Psych Congress MasterClass

IN PARTNERSHIP WITH Sleep Research Society Foundation

Sleep-Wake Symptoms in MDD as Potential Biomarkers for Precision Treatments: Moving Beyond Agent Selection Based on Activating or Sedating Effects

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Faculty Disclosures

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Learning Objectives

1. Describe the prevalence of sleep/wake symptoms in patients with MDD and the potential clinical utility of diagnostic specifications of insomnia and hypersomnia
2. Assess the limitations of current approaches to managing MDD with sleep/wake symptoms, including selection of pharmacotherapies according to their sedating/activating side effects
3. Evaluate the MOAs, latest clinical data, and therapeutic implications associated with investigational pharmacotherapies for patients with MDD and sleep/wake symptoms
4. Implement strategies to improve the assessment of sleep/wake symptoms in patients with MDD and ensure optimal treatment decisions

Treatment Challenges and Efforts Towards Precision Therapies in MDD with Sleep/Wake Symptoms

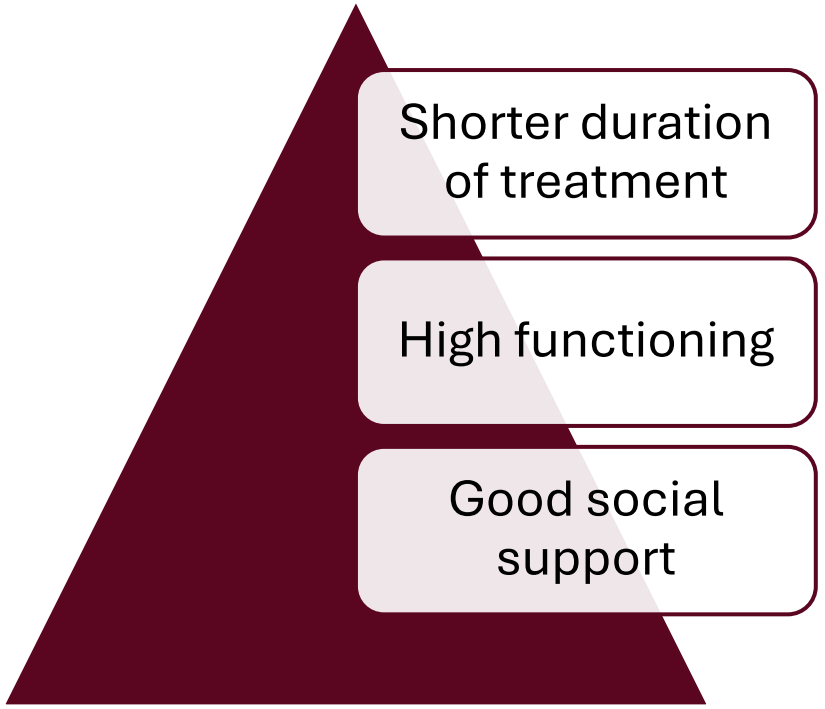
“I Can’t Get Sleep!”

- Sleep continues to be a huge challenge for clinicians and patients
- Challenges continue to underlie hurdles in sleep management
  - Understanding Suboptimal Response and Remission
  - Symptom Heterogeneity
  - DSM specifier evolution
- Clinical decision-making and rationale for precision approaches are a must!

American Psychological Association – Depression Guideline Development Panel (GDP). *APA Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts: (505892019-001)* [Dataset]; 2019. Image: “insomnia.” Accessed September 2025. https://www.deviantart.com/nakovalnya-artist/art/Insomnia-718713095.

Suboptimal Treatment Response and Relapse

- Relapse rates hover around 20%-40% in classic antidepressant trials
  - Insomnia symptoms are associated with *more severe depression*
- Remission is more likely in patients with:



Hengartner MP. *Ther Adv Psychopharmacol*. 2020;10:2045125320921694. Kim HY, et al. *Clin Psychopharmacol Neurosci*. 2021;19(3):490-497. Sakurai H, et al. *World Psychiatry*. 2024;23(1):156-157. Sunderajan P, et al. *CNS Spectr*. 2010;15(6):394-404.

DSM Criteria for MDD

- What is the DSM-V criteria for sleep/wake disorders in MDD?
  - **“Insomnia or Hypersomnia nearly every day”**

Pros	Cons
• Captures broad symptomatology • Easy to categorize	• Non-specific • Reduces treatment predictability • MDD treatments are not targeted towards sleep/wake disorders

MDD = major depressive disorder.

American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. APA Publishing; 2013.

Challenges of Symptom-Based Subcategorization

Informs prognosis, **but…**

- NOT consistently actionable for pharmacotherapy
  - Examples
    - Atypical: Longer episode duration and chronicity

Improves patient education, **but…**

- Increased diagnostic complexity, which can be confusing for patients

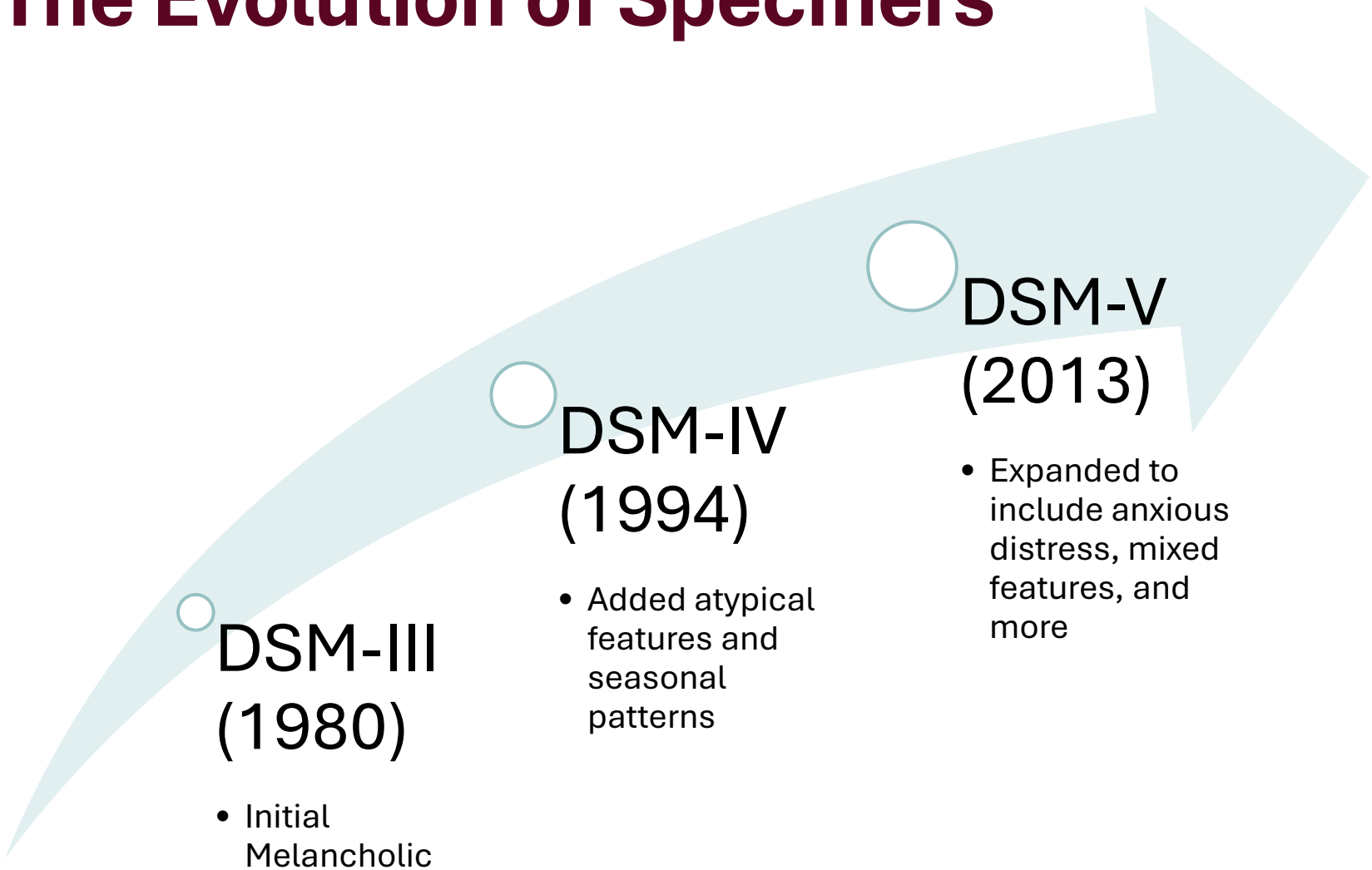
Specific treatment decisions **but…**

- Treatments may still be a mismatch due to symptom rater variability
  - Examples
    - Melancholic: Better response to TCAs/SNRIs vs SSRIs
    - Atypical: Better response to SSRIs/MAOIs vs TCAs
    - Anxious: May benefit from combined SSRI/benzodiazepine initially

TCA = tricyclic antidepressant; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; MAOI = monoamine oxidase inhibitor.

Sanches M, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;106:110157.

The Evolution of Specifiers



DSM-III (1980)

- Initial Melancholic Subtype

DSM-IV (1994)

- Added atypical features and seasonal patterns

DSM-V (2013)

- Expanded to include anxious distress, mixed features, and more

- Anxious
  - Tension
  - Restlessness
  - Difficulty concentrating
- Melancholic
  - Anhedonia
  - Morning worsening
  - Early awakening
- Psychotic
  - Delusions
  - Hallucinations
- Mixed
  - Manic/hypomanic during depression
- Atypical
  - Mood reactivity
  - Hypersomnia
- Seasonal
  - Regular temporal pattern

American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. APA Publishing; 2013.

Clinical Utility of Specifiers

Treatment Selection Implication

- **Melancholic:** Better response to SNRIs/TCAs than SSRIs
- **Atypical:** Better response to MAOIs/SSRIs than TCAs
- **Anxious Distress:** May benefit from combined BZD/SSRI
- **Seasonal:** Likely amenable to non-pharm therapies

Prognostic Significance

- **Melancholic:** Better acute response but higher relapse risk
- **Atypical:** Longer episode duration, higher chronicity
- **Anxious Distress:** 2.5x higher suicide risk
- **Seasonal:** Predictable recurrence pattern

