *Arch Gen Psychiatry*. 2008;65(5):551-62. Fava M, et al. *Biol Psychiatry*. 2006;59(11):1052-60.

When to Refer Sleep-Wake Disorder Patients to Psychiatry

- It is unclear if there is a psychiatric diagnosis
- You do not feel qualified or comfortable managing the patient's mental health condition
- The complexity of the patient's sleep-wake disorder is high enough to demand all your available attention
- The patient is resisting treatment
- The psychiatric condition is severe/life threatening
- A psychiatric condition appears to be driving the sleep-wake disorder making it necessary to treat the psychiatric condition in order to address the sleep-wake disorder

Key Learning Points

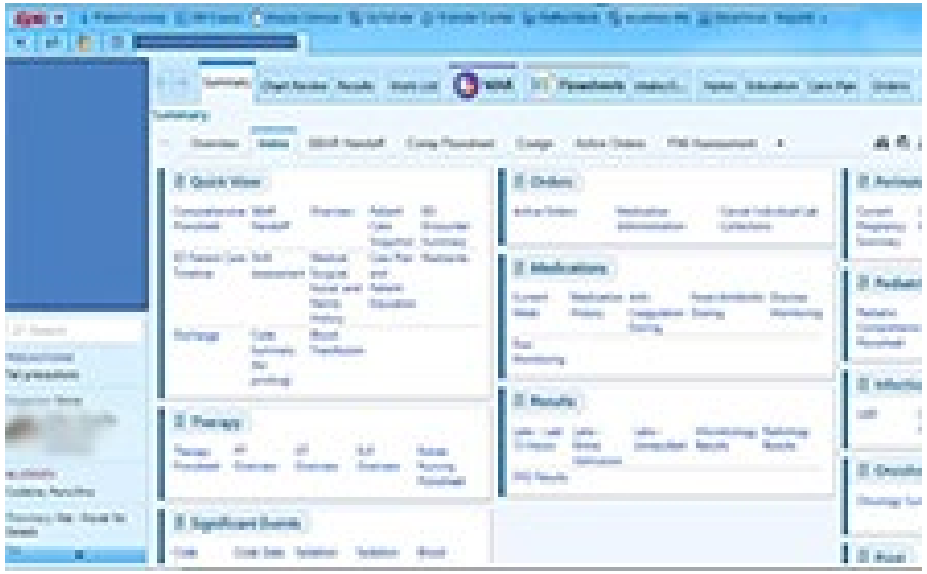
- Sleep-wake and psychiatric disorders have **overlapping symptoms** that can make **differential diagnosis challenging**
- It is important to **understand and apply differentiating diagnostic criteria** when considering a psychiatric diagnosis in a person with a sleep-wake disorder
- **Insomnia** can be treated with an off-label, **single-agent approach** using **one medication to address two disorders**
- **Other** than insomnia, **sleep-wake disorders** require a **dual-agent approach** with separate medications targeting each disorder

Case-Based Strategies at the Intersection of Mental Health and Sleep Medicine

Arwen Podesta, MD, DFAPA, DFASAM & Andrew Krystal, MD

Case 1

- **HISTORY**
  - "Jean" is a 72-year-old woman
  - Previously diagnosed with ADHD, depression, and anxiety
  - Treated with venlafaxine for 15-20 years
- **FOLLOW-UP**
  - Reveals additional symptoms
    - Daytime hypersomnolence
    - Panic attacks
    - PTSD
    - Nightmares
  - Significant family history for ADHD and depression
  - Spouse, who is a physician, reported an episode of "restless leg syndrome" during sleep
- **SLEEP-WAKE DISORDER DIAGNOSIS**
  - Referred for sleep study, which was done 2 years later
  - Sleep-wake disorder diagnosis: REM behavioral disorder



- **CURRENT DISCUSSION**
  - Start benzodiazepine hs?
  - Discontinue/change venlafaxine?

Case 2

- **HISTORY and CLINICAL EVALUATION**
  - "Joe" is a 63-year-old man who works as an executive
  - Presents for treatment of opioid-use disorder
    - Used oral pain pills regularly and heroin occasionally
    - Medically stable after intensive outpatient program
  - Continues outpatient treatment with
    - Monthly buprenorphine injection
    - Trazodone, which he reports helps him fall asleep
- **CHIEF CONCERN**
  - Daytime hypersomnolence
  - Spouse reports significant snoring
- **TREATMENT**
  - CBT-I prescribed
- **DISCUSSION**
  - Stop or continue buprenorphine

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 (requires split dosing)
  - High sedation: quetiapine and olanzapine
  - Mild sedation: aripiprazole and lurasidone

- Antipsychotics can induce or worsen
  - Period limb movement disorder
  - REM behavior disorder
  - Monitor for effects on sleep and movement-disorder symptoms

- Atypical antipsychotics cause weight gain
  - Can worsen or unmask OSA
  - Sedative effects can reduce respiratory tone
  - Consider screening for OSA before initiating

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.

