

Psychopharmacology of Sleep Disorders

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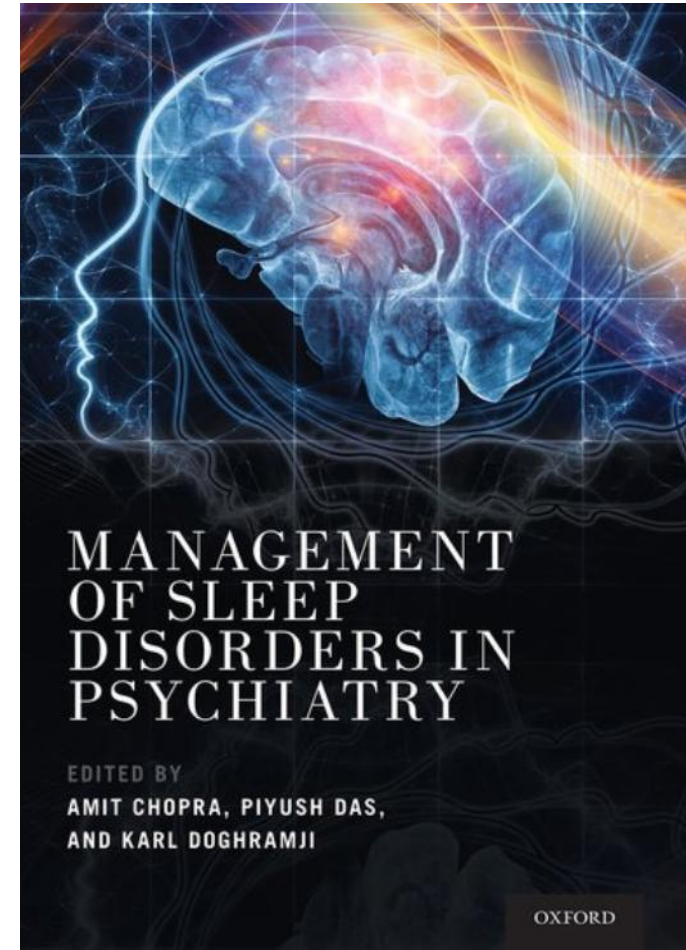
Assistant Professor, Harvard Medical School

Disclosures

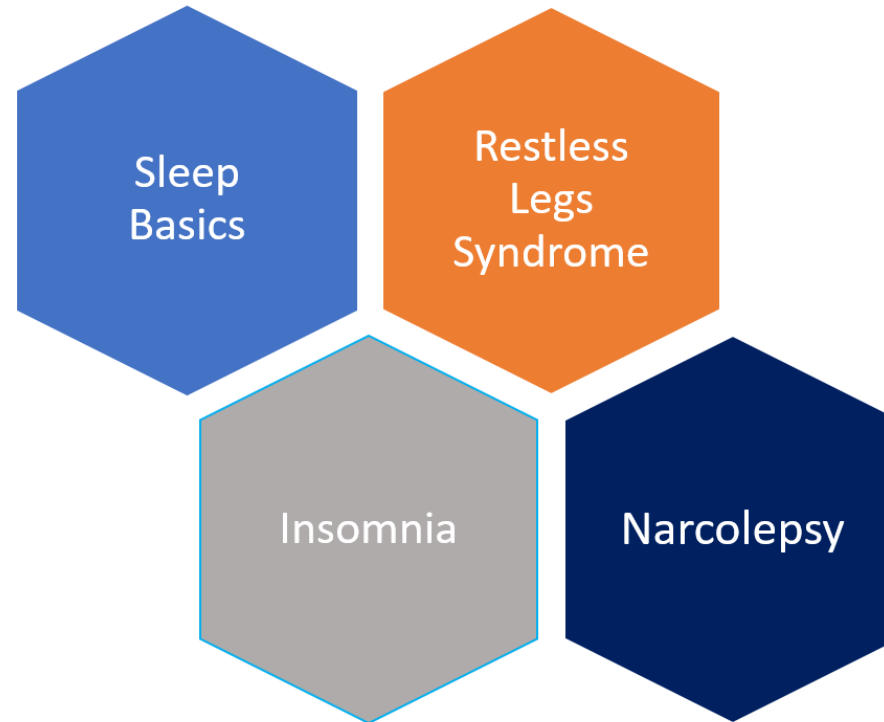
Speaker: Psychopharmacology
Institute

Royalties: Oxford University
Press 'Management of Sleep
Disorders in Psychiatry'

Founder: 'Zen Minds'

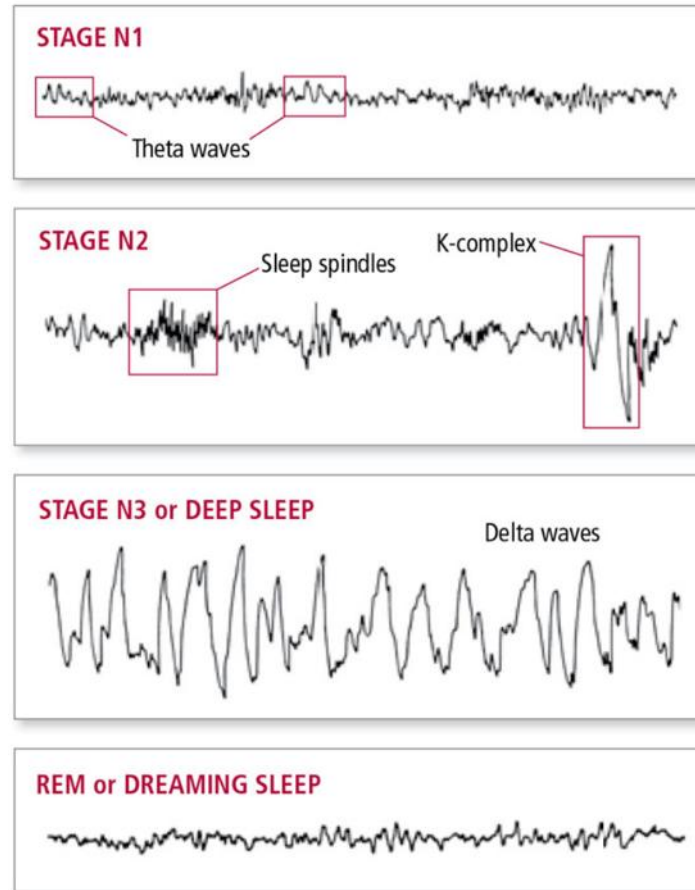


Objectives



Sleep Architecture

Sleep Stage	Characteristic Features
N1	❖ causing awakenings or arousals is easy ❖ the occurrence of slow eye movements ❖ brain wave activity begins to slow ❖ theta activity (4–8 Hz, 50–100 μV) is typical in EEG ❖ the presence of abrupt muscle spasms or hypnic jerks
N2	❖ causing awakenings or arousals becomes harder ❖ the slow eye movements discontinue ❖ brain waves continue to slow with specific sleep structures: sleep spindles and K-complexes ❖ body temperature decreases ❖ heart rate begins to slow
N3	❖ awakenings or arousals are rare ❖ the presence of delta waves (1–4 Hz, 100–200 μV) ❖ the most restorative stage of sleep ❖ the occurrence of parasomnias
REM	❖ awakenings and arousals can occur more easily ❖ brain waves are more active (15–30 Hz, < 50 μV) ❖ eye movements are rapid, moving from side to side ❖ the occurrence of hypotonia of skeletal muscle ❖ the presence of instability of pulse and respiratory rate