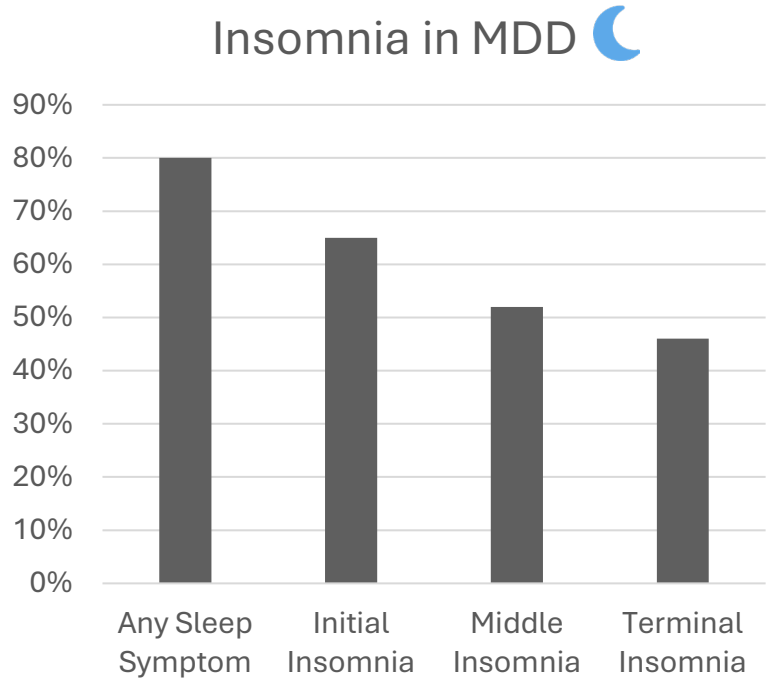
Clinical Decision Support

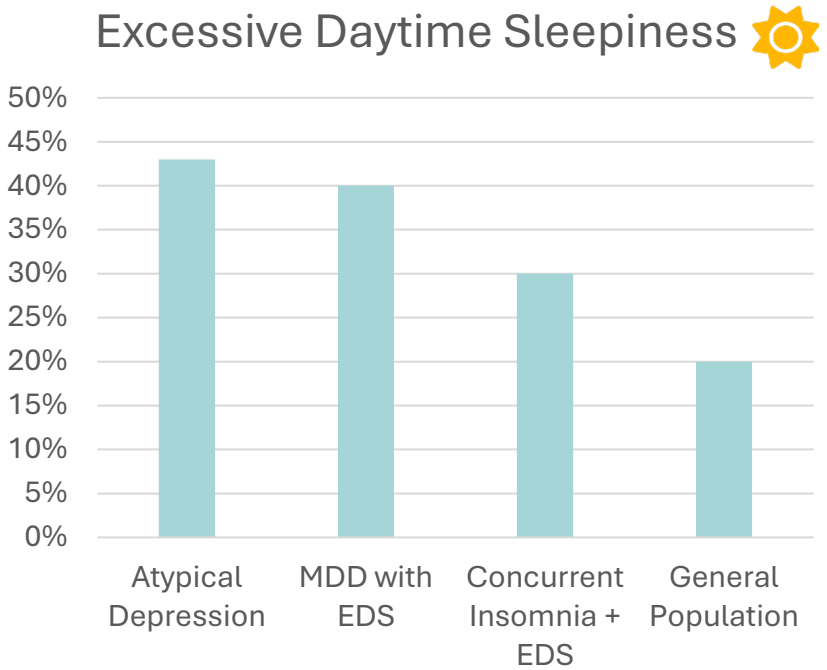
1. Identify predominant specifier
   HAM-D, IDS-SR, etc.
2. Evaluate sleep disturbance pattern
   Hypersomnia vs Insomnia
3. Match treatment to phenotype
   Consider sleep profile and specifier
4. Monitor core and specifier symptoms
   Reassess the specifier status at 4-6 weeks

BZD = benzodiazepine; HAM-D = Hamilton Rating Scale for Depression; IDS-SR = Inventory of Depressive Symptomatology – Self-Report.

Sneed JR, et al. *Am J Geriatr Psychiatry*. 2014;22(1):46-52. Zhou Y, et al. *Transl Psychiatry*. 2021;11(1):97. MDedge. Accessed September 1, 2015. https://www.mdedge.com/currentpsychiatry/article/266771/depression/monoamine-oxidase-inhibitors-and-tricyclic.

Prevalence of Sleep Disturbances in MDD





- Insomnia symptoms affect 60%-80% of patients with MDD
- Most common presenting complaint in primary care settings
- Sleep initiation most common (65%), followed by maintenance (52%) and early morning awakening (46%)
- Associated with increased severity, suicidality, and treatment resistance

- Hypersomnia/EDS affects 30%-40% of MDD patients overall
- Up to 42% in the atypical depression subtype
- Often overlooked in clinical assessment
- ~30% have both insomnia and EDS symptoms (variable across 24-hour cycle)
- Associated with greater functional impairment, cognitive dysfunction

EDS = excessive daytime sleepiness.

Łojko D, Rybakowski JK. *Neuropsychiatr Dis Treat*. 2017;13:2447-2456. Kim KW, et al. *Arch Gerontol Geriatr*. 2017;68:68-75. Nutt D, et al. *Dialogues Clin Neurosci*. 2008;10(3):329-336. Riemann D, et al. *Sleep Med Rev*. 2010;14(1):19-31. Soehner AM, Harvey AG. *Sleep*. 2012;35(10):1367-1375.

Impacts of Persistent Sleep/Wake Symptoms

Functioning and QoL

Cognitive Performance

- Impacted by too little and too much sleep

Mental Health

- Bidirectional relationship between MDD and sleep symptoms

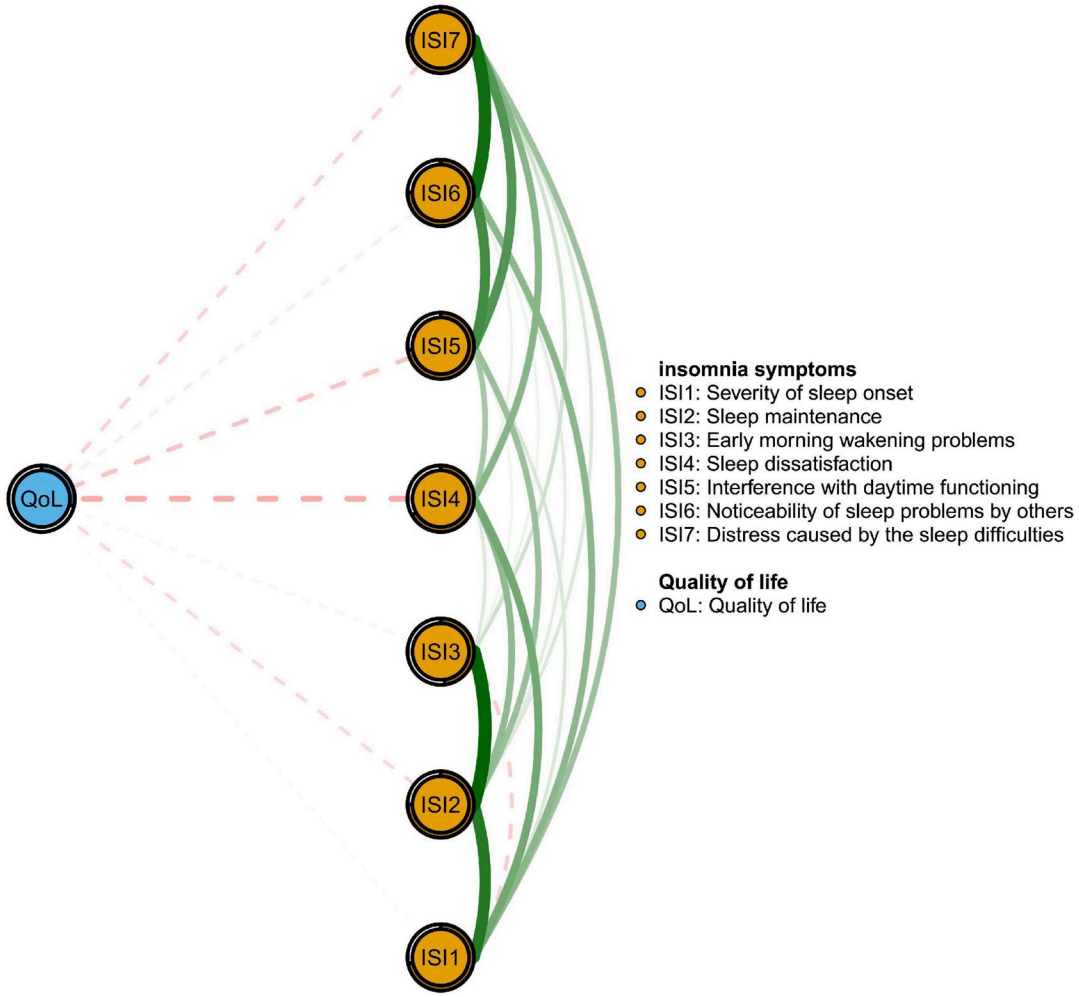
Sleep

Social and Interpersonal

- Decreased sleep increases social isolation, which can worsen MDD

Physical Health

- Higher CV risk independent of MDD severity



QoL = quality of life; CV = cardiovascular.

Morin CM, et al. *Sleep*. 2011;34(5):601-608. Jaspan VN, et al. *Curr Atheroscler Rep*. 2024;26(7):249-262. Scott AJ, et al. *Sleep Med Rev*. 2021;60:101556. Ben Simon E, Walker MP. *Nat Commun*. 2018;9(1):3146. Young VM, et al. *Alzheimer's Dement*. 2025;21(4):e70160.

Rationale for Precision Approaches in Sleep/Wake–Related MDD

Key Limitations of Current Approaches

1. High Residual Symptom Burden

Approximately half of MDD patients continue to experience sleep disturbances despite adequate MDD treatment

2. One-Size-Fits-All Treatment

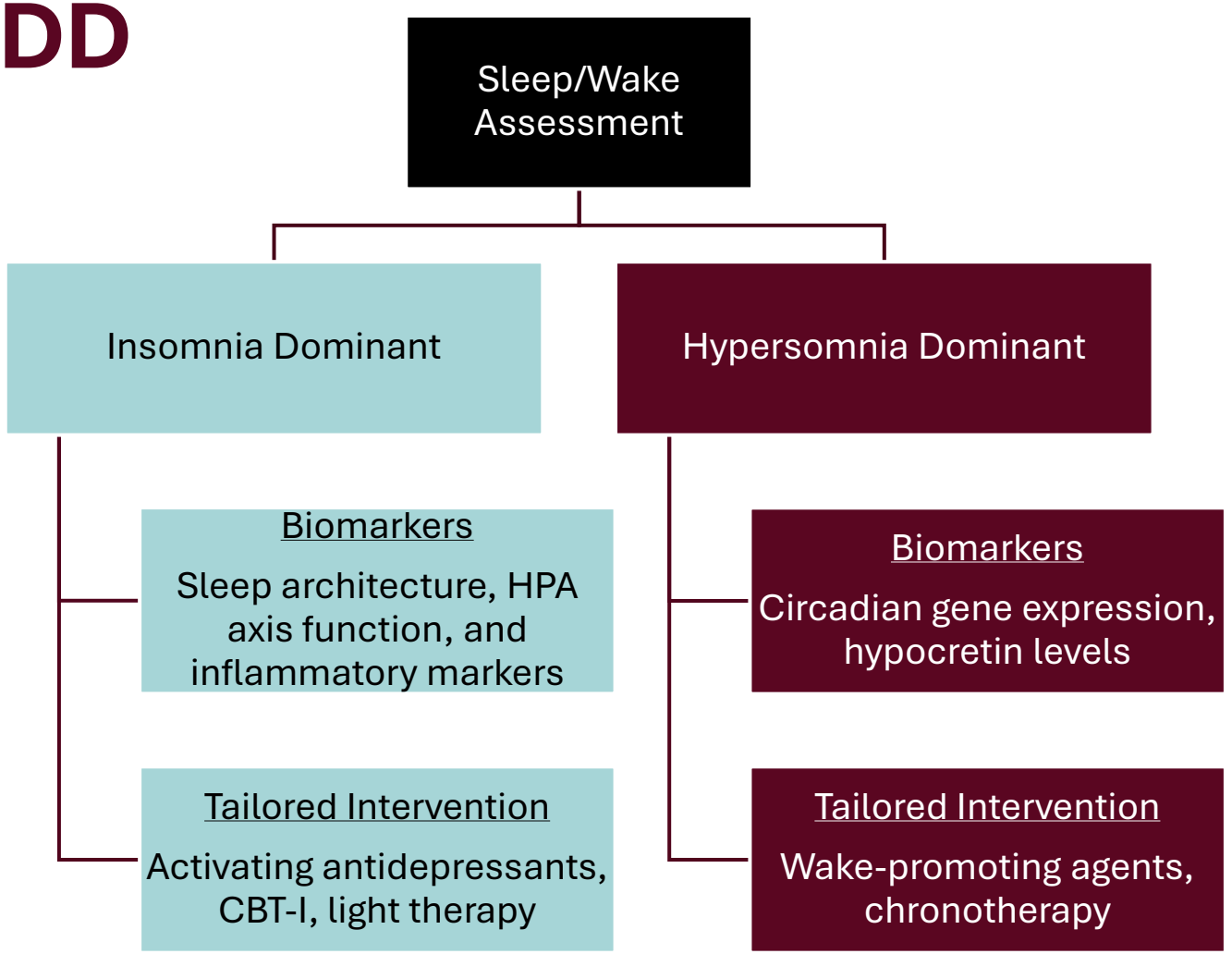
Current algorithms rarely differentiate between insomnia versus hypersomnia

3. Treatment Resistance

Sleep disturbances predict an increased risk of poor treatment response

4. Limited Biomarker Integration

Clinical practice rarely incorporates emerging sleep biomarkers



HPA = hypothalamic-pituitary-adrenal; CBT-I = cognitive behavioral therapy for insomnia.