Managing Medication-Induced Sleep Disruption

Optimize Timing

- ❑ Schedule medications by effects
  - ❑ >8-10 hours before desired wake time for sedating agents
  - ❑ ~1 hour of waking for activating agents
  - ❑ Consider split dosing when appropriate for 24-hour coverage

Consider Counterbalancing Agents

- ❑ Add medications to mitigate effects of psychiatric treatments on sleep
  - ❑ Low-dose trazodone for SSRI/SNRI-induced insomnia
  - ❑ Modafinil for antipsychotic-induced sedation
  - ❑ Melatonin for circadian disruptions

Adjust Formulations

- ❑ Immediate vs extended-release options
  - ❑ ER for smoother coverage and fewer peak effects
  - ❑ IR for more precise timing control
- ❑ Liquid formulations can offer flexible dosing

Behavioral Strategies

- ❑ Use non-pharmacological approaches to address medication effects on sleep
  - ❑ Sleep restriction therapy for early awakening
  - ❑ Strategic light therapy for circadian phase adjustments
  - ❑ Sleep hygiene optimization

Novak M, Shapiro CM. *Drug Saf*. 1997;16(2):133-49.

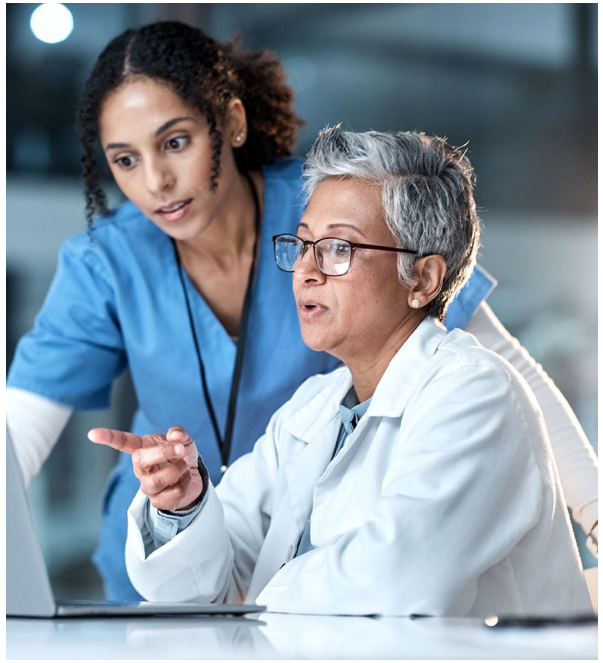
Coordinating Medication Changes with Psychiatric Providers

Information Sharing

- Reach out to psychiatric provider before making recommendations that affect psychiatric medications
- Establish preferred communication method
- Share relevant sleep findings

Joint Planning

- Develop coordinated approach to medication adjustments
- Determine sequence of changes
- Establish monitoring parameters



Synchronize Follow-up

- Coordinate timing of follow-up appointments
- Schedule sleep follow-up after psychiatric visit
- Implement staggered monitoring schedule

Ongoing Communication

- Share outcomes and adjust approach as needed
- Update regarding positive and negative effects
- Coordinate additional adjustments

Suspected Functional Neurological Disorders in Patients with Sleep/Wake Symptoms

- Functional neurological disorders are the intersection of
  - Neurology
  - Sleep medicine
  - Psychiatry
  - Diagnostic uncertainty and treatment challenges are common
- Account for approximately 2%-5% of sleep center referrals
- Common presentations include
  - Non-epileptic events during sleep
  - Functional hypersomnolence
  - Atypical parasomnias
- Often comorbid with psychiatric disorders, particularly
  - Anxiety
  - Depression
  - Trauma-related conditions

Kannan S, et al. *Neurol Sci*. 2025;46(4):1573-80.