Sleep Parameters

- Parameters of Sleep Continuity
 - Sleep onset latency (SOL ≤ 30 minutes)
 - Wake after sleep onset (WASO ≤ 30 minutes)
 - Sleep efficiency = Time slept/Time in bed (SE $\geq 85\%$)
 - Total sleep time (TST)
- Parameters of Sleep Depth
 - Total and relative amounts of N3 sleep (15-20%)
 - Delta sleep ratio (DSR > 1.1)
- Parameters of REM Sleep
 - REM latency (REML = 80-110 minutes)
 - Total and relative amounts of REM sleep (20-25%)
 - REM density (9-12 eye movements per minute)

ICSD-3

Neurobiology of Sleep and Wakefulness

Wake-promoting neurotransmitters	Sleep-promoting neurotransmitters	
	NREM	REM
Glutamate	GABA	Acetylcholine
Acetylcholine	Galanin	Glutamate
Dopamine	Adenosine	GABA
Norepinephrine	Melatonin	Glycine (muscle atonia)
Serotonin		
Histamine		
Orexin/hypocretin		

Note: NREM = nonrapid eye movement; REM = rapid eye movement;

Owens et al, 2012

Insomnia Disorder

Table 1. DSM-V Criteria for Insomnia Disorder

- Complaint of dissatisfaction with quantity or quality of sleep occurs at least 3 nights a week for at least 3 months, associated with one or more of the following:
 - Difficulty falling asleep
 - Difficulty staying asleep, with frequent awakenings or difficulty falling back asleep
 - Early morning awakening
- The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The sleep disturbance occurs even when there is enough time for sleep
- The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia (an unusual behavior or event that occurs during sleep that may lead to intermittent awakenings).
- The sleep disturbance does not occur exclusively during the course of another mental disorder.
- The sleep disturbance is not due to the direct physiologic effects of a substance such as a drug of abuse or a medication, or from a general medical condition.

DSM-V, Diagnostic and Statistical Manual of Mental Disorders, 5th Ed.
Based on reference 4.

Epidemiology and Risk Factors



**~10%
Prevalence**

Prevalence of insomnia disorder in adults
(DSM-5-TR criteria)



**~50%
Chronic Course**

Approximately 50% of patients have a chronic course

BIDIRECTIONAL RELATIONSHIP BETWEEN INSOMNIA DISORDER AND MAJOR DEPRESSIVE DISORDER (MDD)



Insomnia increases risk for developing MDD



MDD increases risk for developing and maintaining insomnia



Each condition can worsen the other over time.



INSOMNIA IS A MODIFIABLE RISK FACTOR FOR SUICIDE

Insomnia is associated with suicidal ideation, attempts, and suicide risk—**independent of depression severity.**



Effective assessment and treatment of insomnia may reduce suicide risk.



RISK FACTORS



Female sex



Older age



Lower socioeconomic status



Comorbid medical and psychiatric disorders



Marital status
(e.g., single, separated, divorced, widowed)



Race
(greater risk in African Americans)



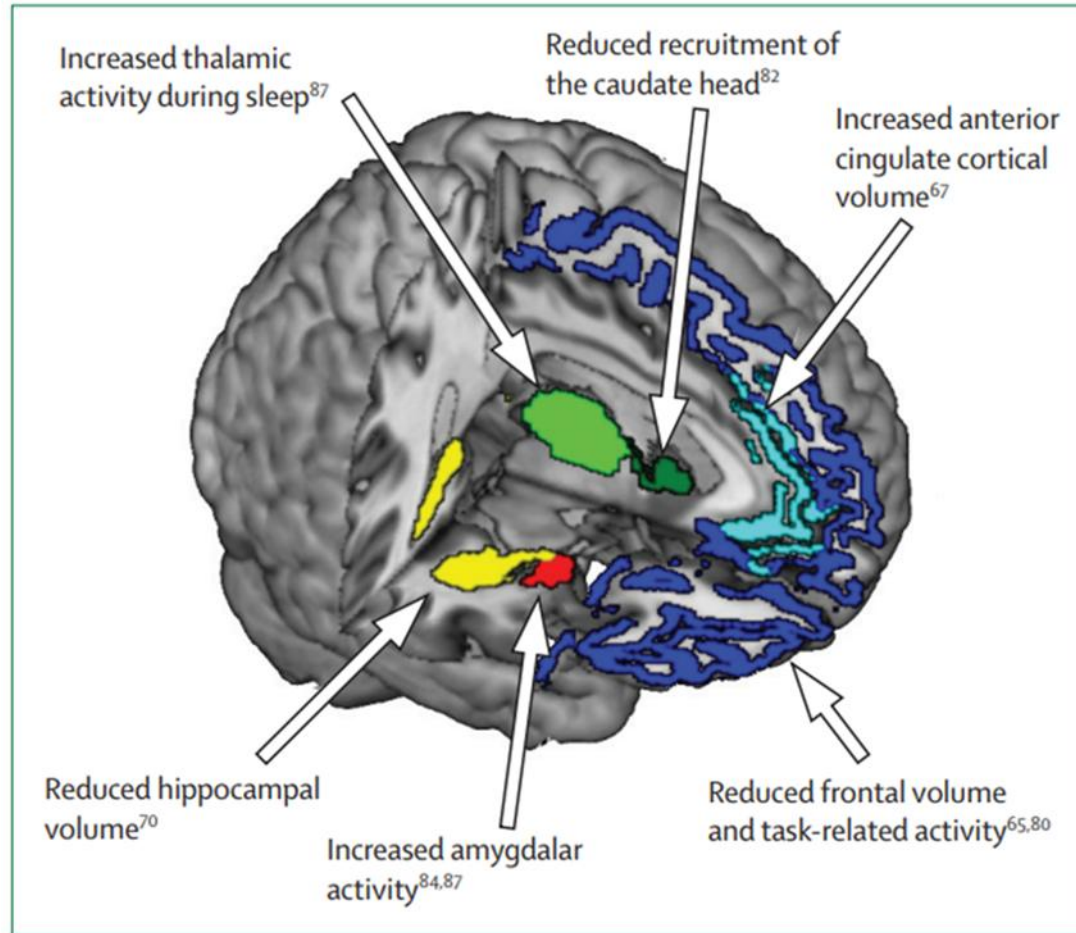
Family history



INSOMNIA IS COMMON, OFTEN CHRONIC, AND CLINICALLY SIGNIFICANT— BUT IT IS TREATABLE.

Morin & Jarrin, 2022

Neurobiology of Insomnia Disorder



Riemann et al, 2015

Clinical Approach

ASSESSMENT OF INSOMNIA DISORDER

A comprehensive evaluation is the foundation for effective treatment.



1 CLINICAL ASSESSMENT

- Detailed sleep history
- Establish sleep-continuity parameters:



- Assess sleep schedule and circadian pattern
- Consider **sleep diary** ± **actigraphy**



2 IDENTIFY CONTRIBUTING / COMORBID CONDITIONS

 **Primary sleep disorders:** OSA, RLS/PLMD, circadian rhythm disorders

 **Psychiatric disorders:** depression, anxiety, PTSD, substance-use disorders

 **Medical / neurologic comorbidity:** pain, cardiovascular disease, endocrine disorders, neurologic disease, etc.



 **Iatrogenic factors:** medications and treatments

 **Substance use:** alcohol, caffeine, nicotine and other substances

 **Lifestyle / environmental factors:** irregular schedule, stress, noise, screen time, bedroom environment



3 SCREENING TOOLS



Insomnia Severity Index (ISI)

- 7-item self-report questionnaire
- Assesses severity of insomnia and monitors treatment response



Pittsburgh Sleep Quality Index (PSQI)

- 19-item self-report questionnaire
- Evaluates sleep quality and disturbances over the past month



4 INVESTIGATIONS



 **Routine polysomnography (PSG) is NOT indicated** for uncomplicated chronic insomnia.

-  **PSG is considered when:**
- Suspicion of another sleep disorder (e.g., OSA, PLMD)
 - Atypical presentation
 - Treatment failure



KEY POINT: Insomnia disorder is primarily a **clinical diagnosis**. Objective sleep testing is usually unnecessary.