Franzen PL, Buysse DJ. *Dialogues Clin Neurosci*. 2008;10(4):473-481. Nierenberg AA, et al. *Psychol Med*. 2010;40(1):41-50. Adams MJ. *medRxiv* [Preprint]. 2024:2024.04.29.24306535. Liu C, Chung M. *Neurosci Bull*. 2015;31(1):141-159. Stolfi F, et al. *Front Psychiatry*. 2024;15:1422939. Chopra A, et al, eds. *Management of Sleep Disorders in Psychiatry*. Oxford University Press; 2020.

Key Learning Points

Key challenges and opportunities

Key Challenges

High residual symptom burden

- Approximately half of MDD patients continue experiencing sleep disturbances with adequate treatment, with relapse rates 20%-40%

Non-specific diagnostic criteria

- DSM-5 criteria lacks specificity within the context of MDD

Treatment resistance predictor

- Sleep disturbances predict an increased risk of poor treatment response and higher suicidality

One-sizes-fits-all approach

- Current algorithms rarely differentiate insomnia versus hypersomnia

Key Opportunities

Biomarker-guided treatment

- Integration of sleep architecture, HPA axis function, and circadian gene expression into clinical decision-making

Phenotype-based approaches

- Tailoring interventions based on insomnia-dominant vs hypersomnia-dominant phenotypes

Systematic assessment protocol

- Implementation of standardized sleep/wake assessment protocols in MDD treatment

Multi-modal treatment integration

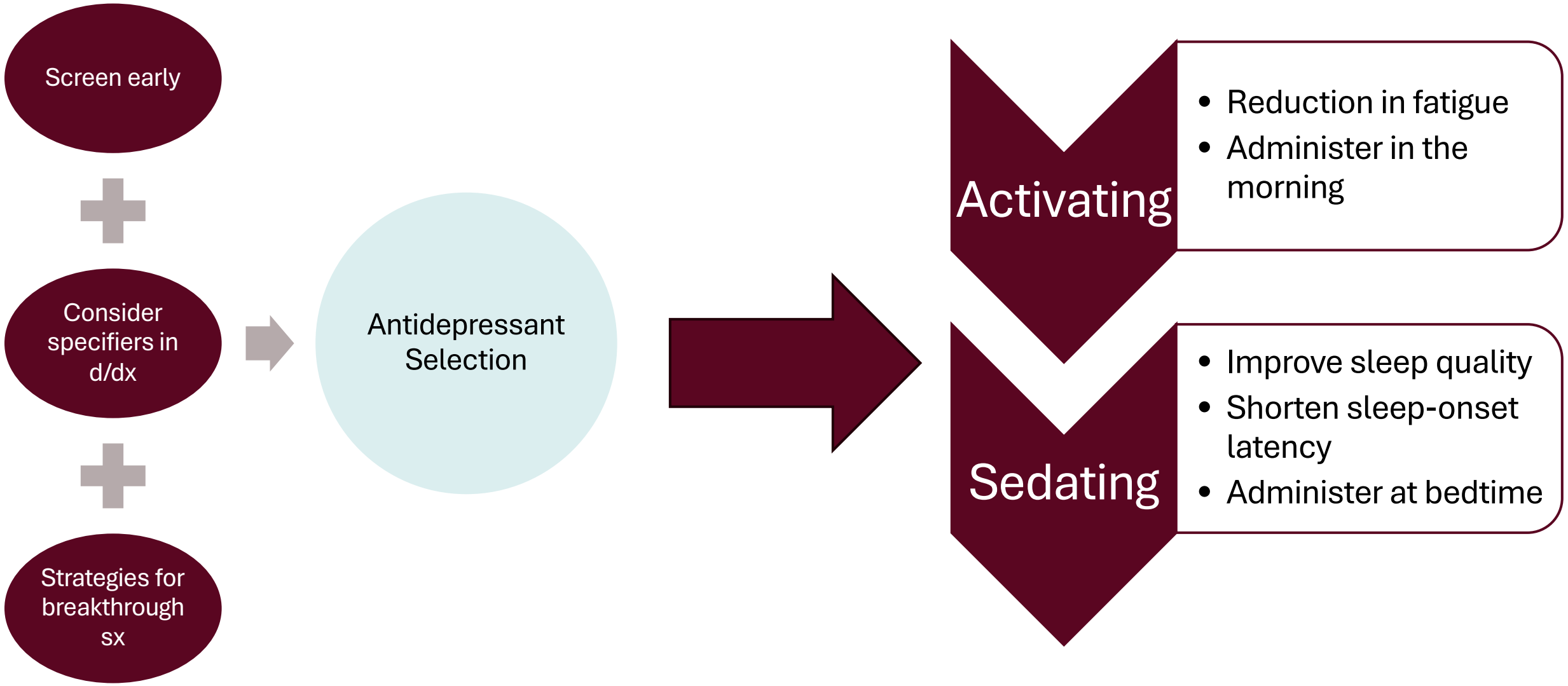
- Combining pharmacologic approaches with CBT-I, chronotherapy, and light therapy based on phenotype

Precision approaches to sleep/wake symptoms in MDD have the potential to significantly improve remission rates and reduce relapse risk

American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. APA Publishing; 2013.

Current Pharmacologic Treatment of MDD with Sleep/Wake Symptoms

Antidepressant Selection by Activating vs Sedating

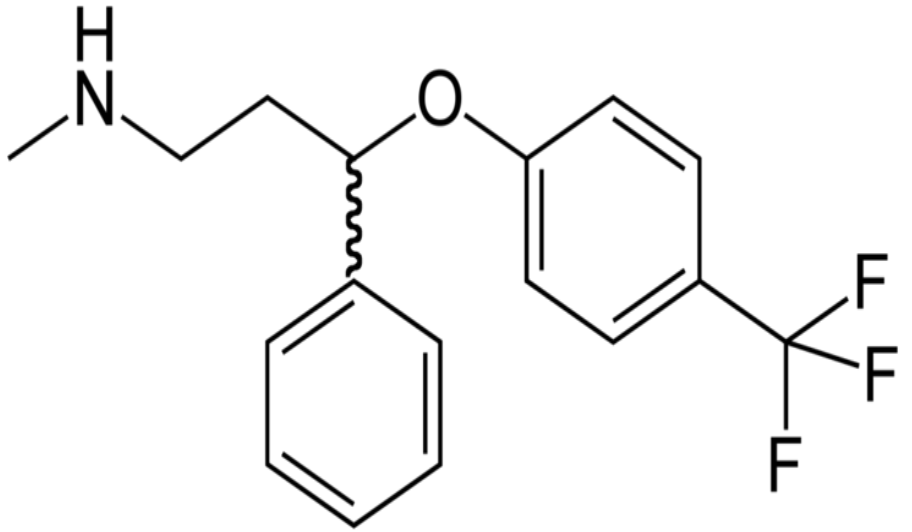


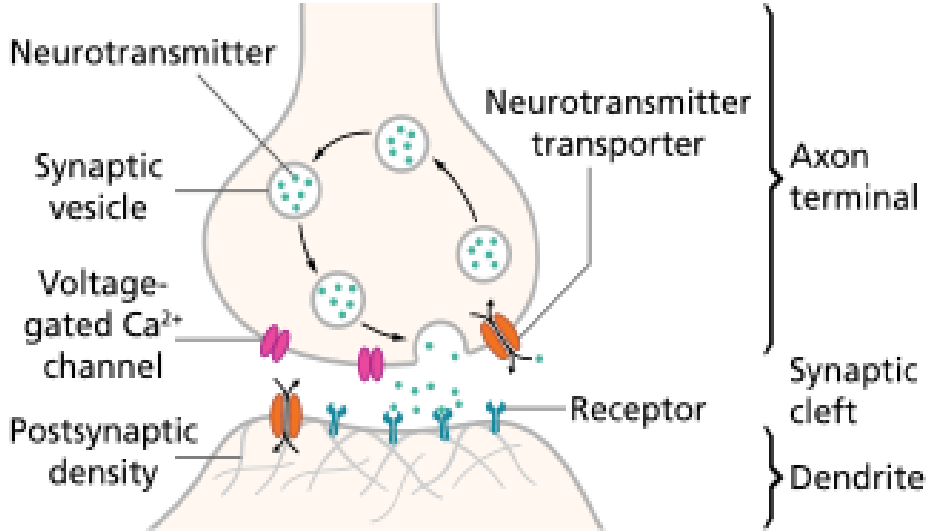
d/dx = differential diagnosis; sx = symptoms.

Fluoxetine

Activating

- **Mechanism:** Blocks 5-HT reuptake (SERT), increases serotonergic neurotransmission
- **Dosing**
  - **Initial:** 10-20 mg QD
  - **Efficacious:** 10-60 mg QD
  - **Max:** 60 mg QD
- **Significant collateral receptors:** 5-HT_{2A}, 5-HT_{2C}
- **Side Effects:** Sexual side effects, appetite changes, diarrhea, insomnia, nervousness, pharyngitis, sweating, tremor, and yawn
- **Prescribing pearls**
  - Caution co-prescribing with antiplatelets or GI dx
  - VERY long half-life (~5 days), meaning little to no risk of discontinuation syndrome





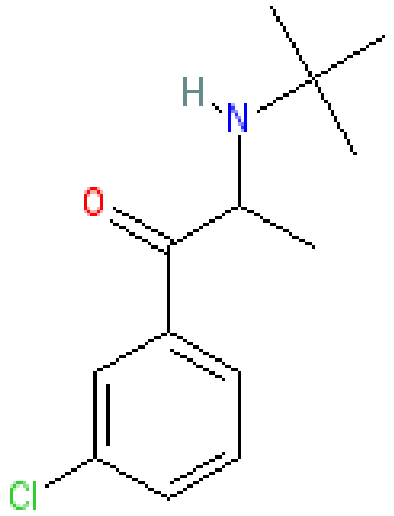
5-HT = serotonin; SERT = serotonin transporter; GI = gastrointestinal.

Fluoxetine PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/018936%20s112lbl.pdf.

Bupropion

Activating

- **Mechanism:** Blocks norepinephrine reuptake (NET) and dopamine transport (DAT)
- **Dosing**
  - **Initial:** IR 75 mg QD-TID, SR 150 mg QD, XL 150 mg QD
  - **Efficacious:** IR 75-150 mg TID, SR 100-150 mg BID, XL 150-450 mg QD
  - **Max:** IR 150 mg TID, SR 200 mg BID, XL 450 mg QD
- **Collateral receptors:** *Negligible at treatment doses*
- **Side Effects:** Insomnia (up to 20%), agitation, anxiety, headache, dry mouth, nausea, tremor, tachycardia, hypertension, decreased appetite, weight loss
- **Prescribing pearls**
  - Caution in seizure disorders
  - Multiple formulations:



	Immediate Release (IR)	Sustained Release (SR)	Extended Release (XR/ER)
Effect time	8 hours	12 hours	24 hours
Doses per day	3 times daily	2 times daily	1 time daily

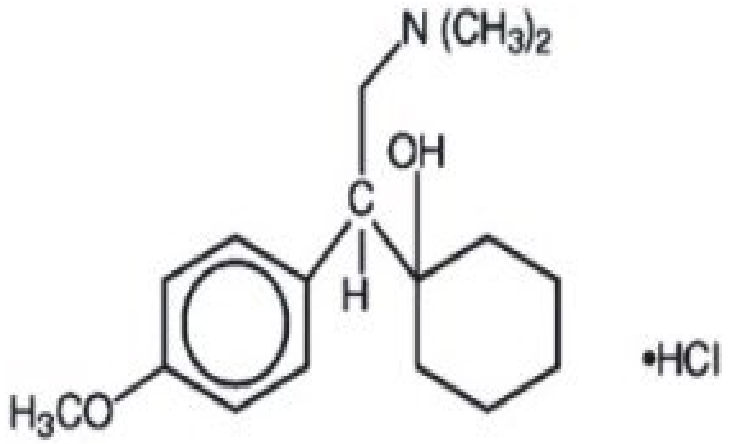
NET = norepinephrine transporter; DAT = dopamine transporter; IR = immediate release; SR = sustained release; XL/XR/ER = extended release.