Case 3

- **HISTORY and CLINICAL EVALUATION**
  - "Lisa" is a 58-year-old woman
  - 12-month history of chronic insomnia
    - Sleep efficiency 58%
    - Sleep onset latency >90 minutes
  - Recent job loss
  - Undisclosed: history of bipolar II disorder
- **TREATMENT COURSE**
  - Sent for sleep study
  - Initiation of CBT-I and daridorexant
  - On week 2 of daridorexant, Lisa reports severe anxiety due to medication not fully addressing sleep issues
    - On further discussion, Lisa exhibits paranoid thoughts about medication, suicidal ideation with plan, and reveals that she has abruptly stopped taking her medications
- **NEXT STEPS**
  - Referred for emergency psychiatric evaluation and crisis hospitalization for 72 hours
  - Implementation of safety planning, daily check-ins, and involvement of adult children for support
  - Discontinuation of daridorexant, addition of quetiapine at bedtime
  - Coordination wit outpatient psychiatrist for mood stabilization and gradual return to modified sleep treatment

IMPORTANT LESSON

In this case, medication-related anxiety triggered latent bipolar symptoms.

Inadequate initial psychiatric screening missed <u>bipolar history</u> which increased vulnerability to medication-induced mood effects.

This crises highlights the need for comprehensive mental health assessment before initiating pharmacological sleep interventions and establishing clear monitoring protocols for high-risk patients.

Mental Health Crises During Sleep Medicine Treatment

Mental Health Crises

- Can emerge unexpectedly during sleep medicine treatment
- Long-standing sleep-wake disorders may have served as coping mechanisms
  - Example 1: successful insomnia treatment may reveal depression/anxiety previously considered sleep deprivation or sleep-focused rumination
  - Example 2: treatment of hypersomnia disorders leading to increased wakefulness can increase awareness of traumatic memories or emotional distress

Require Advance Crisis Plans

- Recognition
  - Identify acute psychiatric decompensation
- Risk assessment
  - Evaluate suicidality and safety concerns
- Immediate intervention
  - Deploy appropriate crisis resources
- Follow-up planning
  - Implement post-crisis care coordination

Recognizing Mental Health Crises in Sleep Medicine

Suicidal Ideation
May emerge during treatment of chronic insomnia as patients experience increased daytime awareness
Also occurs with stimulant initiation or dosage increases for hypersomnia disorders
Requires immediate risk assessment, safety planning, and potential emergency referral

Trauma Recollection
Improved sleep consolidation may increase dream recall, including suppressed trauma-related nightmares.
CPAP therapy sometimes triggers claustrophobic reactions related to past trauma
Requires trauma-informed care approaches and possibly specialized therapy

Acute Anxiety/Panic
Can occur with CPAP initiation in patients with claustrophobia or trauma history
Also common during sleep restriction therapy
Sympathetic arousal during panic episodes may be misinterpreted as medication side effects
Management includes graded exposure and anxiety-specific interventions

Medication-Induced Mania
Risk with stimulants in undiagnosed bipolar disorder
Also possible with certain antidepressants used for cataplexy or insomnia
Presents with decreased sleep need, increased energy, pressured speech, and poor judgment.
Requires immediate psychiatric consultation and medication adjustment

Mental Health and Sleep. Sleep Foundation. https://www.sleepfoundation.org/mental-health. Accessed June 3, 2026. Bernert RA, et al. *Curr Psyciatry Rep.* 2015;17(3):554.

Key Learning Points

- Psychiatric medications often have sedating or activating effects that impact sleep and sleep-wake disorders.
- Complex sleep-related effects of psychiatric medications include **REM sleep suppression**, **period limb movement disorders**, **worsening of OSA** due to weight gain, and **worsening of sleep-disordered breathing**
- Managing co-existing sleep-wake disorders and psychiatric conditions is essential and often requires a **collaborative team care**
- **Crisis plans should be developed in advance** when treating patients with co-existing sleep-wake and psychiatric disorders

Faculty Panel Discussion

- Accessing Psychiatry Education Resources
- Talking to Patients About Mental Health
- Individualizing Treatment
- Collaborating with Psychiatric Specialists

Practical Take-Home Points

- When sleep-wake disorders and psychiatric conditions coexist, addressing one often improves the other
- Careful differential diagnosis of co-existing psychiatric and sleep-wake disorders is essential as this determines treatment targets
- Understanding which criteria differentiate psychiatric disorders from sleep-wake disorders can aid diagnoses, which are often complicated due to overlapping symptoms
- With the exception of insomnia, treatment of comorbid psychiatric and sleep-wake disorders uses at least two separate medications that target each disorder individually

Q&A

Scan the QR code to submit your questions and participate in polling.

Winner of the $100 gift card will be announced at the end of the session and must be present to claim their prize.