REFERENCES

1. Sateia MJ, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults. *J Clin Sleep Med*. 2017;13(2):307-349.
2. Edinger JD, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an AASM systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med*. 2021;17(2):255-262.
3. Riemann D, et al. The European guideline for the diagnosis and treatment of insomnia. *J Sleep Res*. 2023;32:e14035.

SOL = Sleep Onset Latency; WASO = Wake After Sleep Onset; TST = Total Sleep Time; SE = Sleep Efficiency; OSA = Obstructive Sleep Apnea; RLS = Restless Legs Syndrome; PLMD = Periodic Limb Movement Disorder

Non-Benzodiazepine Hypnotics



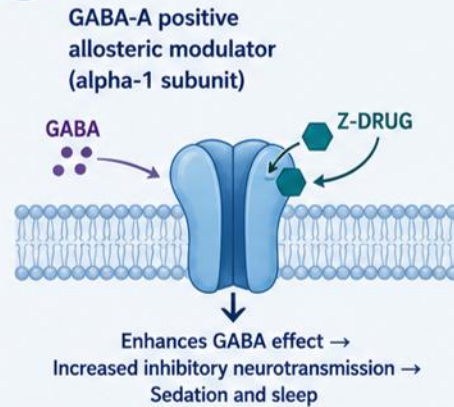
1. INDICATIONS



- Sleep initiation insomnia
- Sleep maintenance insomnia



2. MECHANISM OF ACTION (MOA)



3. DOSAGE



Zaleplon (10–20 mg):
Sleep initiation insomnia



Zolpidem: Sleep initiation and maintenance insomnia

- Zolpidem IR (5–10 mg)
- Zolpidem ER (6.25–12.5 mg)
- Zolpidem SL (1.75–3.5 mg):
Middle of Night Insomnia (MOTN)



Eszopiclone (1–3 mg):
Sleep initiation and maintenance insomnia



4. RELATIVE CONTRAINDICATIONS



- Pulmonary failure
- Untreated sleep apnea
- Hepatic failure
- Substance use



5. SIDE EFFECTS



6. CAUTION



Risk of complex sleep-related behaviors (sleepwalking, sleep driving, other activities).



Use lower doses in females.



Use the lowest effective dose for the shortest duration.
Reassess regularly.



REFERENCES

- Sateia MJ, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults. *J Clin Sleep Med.* 2017;13(2):307-349.
- Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res.* 2023;32:e14035.

IR = Immediate Release; ER = Extended Release; SL = Sublingual; MOTN = Middle of the Night Insomnia.

Dual Orexin Receptor Antagonists (DORAs)



1. INDICATIONS

For the treatment of sleep initiation and sleep maintenance insomnia.

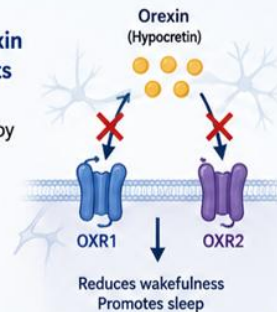


2. MECHANISM OF ACTION (MOA)

Reversible dual orexin receptor antagonists

Block orexin signaling by antagonizing both:

- OXR1 receptors
- OXR2 receptors



3. DOSAGE



Suvorexant

10–20 mg



Lemborexant

5–10 mg



Daridorexant

25–50 mg



4. SIDE EFFECTS



Headaches



Dizziness



Drowsiness



Vivid dreams



Sleep paralysis



5. ADVANTAGES



✓ Not associated with tolerance, withdrawal, or rebound insomnia



✓ No respiratory depression



6. CAUTIONS



Avoid in patients with narcolepsy



Potential for abuse



Key Takeaway:

Dual orexin receptor antagonists target the wake-promoting orexin system to improve sleep without the risks of tolerance, withdrawal, or respiratory depression.



REFERENCES

- Sateia MJ, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults. *J Clin Sleep Med.* 2017;13(2):307-349.
- Herring WJ, et al. Orexin receptor antagonists for the treatment of insomnia. *Nat Sci Sleep.* 2020;12:177-188.
- Rosenberg R, et al. The efficacy and safety of dual orexin receptor antagonists for insomnia. *Expert Opin Drug Saf.* 2021;20(12):1487-1498.

OXR1 = Orexin Receptor 1; OXR2 = Orexin Receptor 2

Melatonin Receptor Agonists

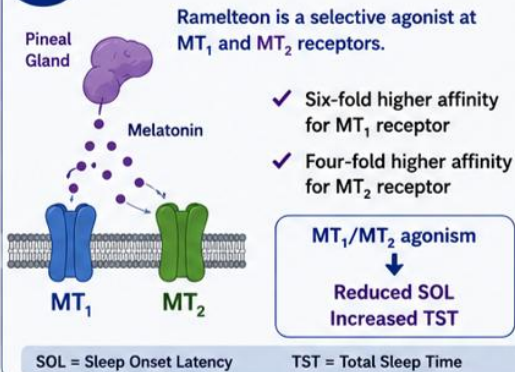


1. INDICATIONS

- Sleep initiation insomnia



2. MECHANISM OF ACTION (MOA)



3. DOSAGE



Ramelteon

8 mg



4. SIDE EFFECTS



Headaches



Dizziness



Fatigue



Drowsiness



Nightmares



5. ADVANTAGES



No tolerance,
withdrawal, or
rebound insomnia



No addiction
potential



No respiratory
depression



Ramelteon works with the body's natural melatonin system to help you fall asleep—without the risks of dependence or respiratory depression.



REFERENCES

- Sateia MJ, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults. *J Clin Sleep Med.* 2017;13(2):307-349.
- Dubovsky SL, et al. Safety and efficacy of ramelteon in older adults with chronic insomnia: a 4-week, randomized, double-blind, placebo-controlled study. *Sleep.* 2004;27(4):685-692.
- Erman MK, et al. A phase 4, 12-month study of ramelteon in the treatment of chronic insomnia. *Sleep Med.* 2009;10(5):530-536.

MT₁ = Melatonin Receptor 1; MT₂ = Melatonin Receptor 2; SOL = Sleep Onset Latency; TST = Total Sleep Time

H-1 Receptor Antagonists

LOW-DOSE DOXEPIN

A Tricyclic Antidepressant for Sleep Maintenance Insomnia



Low-dose doxepin is approved specifically for the treatment of sleep maintenance insomnia.



1. INDICATIONS

- Sleep maintenance insomnia

Difficulty staying asleep with frequent awakenings during the night.

- Prolonged wake after sleep onset (WASO)
- Non-restorative sleep



2. MECHANISM OF ACTION (MOA)

- Selective H₁ receptor antagonist at a low dose

By blocking central histamine H₁ receptors, doxepin:



Reduced WASO and increased TST



3. DOSAGE



Doxepin

3–6 mg

Taken 30 minutes to 1 hour before bedtime



4. SIDE EFFECTS

- Nausea
- Vomiting
- Dizziness
- Dry mouth



5. ADVANTAGES



No tolerance, withdrawal, or rebound insomnia



No addiction potential



Safety established in the elderly (3 mg)



REFERENCES

- Krystal AD, et al. Low-dose doxepin for insomnia: A systematic review. *Sleep Med Rev.* 2010;14(1):41–50.
- Winkelman JW, et al. The efficacy and safety of doxepin 3 mg in elderly patients with chronic insomnia: A randomized, placebo-controlled study. *J Clin Sleep Med.* 2010;6(2):155–162.
- Thorpy MJ, et al. Doxepin for the treatment of insomnia: A review of the evidence. *Drugs.* 2014;74(10):1141–1153.