Bupropion hydrochloride PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/018644s061lbl.pdf.

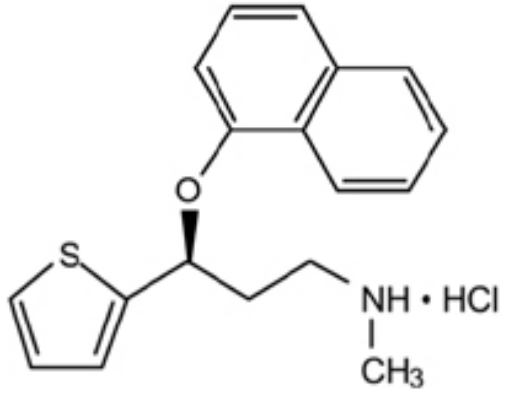
SNRIs (venlafaxine, duloxetine)

Activating

- **Mechanism:** Dual inhibition of SERT and NET increases synaptic serotonin and norepinephrine
- **Dosing**
  - **Venlafaxine:** Initial 37.5–75 mg/day (IR/SR/ER); efficacious 75–225 mg/day; max 225 mg/day
  - **Duloxetine:** Initial 30–60 mg/day; efficacious 60 mg/day; max 120 mg/day
- **Collateral receptors:** *Negligible at treatment doses*
- **Side Effects:** Agitation, insomnia, tremor, *hypertension*, tachycardia, sweating, gastrointestinal and sexual side effects, headache, and *discontinuation syndrome*
- **Prescribing pearls**
  - Venlafaxine only starts affecting NET at doses >150 mg and duloxetine >30 mg
  - High risk of discontinuation syndrome due to short half-lives
  - May benefit patients with neuropathic pain syndromes



venlafaxine hydrochloride



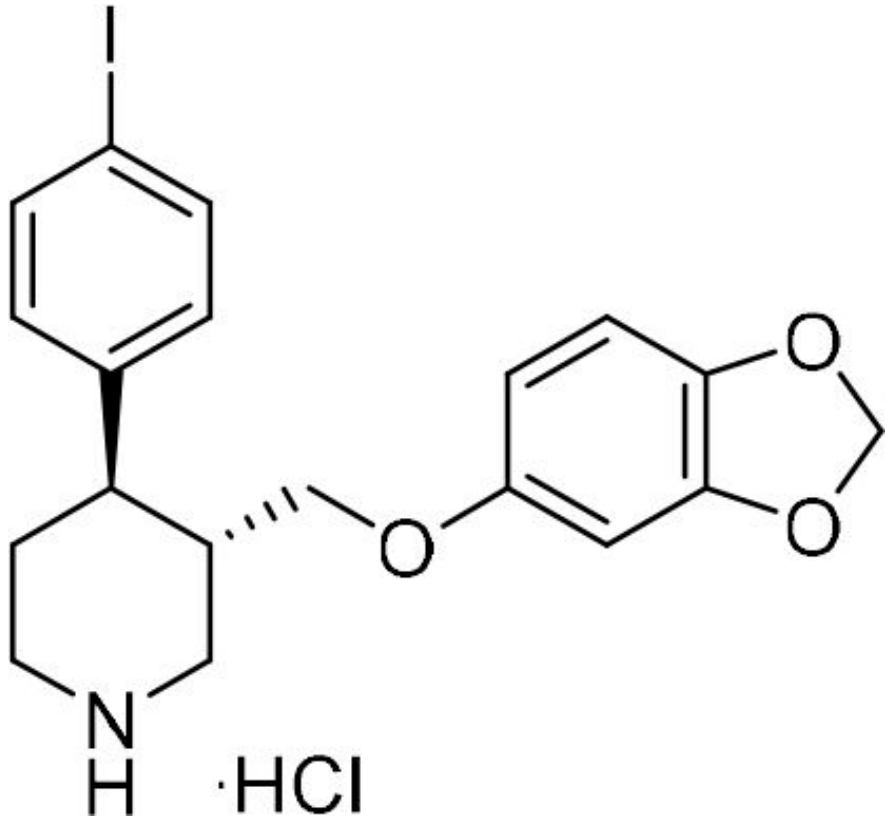
Duloxetine Hydrochloride

Venlafaxine PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020151s031s055s058s060lbl.pdf. Duloxetine PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021427s055s057lbl.pdf.

Paroxetine

Sedating

- **Mechanism:** Blocks 5-HT reuptake (SERT), mild anticholinergic, may have mild NET blockade
- **Dosing**
  - **Initial:** 10 mg QD
  - **Efficacious:** 10-40 mg QD
  - **Max:** 40 mg QD
- **Collateral receptors:** Muscarinic, histaminergic, alpha-adrenergic
- **Side Effects:** anticholinergic effects (weight gain, sedation, constipation), gastrointestinal and sexual side effects, somnolence, dizziness, sweating, tremor, decreased appetite, and discontinuation syndrome
- **Prescribing pearls**
  - Do not use first-line
  - Beer's list for sedation and fall risk
  - May require QTc monitoring

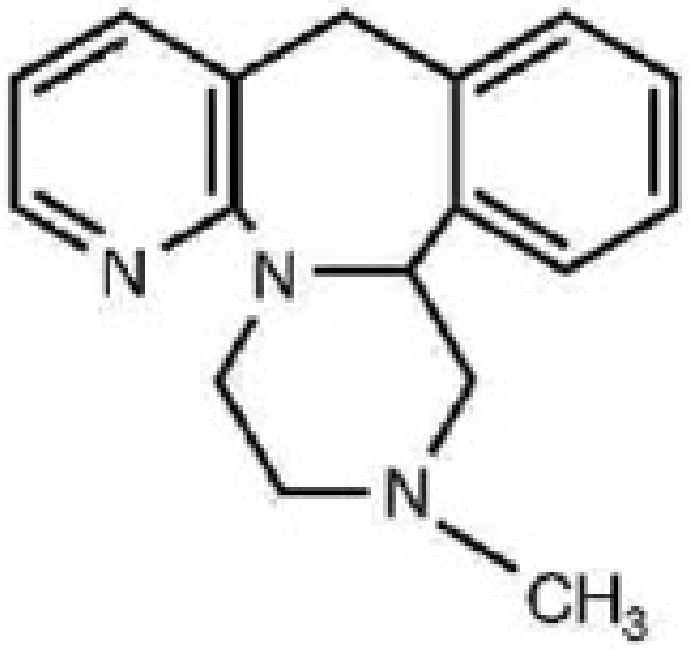


Paroxetine PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/020031s083,020710s051lbl.pdf.

Mirtazapine

Sedating

- **Mechanism:** Pre-synaptic alpha2-adrenergic agonist, increases noradrenergic and serotonergic neurotransmission, blocks 5-HT_2, 5-HT_3, and H_1
- **Dosing**
  - **Initial:** 7.5-15 mg QHS
  - **Efficacious:** 15-45 mg QHS
  - **Max:** 45 mg QHS
- **Significant collateral receptors:** H_1, alpha1-adrenergic, muscarinic
- Side effects: Somnolence (up to 54%), increased appetite, weight gain, dry mouth, dizziness, constipation, and, less commonly, orthostatic hypotension. Sexual dysfunction is rare. Agranulocytosis and neutropenia are rare but serious risks. Discontinuation syndrome can occur if stopped abruptly
- **Prescribing pearls**
  - H_1 blockade is a "collateral" receptor, but is often used for sleep properties
  - Potent H1 blockade at 7.5-15 mg, but lower 5-HT effects; therefore, it becomes slightly more activating at doses of 30 mg or greater
  - Monitor for weight gain



QHS = every night at bedtime.

Mirtazapine PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020415s038,021208s028lbl.pdf.

Polypharmacy to Address Partial Response or Persistent Symptoms

Activating

Bupropion

Benefits

- Decreased appetite/weight
- Low risk of sexual dysfunction
- Low risk of movement disorders (vs ARI)

Cautions

- Seizure risk
- Drug interactions
  - CYP2D6 inhibitor
  - CYP2B6 substrate
- May increase anxiety
- Monitor QTc

Aripiprazole

Benefits

- Slightly higher chance of MDD remission versus bupropion (VAST-D trial)
- Well-tolerated with low discontinuation rates
- Slightly more efficacious for older adults

Cautions

- Movement AE (EPS, akathisia)
- Weight gain/metabolic effects
- Drug interactions
  - CYP3A4 and CYP2D6 substrate

ARI = aripiprazole; AE = adverse events; EPS = extrapyramidal symptoms.

Mohamed S, et al. *JAMA*. 2017;318(2):132-145. Abilify® (aripiprazole) PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/021436s046s050lbl.pdf. Bupropion hydrochloride PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/018644s061lbl.pdf. Lenze EJ, et al. *N Engl J Med*. 2023;388(12):1067-1079.

Polypharmacy to Address Partial Response or Persistent Symptoms

Sedating

Z-drugs

Benefits

- Fast onset
- Effective for total sleep time, maintenance, and sleep onset
- Short-term usage with AD increases remission rates
- Well-tolerated in the short-term

Cautions

- Addiction/dependence potential
- Adverse events: dizziness, somnolence, amnesia, next-day impairment
- Poor choice for older adults

Quetiapine

Benefits

- Primarily histaminergic at lower doses (12.5-150 mg)
- Benefit for personality disorder and anxiety at higher doses (150-300+ mg)
- Effective for sleep maintenance

Cautions

- Higher relative risk of metabolic syndromes and movement symptoms
- High fall risk
- Dementia risk

Trazodone

Benefits

- Low dose (50-150 mg) for sleep and higher doses (150-300 mg) for MDD augmentations
- Low metabolic risk compared to QTP
- Low anticholinergic

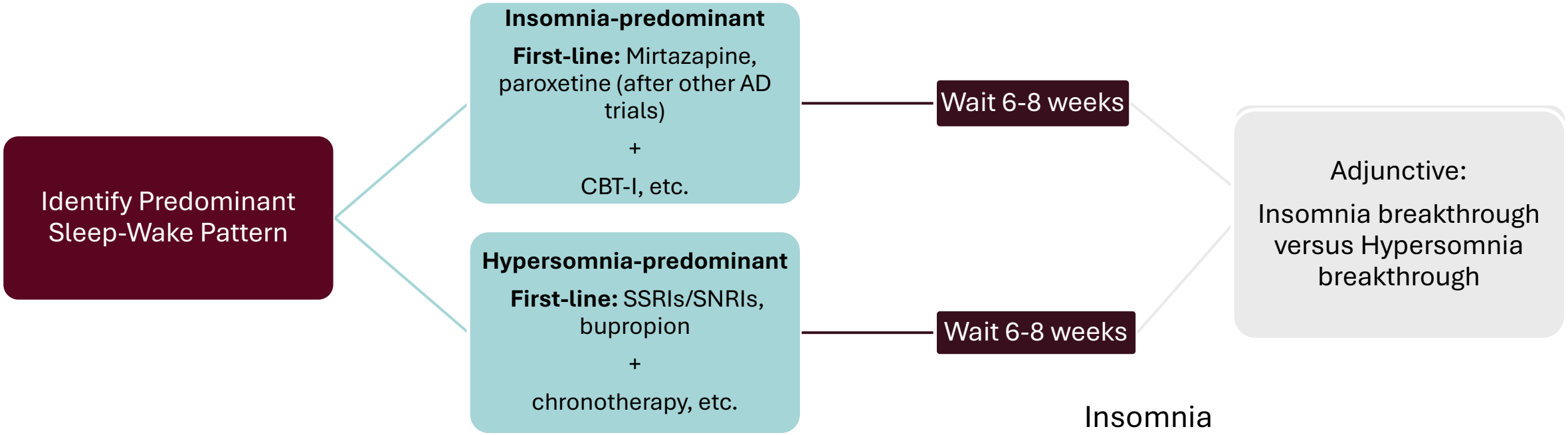
Cautions

- Orthostatic hypotension
- Daytime sedation
- Fall risk in older adults
- Monitor QTc

Z-drugs = zaleplon, zolpidem, zopiclone, eszopiclone; QTP = Quetiapine; QTc = Corrected QT interval

Vincent M, et al. *Ann Intern Med*. 2020;172:325-336. Seroquel® (quetiapine) PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020639s061lbl.pdf. Trazodone hydrochloride PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018207s032lbl.pdf. Lin Che-Yin, et al. *Eur J Neuropsychopharmacol*. 2023;67:22-36. Kishi T, et al. *Eur Arch Psychiatry Clin Neurosci*. 2017;267(2):149-161.