WASO = Wake After Sleep Onset
TST = Total Sleep Time
H₁ = Histamine-1

Question 1

- A 67-year-old widowed female with a history of generalized anxiety disorder presents with sleep-maintenance insomnia complaints. Her medical history includes HTN, CAD, and obesity (BMI=36.5). She reports dry mouth and headaches upon waking and excessive daytime sleepiness. She denies any substance use. She denies any significant mood symptoms. Her anxiety is well controlled by taking sertraline 75 mg daily without any noticeable side effects.

Which of the following is the next best step in terms of management?

- A. Start a trial of Trazodone
- B. Start a trial of Doxepin
- C. Screen for obstructive sleep apnea
- D. Start a trial of Eszopiclone
- E. Stop Sertraline

Restless Legs Syndrome (RLS)

Box 1 | Diagnostic criteria for RLS⁷

Essential criteria

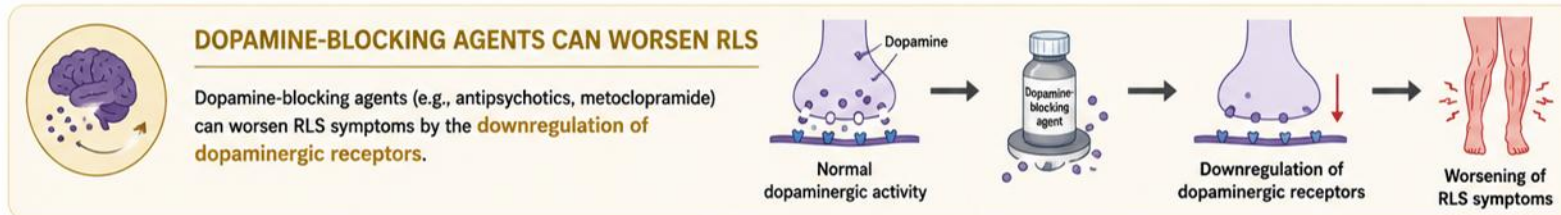
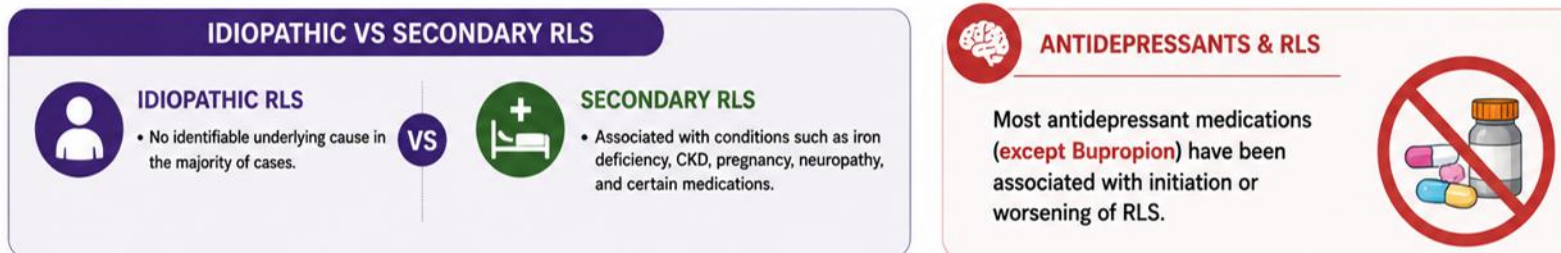
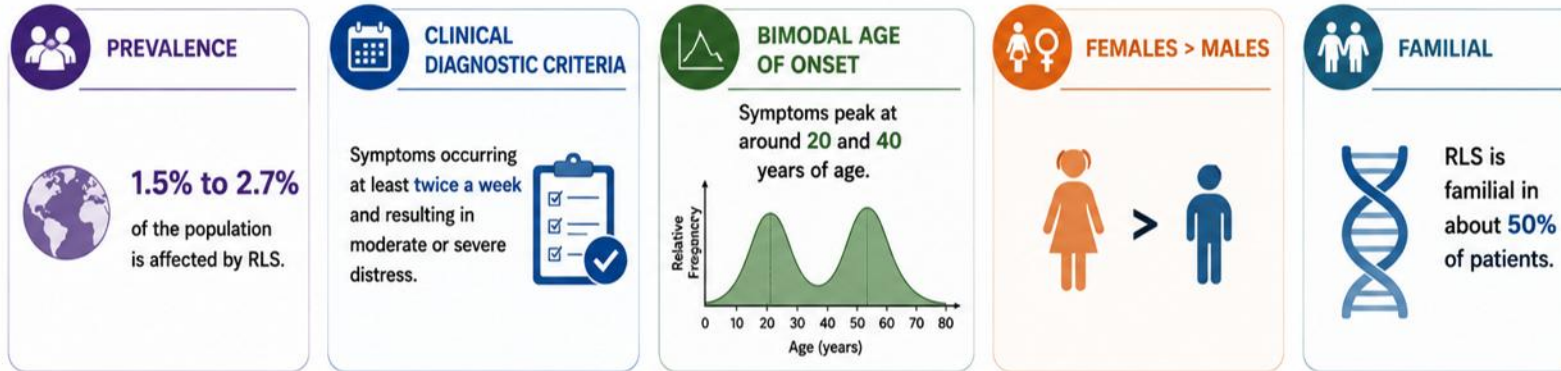
1. An urge to move the legs that is usually accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs (or sometimes other body parts).
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur at night or are worse in the evening or night than during the day.
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioural condition (such as myalgia, venous stasis, leg oedema, arthritis, leg cramps, positional discomfort or habitual foot tapping).

Supportive criteria

1. Periodic limb movements (PLM): presence of periodic leg movements in sleep (PLMS) or resting wakefulness (PLMW) at rates or intensity greater than expected for age or medical/medication status.
2. Dopaminergic treatment response: reduction in symptoms at least initially with dopaminergic treatment.
3. Family history of restless legs syndrome (RLS) among first-degree relatives.
4. Lack of profound daytime sleepiness.

Manconi et al, 2021

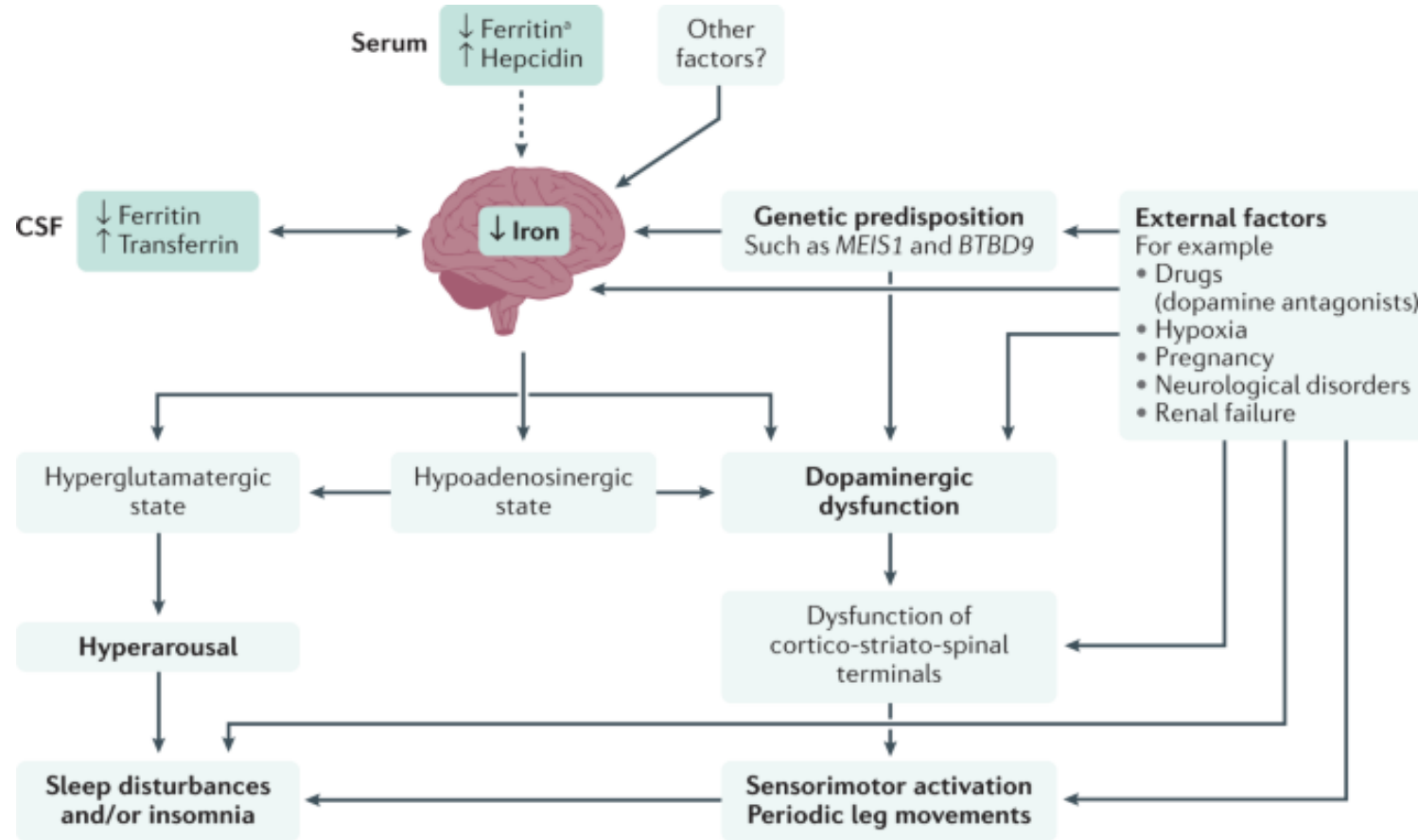
Epidemiology and Risk Factors



RLS diagnostic criteria per the International Restless Legs Syndrome Study Group (IRLSSG).

Manconi et al, 2021

Neurobiology of RLS



Manconi et al, 2021

Clinical Approach

ASSESSMENT OF RESTLESS LEGS SYNDROME (RLS)

A comprehensive evaluation to guide accurate diagnosis and effective management



1 CLINICAL ASSESSMENT



- Assess the nature, frequency, and severity of RLS symptoms
- Determine impact on sleep and daytime functioning

CHARACTERIZE CLINICAL COURSE



Intermittent RLS



Chronic Persistent RLS



Refractory RLS



2 EVALUATE FOR SECONDARY CAUSES



Iron deficiency (check ferritin & transferrin saturation)



Chronic kidney disease



Pregnancy



Neuropathy



Medications that may exacerbate RLS (e.g., antidepressants, antipsychotics, dopamine blockers, metoclopramide)



3 ASSOCIATED SLEEP & PSYCHIATRIC FEATURES



Sleep-onset or maintenance insomnia (60–70%)



Periodic limb movements of sleep (PLMS)



Depression



Reduced quality of life

4 SCREENING TOOL



IRLS

International Restless Legs Syndrome Study Group Rating Scale



sIRLS

simplified IRLS rating scale



CLINICAL PEARL: In every patient with RLS, assess iron status (serum ferritin and transferrin saturation) and review medications that may exacerbate symptoms.



Gossard et al, 2021

Alpha-2-Delta Ligands



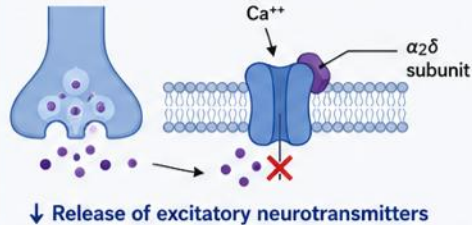
1. INDICATIONS

- Chronic persistent RLS
- RLS comorbid with chronic pain, insomnia, and anxiety



2. MECHANISM OF ACTION (MOA)

- Binds to the $\alpha_2\delta$ subunit of the voltage-dependent Ca^{++} channels
- Inhibition of the release of excitatory neurotransmitters



3. DOSAGE



Gabapentin

300–600 mg daily
(1 to 2 hours in advance of the evening symptoms)



Gabapentin Encarbil

600 mg daily
(FDA-approved)



Pregabalin

150–450 mg daily



4. SIDE EFFECTS



Drowsiness



Dizziness



Unsteadiness



Weight gain



Peripheral edema



5. CAUTIONS



Respiratory depression
when used in combination with opioids



Abuse potential
in patients with a history of substance use disorder



Lower dose
in patients with renal dysfunction



Clinical pearl: Start low and titrate slowly based on efficacy and tolerability. Take in the evening to target nighttime RLS symptoms.

Gossard et al, 2021

Dopamine Agonists



1. INDICATIONS

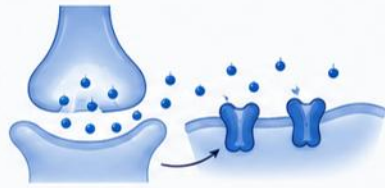
- Chronic persistent RLS
- Comorbid depression, renal insufficiency, severe PLMS

 Depression
  Renal insufficiency
  Severe PLMS



2. MECHANISM OF ACTION (MOA)

D₂/D₃ agonism



Activation of D₂/D₃ receptors in the central nervous system



3. DOSAGE

 **Pramipexole**
0.125–0.5 mg daily

 **Ropinirole**
0.5–4 mg daily

 **Rotigotine patch**
1–3 mg daily



4. SIDE EFFECTS

 Nausea
  Dizziness, headaches
  Excessive daytime sleepiness (sleep attacks)
  Impulse control disorders (5–17%)



5. CAUTIONS

 **Worsening of psychosis/mania**

- Monitor for hallucinations, delusions
- Use caution in patients with history of psychosis or bipolar disorder

 **Augmentation**

- May occur with long-term use
- Monitor for earlier onset of symptoms, increased severity, or spread to other body parts



CLINICAL PEARL

Dopamine agonists are effective for RLS but require careful monitoring for augmentation and impulse control disorders.




Heim et al., 2021

Opiates

1. INDICATIONS

- Refractory RLS

2. MECHANISM OF ACTION (MOA)

Improve endogenous opioid system function

Endogenous opioid peptides (enkephalins, endorphins, dynorphins)

Opioids enhance endogenous opioid activity
→ Reduced pain perception & sensory hyperexcitability

3. DOSAGE

Tramadol 50–200 mg daily	
Oxycodone 5–20 mg daily	
Methadone 5–10 mg daily	

4. SIDE EFFECTS

Nausea
 Vomiting
 Constipation
 Urinary retention
 Sexual dysfunction
 Cognitive dysfunction
 Unsteadiness, falls

QTc prolongation and cardiac arrhythmias
(baseline and serial EKG monitoring with Methadone)

5. CAUTIONS

Respiratory depression
(avoid co-prescription of BZDs)
 Worsening of sleep-disordered breathing
(screen for sleep apnea)
 Screen for substance use disorders
(Urine drug screen)

CLINICAL PEARL: Opioids can be effective for refractory RLS, but require careful patient selection, ongoing monitoring, and risk mitigation.