Practical Algorithm



Insomnia

- Trazodone 25-150 mg QHS
- Quetiapine 12.5-300 mg QHS

Hypersomnia

- Bupropion 75-300 mg QD (IR/SR/XL)
- Aripiprazole 2-15 mg QD

AD = antidepressant.

Trazodone hydrochloride PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/071196s062lbl.pdf. Quetiapine PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/020639s074lbl.pdf. Bupropion hydrochloride PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/018644s061lbl.pdf. Aripiprazole PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/021436s046s050lbl.pdf.

Common Pitfalls

Treating MDD and ignoring the sleep patterns

(Differentiate between insomnia vs hypersomnia!)

Overreliance on short-term solutions

(Benzodiazepines)

Premature treatment switching

(Give it the full 6-8 weeks)

Overlooking medical comorbidities, which should drive treatment selection

(Screen for OSA, RLS, thyroid dysfunction, AND potential side-effect drivers like metabolic syndrome)

Neglecting non-pharmacological approaches

(CBT-I, sleep hygiene, light therapy)

Suboptimal medication timing

(Activating in the AM and sedating in the PM)

OSA = obstructive sleep apnea; RLS = restless leg syndrome.

Key Learning Points

Principles

Select pharmacology by phenotype

- Consider whether antidepressants are activating or sedating

Become aware of receptor profiles

- Receptors drive efficacy and side effects, for example:
  - Histamine: sleep, adrenergic: blood pressure, etc.

Timing and circadian rhythm

- Align drug timing with desired effects. Sounds simple, but patient education often skipped!

Key Strategies

Targeted augmentation

- When things aren't working, choose secondary agents that address breakthrough symptoms

Algorithm-based approach

- Implement a structured decision-pathway

Risk/benefit Assessment

- Balance therapeutic goals with safety concerns through careful agent selection (QTc prolongation, movement AE, metabolic effects)

Let's Start by Facing *An Inconvenient Truth*....

We Have Some Amazing Guidelines from Around the World, But... They Offer Limited Guidance on How to Address Sleep-Wake Disorders in Our Patients with MDD

Some Guidelines Do Offer Scattershot Recommendations

- **Always assess and treat the sleep disorder** rather than ignoring sleep as a mere symptom. Guidelines consistently say sleep problems should be screened for and actively managed as part of MDD care
- **For comorbid insomnia, cognitive behavioral therapy for insomnia (CBT-I) is first-line** and can improve both sleep and depressive outcomes when added to antidepressant treatment. (Strong, repeated guideline and trial support)
- **For obstructive sleep apnea (OSA)**: screen patients with risk factors or residual symptoms; treat confirmed OSA (usually CPAP) — treatment often reduces depressive symptoms and may improve antidepressant response
- **For circadian problems / SAD**: timed bright-light therapy and strategic melatonin/chronotherapy are guideline-recommended approaches (especially for seasonal or delayed/advanced sleep-phase problems)

For the Most Part, We Clinicians Are Left to Fend for Ourselves on How to Best Manage Sleep Wake Disorders and MDD

CPAP = continuous positive airway pressure; SAD = social anxiety disorder.

VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. Accessed September 2025. https://www.healthquality.va.gov/guidelines/MH/mdd/VADODMDDCPGFinal508.pdf. Sateia MJ, et al. *J Clin Sleep Med*. 2017;13(2):307-349.

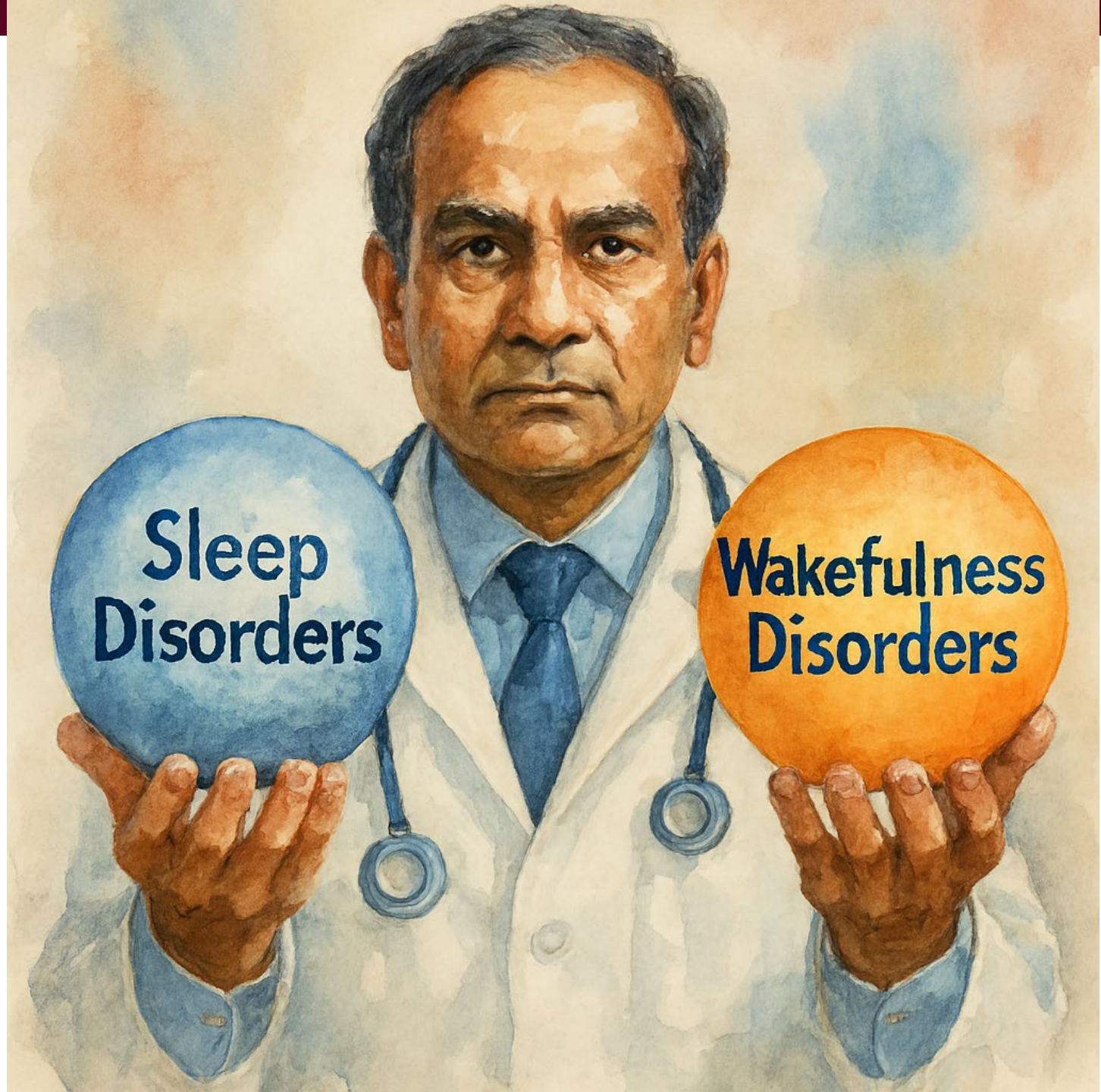
Besides the Shortcomings with Treatment Guidelines, Here Are Two Major Challenges –

1) There Is a Lack of Prospective Data for Antidepressants in Individuals with Sleep/Wake Symptoms

2) There Is a Lack of Guidance for Individuals with Sleep/Wake Symptoms in Current Guidelines

The “Reality” in Our Clinics Is …

We Clinicians Are Immediately and Urgently Challenged with Thousands of Patients with MDD with Co-Morbid Sleep-Wake Disorders



But ,... There IS a Potential Silver lining –

There Is The Potential We Clinicians Could Use Sleep/Wake Disorder Symptoms as a Phenotype / Biomarker for Subgroups of People with MDD

Potential Precision Treatments for Sleep/Wake Symptoms in MDD

Solriamfetol (A Wake Promoting Medication)

Introducing – Solriamfetol

Current Indications:

Solriamfetol is a dopamine and norepinephrine reuptake inhibitor (DNRI) indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA)

Additional Indications Investigated/Plan for Investigation

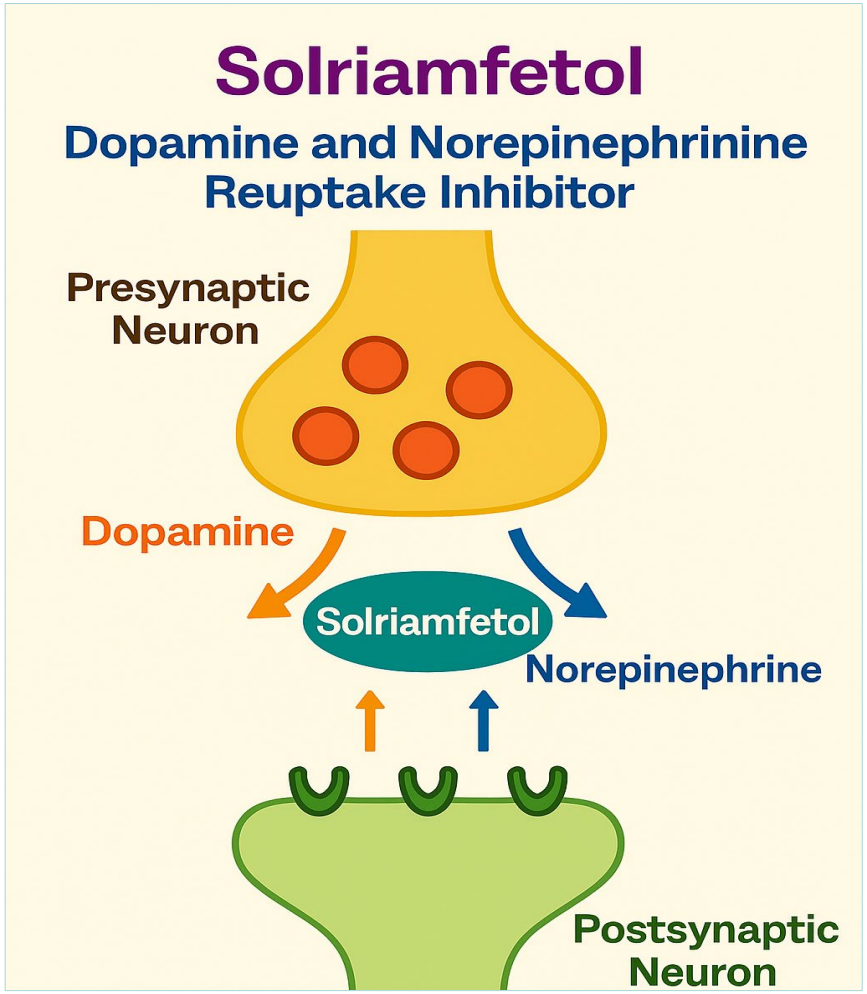
- ADHD
- MDD with EDS (Excess Daytime Sedation)

ADHD = attention-deficit/hyperactivity disorder.