Gossard et al, 2021

Question 2

- A 45-year-old female diagnosed with bipolar disorder presents for evaluation of sleep complaints. She reports uncomfortable sensations in her legs with an urge to move them in the evening, especially at rest. She reports the onset of these symptoms after starting Aripiprazole a few weeks ago. She reports that moving her legs provides temporary relief. She reports difficulty initiating sleep most nights of the week due to having these symptoms. Which of the following is the most likely diagnosis?
 - A. Akathisia
 - B. Peripheral Neuropathy
 - C. Restless Legs Syndrome
 - D. Leg cramps
 - E. Insomnia Disorder

Narcolepsy

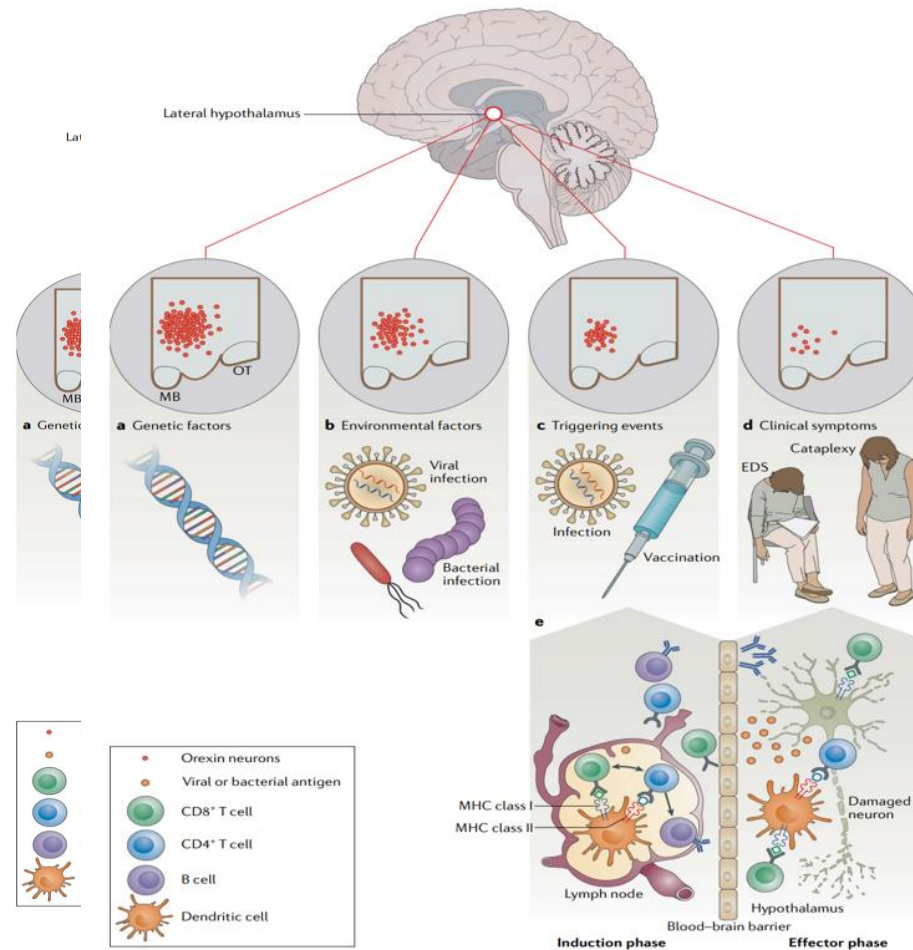
FEATURE	NARCOLEPSY TYPE 1 (NT1)	NARCOLEPSY TYPE 2 (NT2)	KEY DIFFERENCE
 CLINICAL SYMPTOMS	- Excessive daytime sleepiness (daily) Cataplexy (sudden loss of muscle tone triggered by emotions) - Hypnagogic/hypnopompic hallucinations - Sleep paralysis - Disturbed night sleep (frequent awakenings, non-restorative sleep) 	- Excessive daytime sleepiness (daily) - Hypnagogic/hypnopompic hallucinations - Sleep paralysis - Disturbed night sleep (frequent awakenings, non-restorative sleep) 	 Cataplexy with sudden muscle weakness is present in NT1 and absent in NT2
 MSLT FINDINGS	- Mean sleep latency ≤ 8 minutes ≥ 2 Sleep Onset REM Periods (SOREMPs) out of 5 naps 	- Mean sleep latency ≤ 8 minutes ≥ 2 Sleep Onset REM Periods (SOREMPs) out of 5 naps 	 MSLT findings are similar in NT1 and NT2
 CSF HYPOCRETIN LEVELS	Low / Undetectable ≤ 110 pg/mL (often < 50 pg/mL or undetectable) 	Normal > 110 pg/mL (typically normal range) 	Low/undetectable hypocretin-1 in NT1; normal in NT2
 Key Point	NT1 is defined by the presence of cataplexy and low CSF hypocretin-1 levels. NT2 lacks cataplexy and has normal CSF hypocretin-1 levels, while MSLT findings and other core symptoms are similar in both types.		CSF = Cerebrospinal Fluid MSLT = Multiple Sleep Latency Test REM = Rapid Eye Movement SOREMP = Sleep Onset REM Period

Epidemiology and Risk Factors

- Prevalence of narcolepsy is approximately 1 in 4000 patients
- Bimodal age of onset (15 and 35 years)
 - Mean delay from symptom onset to diagnosis > 10 years
- Genetic Factors
 - NT1 is strongly associated with HLA-DQB1*0602
 - Approximately 95% of those affected with NT1 have at least one allele
- Autoimmune Factors
 - NT1 is thought to be associated with autoimmune destruction of the hypocretin-producing neurons in the lateral hypothalamus

Barateau et al, 2022

Neurobiology of Narcolepsy



Bassetti et al, 2019

Clinical Approach

1. ASSESSMENT – PENTAD OF SYMPTOMS

- Hypersomnolence
- Cataplexy
- Disturbed night sleep (DNS)
- Hypnagogic / hypnopompic hallucinations
- Sleep paralysis



Children may display irritability, inattentiveness, and hyperactivity rather than classic symptoms.

PSYCHIATRIC COMORBIDITIES ARE FREQUENT IN NT1



Mood Disorders



Anxiety Disorders



ADHD



Eating Disorders



Suicidal Thoughts



Rarely Psychosis

Early recognition and treatment of comorbidities improve quality of life and outcomes.

2. SCREENING TOOL

Epworth Sleepiness Scale (ESS)

A simple, validated tool to assess daytime sleepiness.



ESS > 10

Suggests clinically significant daytime sleepiness

ESS is not diagnostic but helpful for screening and monitoring.



In children, use age-appropriate sleepiness and behavior scales in conjunction with clinical history.

3. INVESTIGATIONS



Polysomnography (PSG)

- Overnight study to evaluate sleep architecture
- Rule out other sleep disorders (e.g., OSA, PLMD)



Multiple Sleep Latency Test (MSLT)

- Performed the day after PSG
- Measures mean sleep latency and SOREMPs
- Essential for diagnosis



Actigraphy / Sleep Logs

- Assess sleep–wake patterns over several days to weeks
- Helps document sleep habits and circadian rhythms



Urine Drug Screen (UDS)

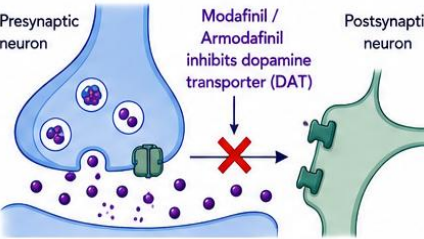
- Rule out substances that may cause or mimic hypersomnolence
- Recommended prior to MSLT



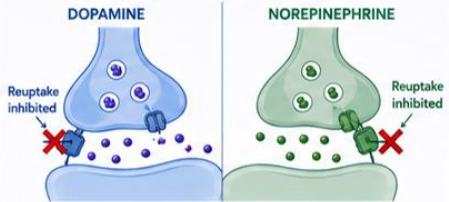
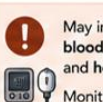
KEY POINT: Diagnosis of narcolepsy requires a combination of detailed clinical assessment, objective testing (PSG + MSLT), and exclusion of other causes of hypersomnolence.

Barateau et al, 2022

Modafinil/Armodafinil

INDICATIONS	MECHANISM OF ACTION (MOA)	DOSAGE
 - EDS associated with narcolepsy  - EDS associated with obstructive sleep apnea (OSA)  - EDS associated with shift work disorder 	Inhibition of dopamine reuptake  By inhibiting dopamine reuptake, modafinil/armodafinil increases extracellular dopamine in key wake-promoting pathways (e.g., hypothalamus, cortex, basal ganglia). <i>Exact mechanism of wake promotion is not fully understood.</i>	Modafinil 200 mg once daily in the morning - Doses should be taken early in the day to reduce risk of insomnia Armodafinil 150–250 mg once daily in the morning for narcolepsy / OSA - For shift work disorder: take ~1 hour before the start of the work shift  Administer in the morning to minimize risk of insomnia.
COMMON SIDE EFFECTS	SERIOUS ADVERSE EFFECTS	CAUTIONS
 Headache  Anxiety / Nervousness  Palpitations / Tachycardia  Insomnia	 Serious rash including Stevens–Johnson syndrome (SJS)  Psychiatric reactions Mania, hallucinations, psychosis, aggression, suicidal ideation  Cardiovascular Palpitations, hypertension (rare but reported)	 Potential for abuse and dependence - Schedule IV controlled substance - Use the lowest effective dose and monitor for misuse or diversion  Decreases effectiveness of hormonal contraceptive pills - Inducer of CYP3A4 → decreases plasma levels of ethinyl estradiol and progestins - Use alternative or additional non-hormonal contraception during treatment and for 1 month after discontinuation
 REFERENCES - Provigil (modafinil) [prescribing information]. Cephalon, Inc.; Revised 2023. - Nuvigil [armodafinil] [prescribing information]. Cephalon, Inc.; Revised 2022. - Thorpy MJ, et al. Management of narcolepsy in adults: An American Academy of Sleep Medicine clinical practice guideline. <i>J Clin Sleep Med</i>. 2021;17(9):1881-1893. - Bogan RK, et al. Clinical use of wake-promoting agents. <i>Sleep Med Clin</i>. 2013;8(4):549-566.	 SCAN FOR FULL PI	

Solriamfetol

INDICATIONS  - EDS associated with Narcolepsy Reduces excessive daytime sleepiness and improves wakefulness.   - EDS associated with Obstructive Sleep Apnea (OSA) Treats residual sleepiness. Does not replace treatment of the underlying airway obstruction. 	MECHANISM OF ACTION (MOA) Norepinephrine and Dopamine Reuptake Inhibitor (DNRI)  Increases synaptic concentrations of dopamine and norepinephrine in brain regions involved in wakefulness. Exact mechanism of wake promotion is not fully understood.	DOSAGE  NARCOLEPSY - Start: 75 mg once daily in the morning - Dose range: 75 – 150 mg once daily - Maximum dose: 150 mg/day  OBSTRUCTIVE SLEEP APNEA (OSA) - Start: 37.5 mg once daily in the morning - Dose range: 37.5 – 150 mg once daily - Maximum dose: 150 mg/day  Take upon awakening. Avoid within 9 hours of bedtime.
SIDE EFFECTS  Headache  Anxiety  Palpitations / Increased HR  Insomnia  Nausea  Decreased appetite  May increase blood pressure and heart rate. Monitor regularly.	CAUTIONS  Schedule IV controlled substance – Potential for abuse.  May increase blood pressure and heart rate. Monitor BP and HR before and during treatment.  Use with caution in patients with significant cardiovascular disease.  Avoid use with MAO inhibitors or within 14 days of stopping an MAOI.  Dose adjustment required in renal impairment.	KEY POINTS  - Improves wakefulness and reduces excessive daytime sleepiness. - Does not replace primary therapy for OSA. Patient Counseling - Take in the morning. - Avoid taking late in the day to prevent insomnia. - Notify your doctor if you have a history of heart problems or high blood pressure. - Report any mood changes, anxiety, or palpitations.
REFERENCES - SUNOSI® (solriamfetol) [prescribing information]. Jazz Pharmaceuticals, Inc.; May 2026. - Schweitzer PK, Rosenberg R, Zammit GK, et al. Solriamfetol for excessive sleepiness in obstructive sleep apnea: a randomized, placebo-controlled trial. <i>Sleep</i>. 2019;42(4):zsz010. - Seiden D, Wang J, Onen F, et al. Solriamfetol for excessive daytime sleepiness associated with narcolepsy: a randomized trial. <i>Neurology</i>. 2019;92(15):e1756-e1767. - Bogan RK, et al. Clinical use of wake-promoting agents. <i>Sleep Med Clin</i>. 2013;8(4):549-566.		

Pitolisant

INDICATIONS



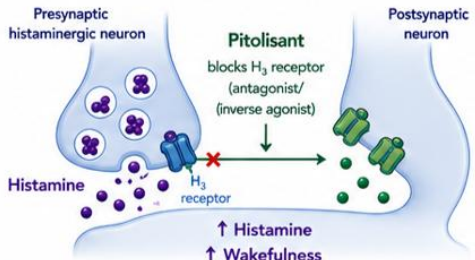
Approved for the treatment of:

- **EDS** associated with **narcolepsy** with or without cataplexy
- **Cataplexy** associated with narcolepsy (with or without EDS)

Indicated in patients ≥ 6 years of age.

MECHANISM OF ACTION (MOA)

Selective H₃ receptor antagonist/inverse agonist
Increases histamine release in the tuberomammillary nucleus and other brain regions, promoting wakefulness.



Not a controlled substance – Low abuse potential.

DOSAGE (Adults)

Take once daily in the morning upon awakening.

WEEK 1	WEEK 2	WEEK 3 AND BEYOND
8.9 mg once daily	17.8 mg once daily	35.6 mg once daily

DOSAGE MODIFICATIONS WITH CONCOMITANT MEDICATIONS

CYP2D6 INHIBITORS (e.g., paroxetine, fluoxetine, quinidine) → Increase pitolisant exposure. Limit maximum dose per prescribing information.

CYP3A4 INDUCERS (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) → Decrease pitolisant exposure. Dose increase may be required.

See prescribing information for full recommendations.

SIDE EFFECTS



Nausea Headache Anxiety Insomnia

Most adverse effects are mild to moderate and often improve with continued treatment.

CAUTION

Prolongs QTc interval

- Consider ECG/QTc assessment in patients with risk factors (e.g., congenital long QT, electrolyte abnormalities, bradycardia, or use of other QT-prolonging drugs).

Avoid concomitant use with other drugs that prolong QTc.

DRUG INTERACTION – ORAL CONTRACEPTIVES

Pitolisant reduces the effectiveness of hormonal contraceptive pills.



Use non-hormonal contraception during treatment and for at least 21 days after discontinuation.

KEY POINTS

- ✓ Improves EDS and cataplexy in narcolepsy.
- ✓ MOA: Selective H₃ receptor antagonist/inverse agonist.
- ✓ Titration: 8.9 mg x 1 week → 17.8 mg x 1 week → 35.6 mg once daily.
- ✓ Not a controlled substance – Low abuse potential.
- ✓ Monitor QTc, especially in at-risk patients.
- ✓ Reduces efficacy of oral contraceptive pill.