Sunosi (solriamfetol) PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211230s009lbl.pdf. Axsome Therapeutics. April 1, 2025. Accessed September 2025. https://axsometherapeuticsinc.gcs-web.com/news-releases/news-release-details/axsome-therapeutics-announces-topline-results-paradigm-phase-3. Axsome Therapeutics. March 25, 2025. Accessed September 2025. https://axsometherapeuticsinc.gcs-web.com/node/11946/pdf.

Mechanism of Action of Solriamfetol

- It's a DNRI – Dopamine Norepinephrine Reuptake Inhibitor
- **IC_{50} (functional uptake inhibition)**: DAT ≈ **2.9 µM**, NET ≈ **4.4 µM** (these are concentrations producing 50% inhibition in uptake assays)
- **Additionally**, as a **TAAR1 agonist (EC_{50} ≈ 10–16 µM)**, it may contribute to its wake-promoting and neurobehavioral effects through TAAR1-mediated modulation of monoamine signaling
- It also has **low-affinity agonist activity at the human 5-HT_1A receptor** with an **EC_{50} in the mid-micromolar range** (around 25 µM)



DNRI = dopamine norepinephrine reuptake inhibitor.

Baladi MG, et al. *J Pharmacol Exp Ther*. 2018;366(2):367-376. Hema Gursahani, et al. *Sleep*. 2021;45(Supp1):A329.

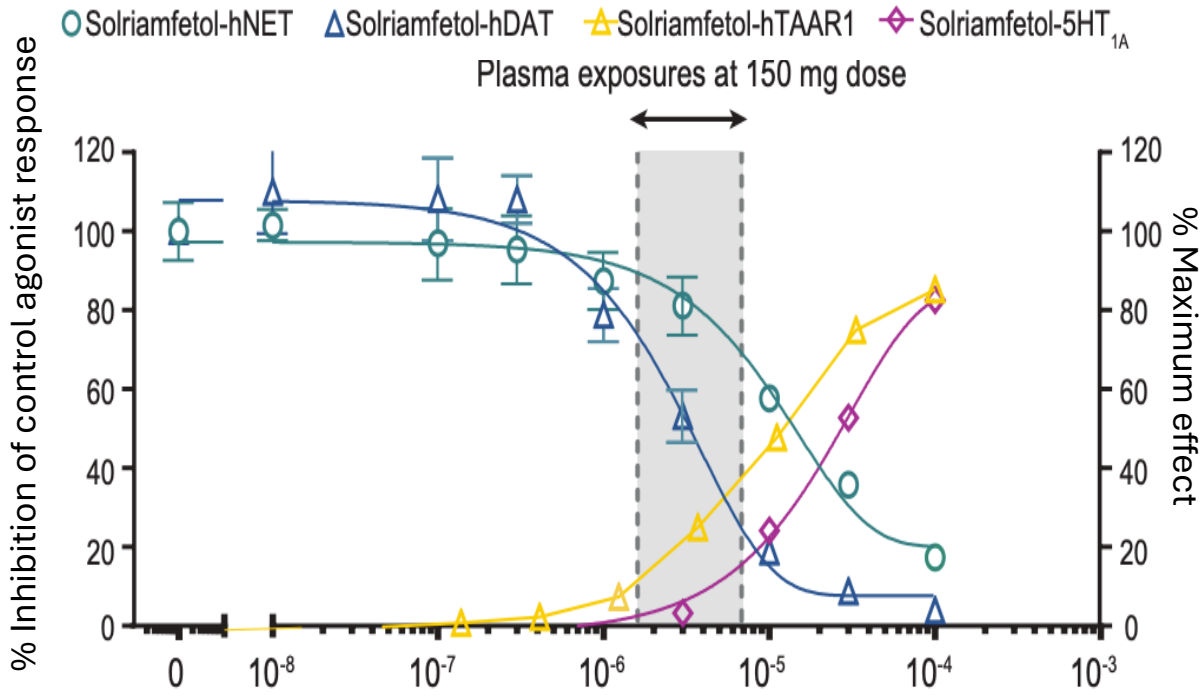
Solriamfetol, Approved for Excessive Daytime Sleepiness in Narcolepsy or OSA, Has TAAR-1 Agonist Properties

Solriamfetol is dopamine-norepinephrine reuptake inhibitor indicated for treatment of EDS in OSA or narcolepsy

Solriamfetol is not classified as a stimulant.

It is schedule IV, but showed no evidence of tolerance, withdrawal, or dependence, in trials

At 8x maximum recommended dose, the abuse potential was similar to or lower than phentermine



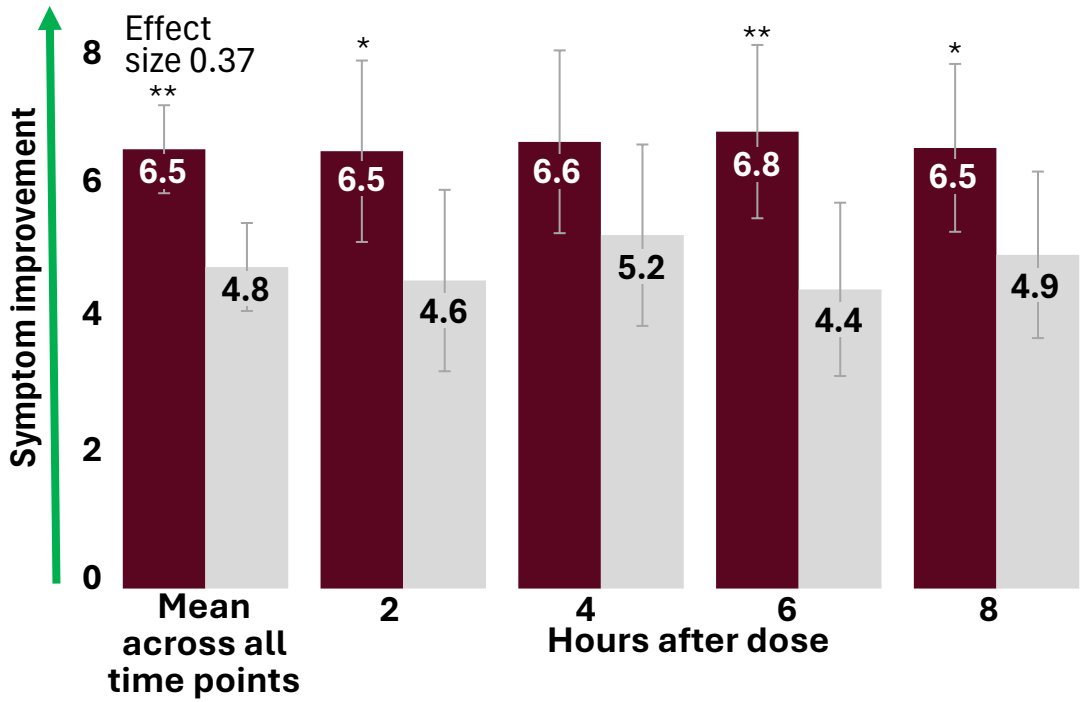
Subsequent pharmacologic characterization showed agonist activity at TAAR1 and 5-HT$_{1A}$

WPA = wake-promoting agent.

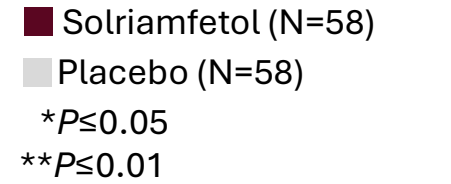
Solriamfetol PI. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211230s009lbl.pdf. Carter LP, et al. J Psychopharmacol. 2018;32(12):1351-1361. Gurashani H, et al. Poster presented at: 2022 SLEEP meeting, 36th Annual Meeting of the APSS; June 4-8, 2022; Charlotte, NC.

Solriamfetol May Provide Cognitive Benefits for Those With Cognitive Impairment Associated with EDS in OSA

A phase 4 randomized, double-blind, placebo-controlled, crossover trial



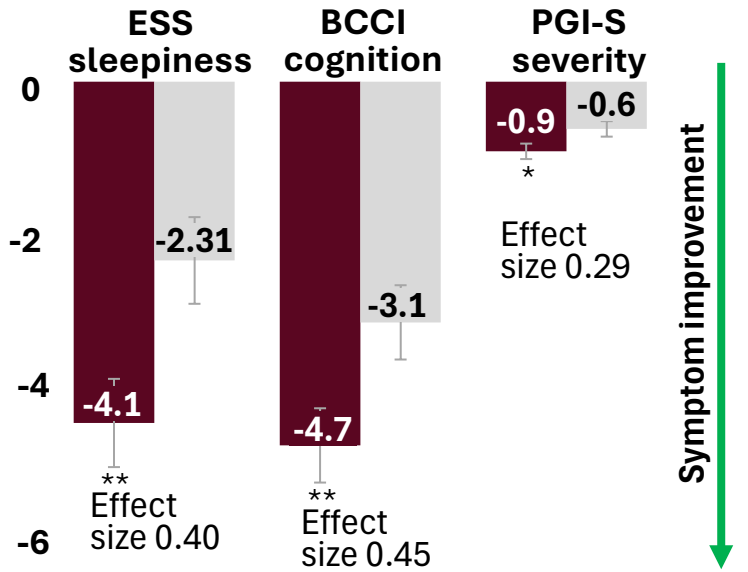
DSST RBANS score improved overall and throughout the day with solriamfetol vs placebo



Adverse events with solriamfetol vs placebo in ≥2% of participants

Any	19% vs 10%
Nausea	7% vs 3%
Anxiety	3% vs 0%

None were serious



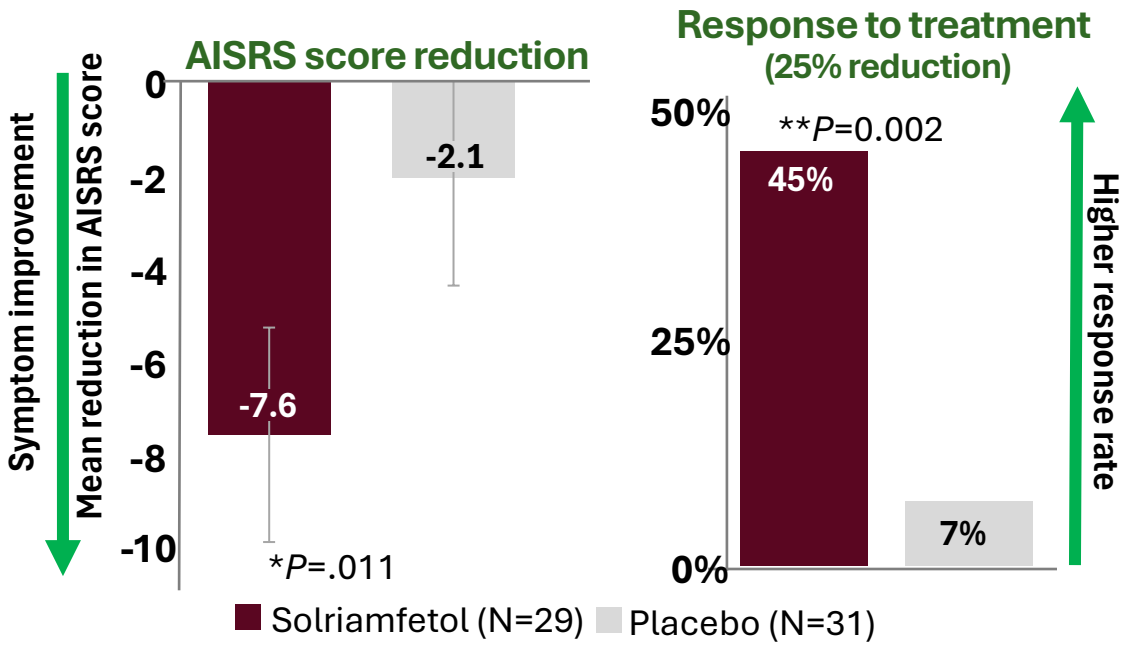
Solriamfetol vs placebo also significantly improved secondary outcomes

BCI = British Columbia Cognitive Complaints Inventory; DSST = Digit Symbol Substitution Test; PGI-S = Patient Global Impression of Change-Severity. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

Van Dongen HPA, et al. *Chest*. 2025;167(3):863-875.