REFERENCES

1. WAKIX® (pitolisant) [prescribing information]. Harmony Biosciences, LLC; May 2024.
2. Zamarrón C, et al. Pitolisant for the treatment of narcolepsy. *Expert Rev Clin Pharmacol*. 2020;13(8):875-886.
3. Seiden D, Wang J, Onen F, et al. Pitolisant in patients with narcolepsy: 12-week results from a phase 3 randomized withdrawal study. *Neurology*. 2016;87(10):1016-1024.
4. Bogan RK, et al. Clinical use of wake-promoting agents. *Sleep Med Clin*. 2013;8(4):549-566.



SCAN FOR FULL PI

Sodium Oxybate

INDICATIONS

Treatment of:

- Cataplexy or excessive daytime sleepiness (EDS) associated with narcolepsy
- In adults and children ≥ 7 years of age

MECHANISM OF ACTION (MOA)

Oxybate = sodium salt of γ -hydroxybutyrate (GHB)

- GHB is an endogenous metabolite of GABA
- The precise mechanism in narcolepsy is not fully established.
- Therapeutic effects are hypothesized to be mediated predominantly through GABA-B receptor activity.

HOW OXYBATE WORKS DURING NIGHTTIME SLEEP

CLINICAL DOWNSTREAM EFFECTS

DOSAGE (Adults)

TWICE-NIGHTLY FORMULATIONS (XYREM®, XYWAV®)

Bedtime 1st dose 2.5 – 4 hours later 2nd dose

2.25 – 4.5 g at 2nd dose

- Starting dose: 4.5 g/night (2.25 g + 2.25 g)
- Titrate by 1.5 g/night weekly to effective dose
- Usual target range: 6 – 9 g/night (max 9 g/night)

ONCE-NIGHTLY FORMULATION (LUMRYZ™)

Bedtime once nightly Extended-release formulation (effective all night)

Take upon going to bed with ≥ 2 hours remaining in bed.

SIDE EFFECTS

Nausea Bedwetting (enuresis) Dizziness NREM parasomnias (sleepwalking)

Neuropsychiatric Effects (less common but serious)

Depression Suicidal ideations Psychosis (rare)

CAUTIONS

- Respiratory depression**
Can cause CNS and respiratory depression, especially when combined with other CNS depressants.
- Avoid benzodiazepines and other sedative-hypnotics or alcohol.**
Risk of profound sedation and respiratory depression.
- Screen for sleep apnea**
Assess for sleep-disordered breathing and treat appropriately before starting.
- Rule out substance use disorder**
Use cautiously in patients with current or past substance use disorder.

ABUSE, DIVERSION & REMS

- Risk for abuse and diversion**
Can cause is a Schedule III controlled substance with known abuse potential.
- Dispensed through a centralized pharmacy (REMS program)**
FDA-approved oxybate products are available only through a restricted REMS distribution program.
- Patient enrollment, prescriber certification, pharmacy certification and informed consent are required.**

KEY CLINICAL PEARLS

- First-line therapy for cataplexy and EDS in narcolepsy.
- Most effective when taken as prescribed with two doses at night (or once-nightly extended release).
- Do not drive or operate machinery until you know how you respond.
- Set an alarm for the second dose (2.5 – 4 hours after the first dose).
- Maintain a consistent sleep schedule for best benefit.

REFERENCES

- XYREM® (sodium oxybate) [prescribing information]. Jazz Pharmaceuticals, Inc.; Revised May 2024.
- XYWAV® (calcium, magnesium, potassium, and sodium oxybates) [prescribing information]. Jazz Pharmaceuticals, Inc.; Revised May 2024.
- LUMRYZ™ (sodium oxybate) extended-release oral suspension [prescribing information]. Jazz Pharmaceuticals, Inc.; Revised Apr 2024.
- American Academy of Sleep Medicine. The treatment of narcolepsy and other central disorders of hypersomnolence. *J Clin Sleep Med*. 2021;17(9):1881-1893.

Oxybates consolidate nighttime sleep and increase slow-wave sleep, leading to meaningful reductions in cataplexy and daytime sleepiness.

SCAN FOR FULL PI

Stimulants

- Indications
 - EDS in narcolepsy (adults and children)
- MOA
 - Block reuptake of DA and NE
- Dosage
 - Long-acting formulations of stimulants preferred (in conjunction with a short-acting formulation)
 - Methylphenidate 10-60 mg daily
 - Dextroamphetamine 10-60 mg daily
 - Amphetamine-dextroamphetamine 10-60 mg daily
- Side effects
 - Irritability, anxiety, insomnia, hypertension, tachycardia, arrhythmias, seizures, hepatotoxicity
 - Mania, psychosis (higher doses)
- Caution
 - Risk of dependence and abuse

Bassetti, 2019

Antidepressants

- Indications
 - Cataplexy
- MOA
 - REM suppressant action
 - Immediate effects on cataplexy
- Dosage
 - Venlafaxine XR 75-225 mg daily
 - Fluoxetine 20-60 mg daily
 - Clomipramine 25-100 mg daily
- Side effects
 - Nausea, dizziness, dry mouth, headaches, insomnia, sexual dysfunction
- Caution
 - Prolonged cataplexy or “status cataplecticus”
 - Sudden withdrawal from antidepressants

Bassetti, 2019

Orexin-2 Receptor Agonist

Oveporexton (Orzeyful™)

Selective Orexin 2 Receptor Agonist for Narcolepsy

Indications



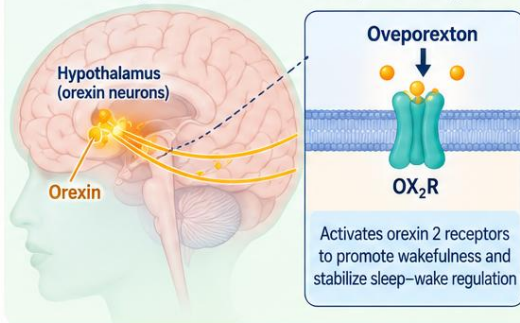
Excessive daytime sleepiness (EDS) in adults with narcolepsy (type 1 and type 2)



Cataplexy
(in narcolepsy type 1)

Mechanism of Action

Selective agonist at orexin 2 receptors (OX₂R)



Dosage

Oral tablet: 1 mg or 2 mg, **taken twice daily**



Maximum daily dose: 4 mg per day
(e.g., 2 mg twice daily)

Common Side Effects



Headache
(~6–11%)



Nausea
(~5–7%)



Insomnia
(~3–6%)



Increased heart rate
(~2–3%)



Anxiety
(~2–4%)

Therapeutic Effects



Reduces excessive daytime sleepiness



Reduces cataplexy
(in type 1 narcolepsy)



Improves wakefulness, alertness, and daily functioning

Contraindications



Hypersensitivity to oveporexton or any component of the formulation



Use during pregnancy
(insufficient human data)



Use during breastfeeding
(unknown risk to infant)

Question 3

- A 21-year-old male college student presents for evaluation of disturbed night sleep. He endorses excessive daytime sleepiness since high school. He has frequent episodes of sleep paralysis but denies episodes of cataplexy. He denies any significant mood symptoms. Sleep logs and actigraphy show adequate sleep duration. Polysomnography shows a total sleep time of 8.5 hours and an apnea-hypopnea index (AHI) of 2/hour. UDS is negative for substance use. Multiple sleep latency test (MSLT) is significant for a mean sleep onset latency of 4.5 minutes and two sleep-onset REM periods (SOREMPs) during the five nap opportunities.

What is the most likely diagnosis?

- A. Idiopathic Hypersomnia
- B. Narcolepsy Type 1
- C. Insufficient Sleep Syndrome
- D. Narcolepsy Type 2
- E. Kleine-Levine Syndrome

Resources

- National Sleep Foundation <https://www.sleepfoundation.org/>
- Wake up Narcolepsy <https://www.wakeupnarcolepsy.org/>
- Restless Legs Syndrome Foundation www.rls.org
- American Academy of Sleep Medicine <https://www.aasm.org/>

Thank You!