Solriamfetol Is Also Being Evaluated for Potential Treatment of ADHD

Investigator-Initiated 6-week, Double-Blind, Placebo-Controlled Trial of Adults with ADHD



Solriamfetol 150 mg reduced ADHD symptoms and increased response rates significantly more than placebo in adults with ADHD

AEs in solriamfetol group ≥5% and ≥2x Placebo		
AE	Solriamfetol	Placebo
Cardiovascular	17%	3%
Nausea/Vomiting/Diarrhea	24%	6%
Sedation	10%	3%
Increased Energy	14%	3%
Agitated/irritable	10%	5%
Decreased Appetite	17%	6%
Neurological	14%	3%

Solriamfetol also showed efficacy in a phase 3 trial of 516 adults with ADHD

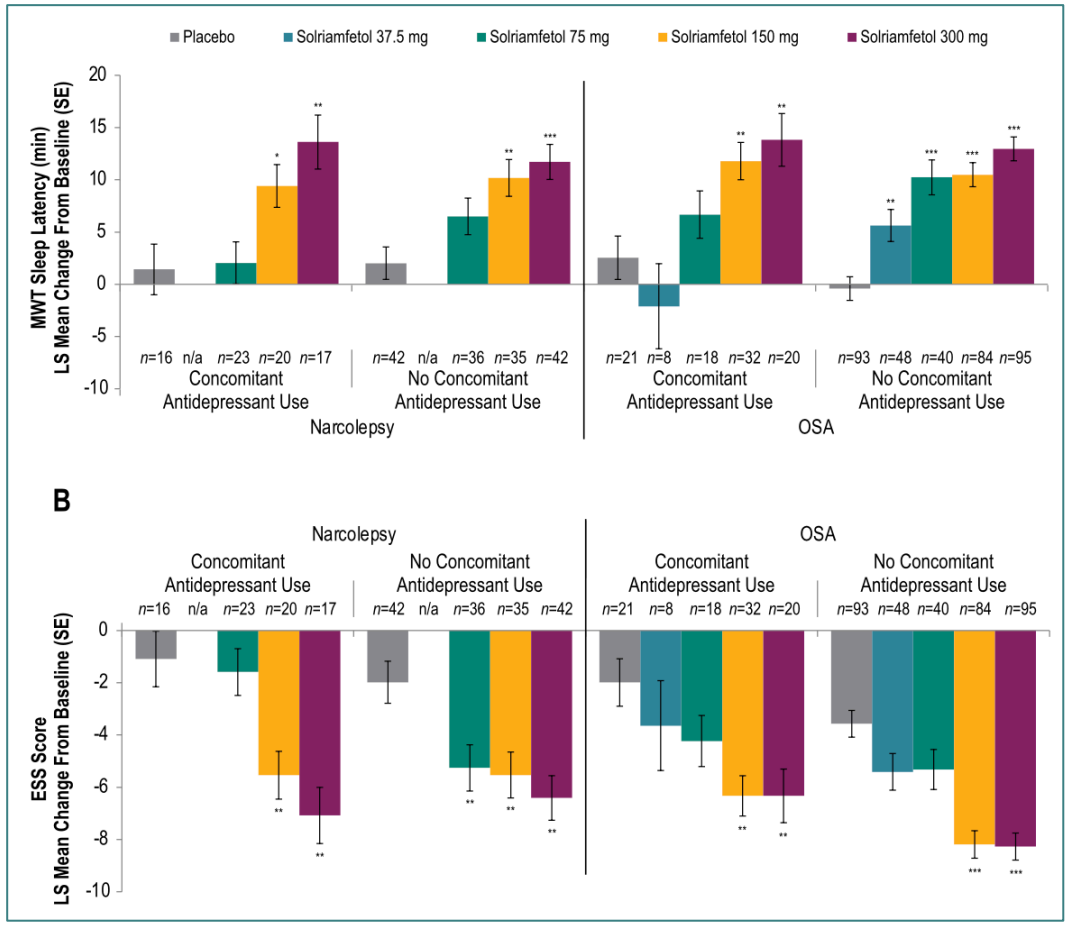
AISRS reduced by 17.7 points for solriamfetol 150 mg and 14.3 points for placebo (p=0.039)

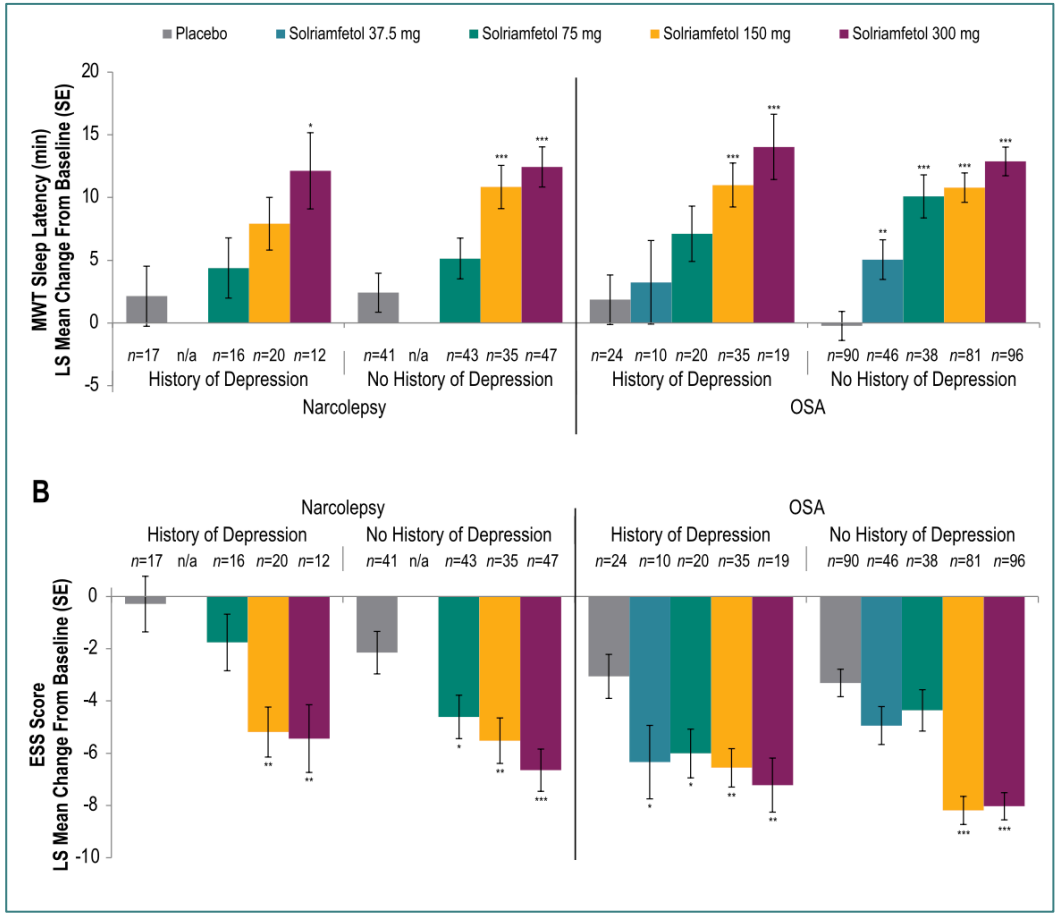
AEs were consistent with the established safety profile of solriamfetol

AISRS = Adult ADHD Investigator Symptom Rating Scale.

Surman CBH, et al. *J Clin Psychiatry.* 2023;84(6):23m14934. GlobeNewswire. March 25, 2025. Accessed May 20, 2025. https://www.globenewswire.com/news-release/2025/3/25/3048592/33090/en/Axsome-Therapeutics-Announces-FOCUS-Phase-3-Trial-of-Solriamfetol-in-Adults-with-Attention-Deficit-Hyperactivity-Disorder-ADHD-Achieves-Primary-Endpoint.html.

And… Solriemfetol Helps Excess Daytime Sedation (EDS), Independent of Past Hx of MDD or Being on Antidepressants





Hx = history.

Krystal AD, et al. *J Psychiatr Res*. 2022;155:202-210.

Solriamfetol Is Also Under Investigation for MDD

In a 6-week, double-blind, placebo-controlled Phase 3 Proof of Concept Study:

No statistically significant difference in the overall population of 295 participants in MADRS scores vs placebo

However, clinically meaningful improvements occurred with solriamfetol vs placebo among 51 participants with severe EDS (ESS score ≥16)

Future trials of solriamfetol for MDD with EDS are being planned

MADRS = Montgomery-Åsberg Depression Rating Scale.

GlobeNewswire. April 1, 2025. Accessed May 7, 2025. https://www.globenewswire.com/news-release/2025/04/01/3053170/33090/en/Axsome-Therapeutics-Announces-Topline-Results-of-PARADIGM-Phase-3-Proof-of-Concept-Trial-of-Solriamfetol-in-Major-Depressive-Disorder-MDD-with-and-without-Excessive-Daytime-Sleepin.html.

Solriamfetol: Safety and Efficacy

Side Effects/Risks

- Most common side effects are headache, nausea, decreased appetite, and anxiety
- In the largest randomized trial, rates of discontinuation for adverse effects for solriamfetol 150 mg and placebo were 5.1 and 1.7 percent, respectively
- Small, dose-dependent increases in mean blood pressure and heart rate were observed

Efficacy

- Randomized trial of 236 adults with narcolepsy who were randomly assigned to one of three doses of solriamfetol (75, 150, or 300 mg daily) or placebo
- At 12 weeks, sleep latency on the MWT improved more in the 150 mg group than in the placebo group (mean change from baseline 9.8 versus 2.1 minutes)
- Epworth Sleepiness Scale and global impression scores improved in both dose groups compared with placebo
- Responses were maximal or near-maximal by one week and were sustained across the 12-week treatment period, as well as in an open-label follow-up for up to a year

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

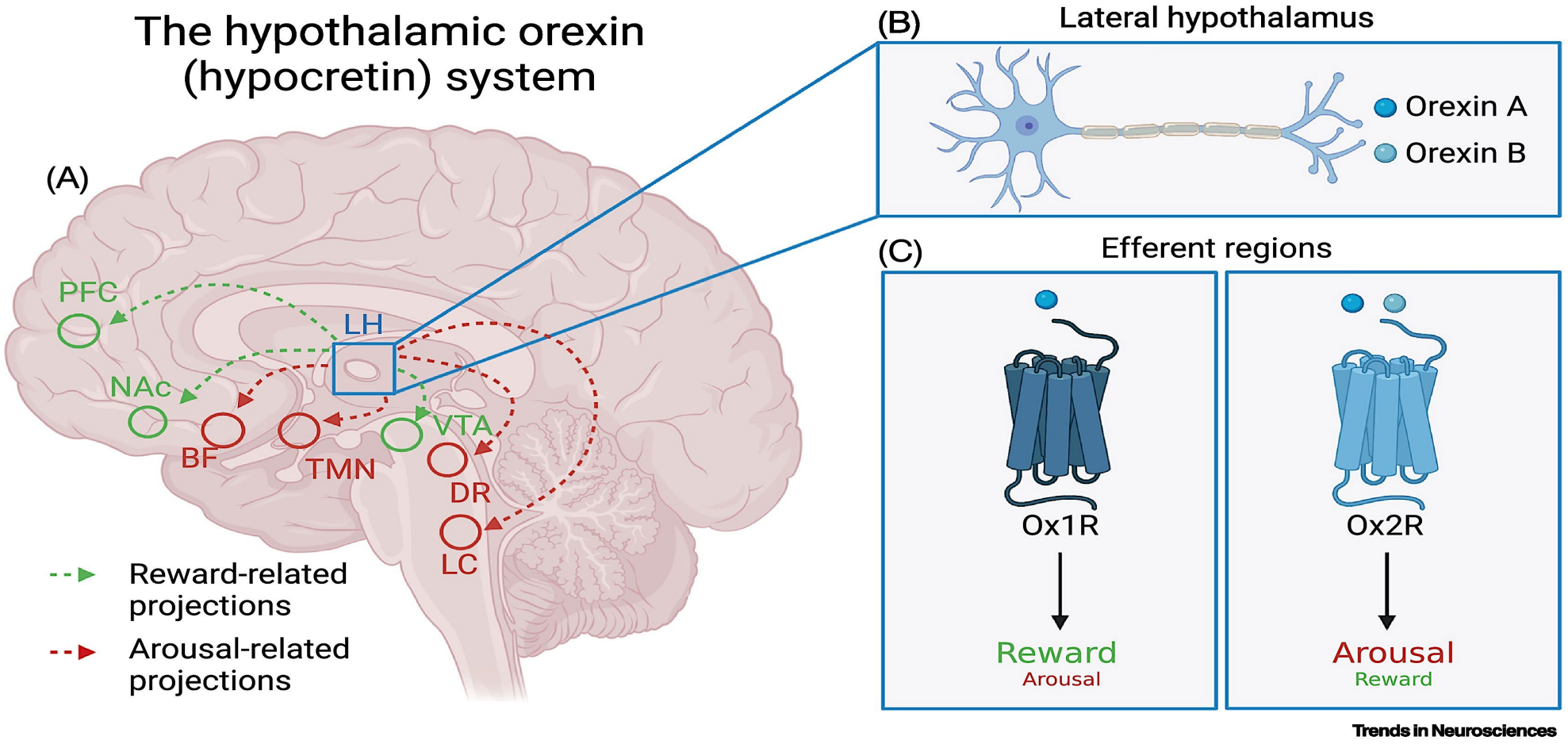
Concluding Thoughts on Solriamfetol –

- It is a unique DNRI, with TAAR-1 and 5HT1A properties
- It is not a stimulant. It is a Schedule IV
- It has robust data in reducing EDS in a variety of conditions
- ADHD trial data is positive, and MDD with EDS data is awaited from upcoming trial

Potential Precision Treatments for Sleep/Wake Symptoms in MDD

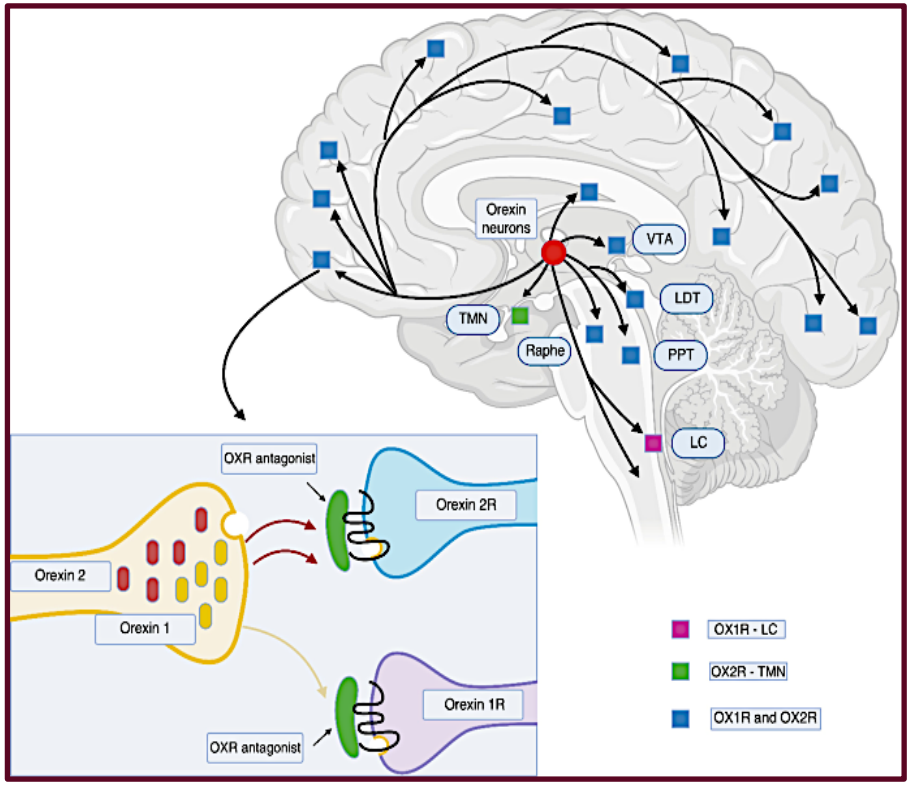
Seltorexton (A Sleep Promoting Medication)

A Deep Dive into Orexin A and B, and Orexin Receptors (OX1R and OX2R)



Mehr JB, et al. *Trends Neurosci*. 2021;44(11):852-855.

Orexin Receptor Distribution:
Location, Location, Location



Both Orexin receptors are widely distributed in many areas of the central nervous system such as

Ventral tegmental area (VTA),

Pedunculopontine tegmental nucleus (PPT)

Laterodorsal tegmental nucleus (LDT)

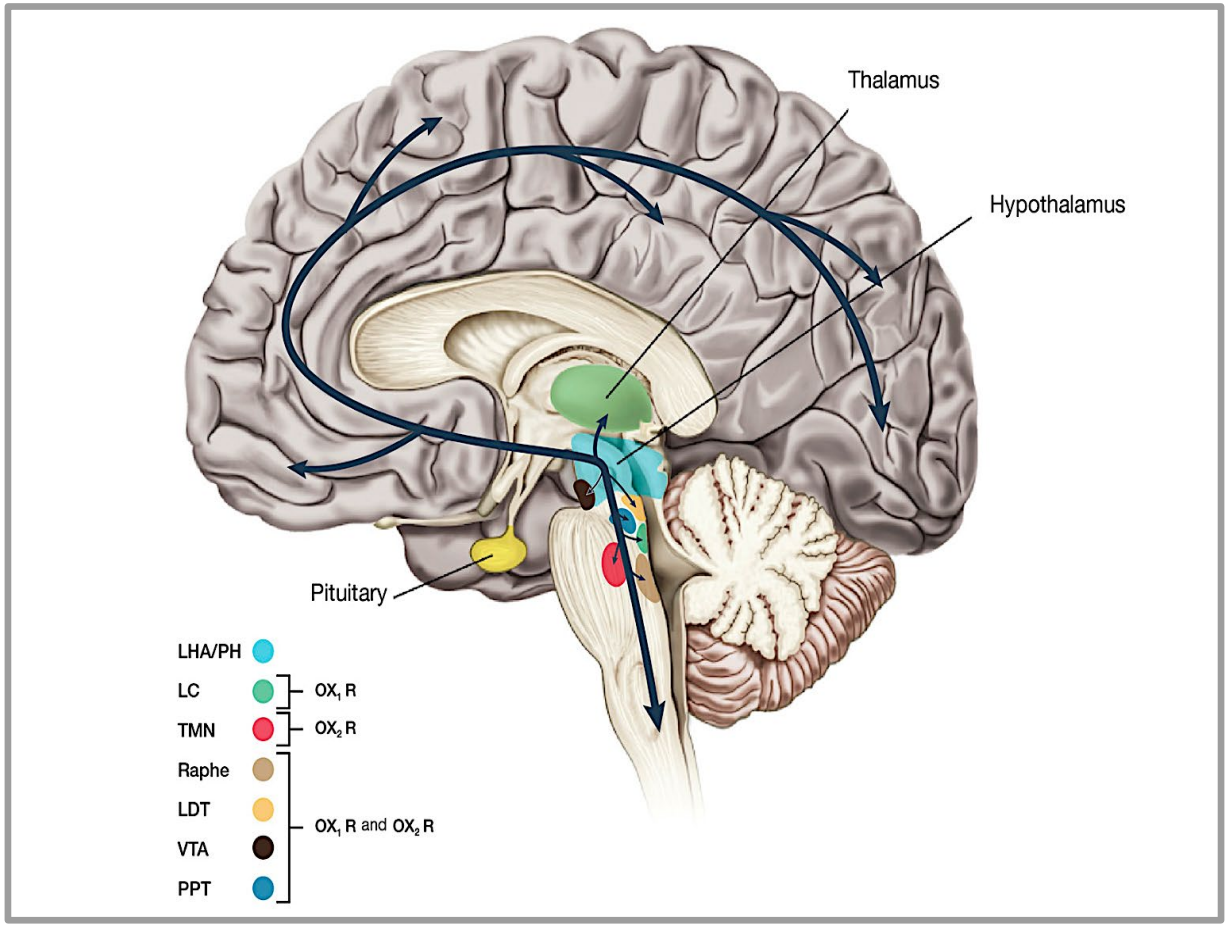
- Orexin 1 Receptor (OX1R) is preferentially distributed in the Locus Coeruleus (LC) (meaning – it controls the Norepinephrine system)
- Orexin 2 Receptor (OX2R) is preferentially distributed in the Tuberomammillary Nucleus (TMN) (meaning – controls the Histamine System)

VTA = ventral tegmental area; PPT = pedunculopontine tegmental nucleus; LDT = laterodorsal tegmental nucleus; LC = locus coeruleus; TMN = tuberomammillary nucleus.

Fathima S, et al. Orexins. In: Bollu PC, ed. *Neurochemistry in Clinical Practice*. Springer, Cham; 2022:181-209. Wang C, et al. *Front Mol Neurosci*. 2018;11:220.

Orexin Neurons at Interface of Sleep, Stress, Reward, and Energy Homeostasis

LC, DR, and TMN are wake-active regions, VLPO is a sleep-active region, and LDT/PPT is a REM-active region. Orexin neurons promote wakefulness through monoaminergic nuclei that are wake-active. Stimulation of dopaminergic centers by orexins modulates reward systems (VTA). Peripheral metabolic signals influence orexin neuronal activity to coordinate arousal and energy homeostasis. Stimulation of neuropeptide Y neurons by orexin increases food intake. The SCN, the central body clock, sends input to orexin neurons via the DMH. Input from the limbic system (amygdala and BST) might be important to regulate the activity of orexin neurons upon emotional stimuli to evoke emotional arousal or fear-related responses.



BST = bed nucleus of the stria terminalis; VLPO = ventrolateral preoptic area; DR = dorsal raphe; SCN = suprachiasmatic nucleus; DMH = dorsomedial hypothalamus.

Chieffi S, et al. *Front Physiol*. 2017;8:357.

Orexin's Involvement in Emotion Regulation and Depression Is Deep, and Multi-factorial

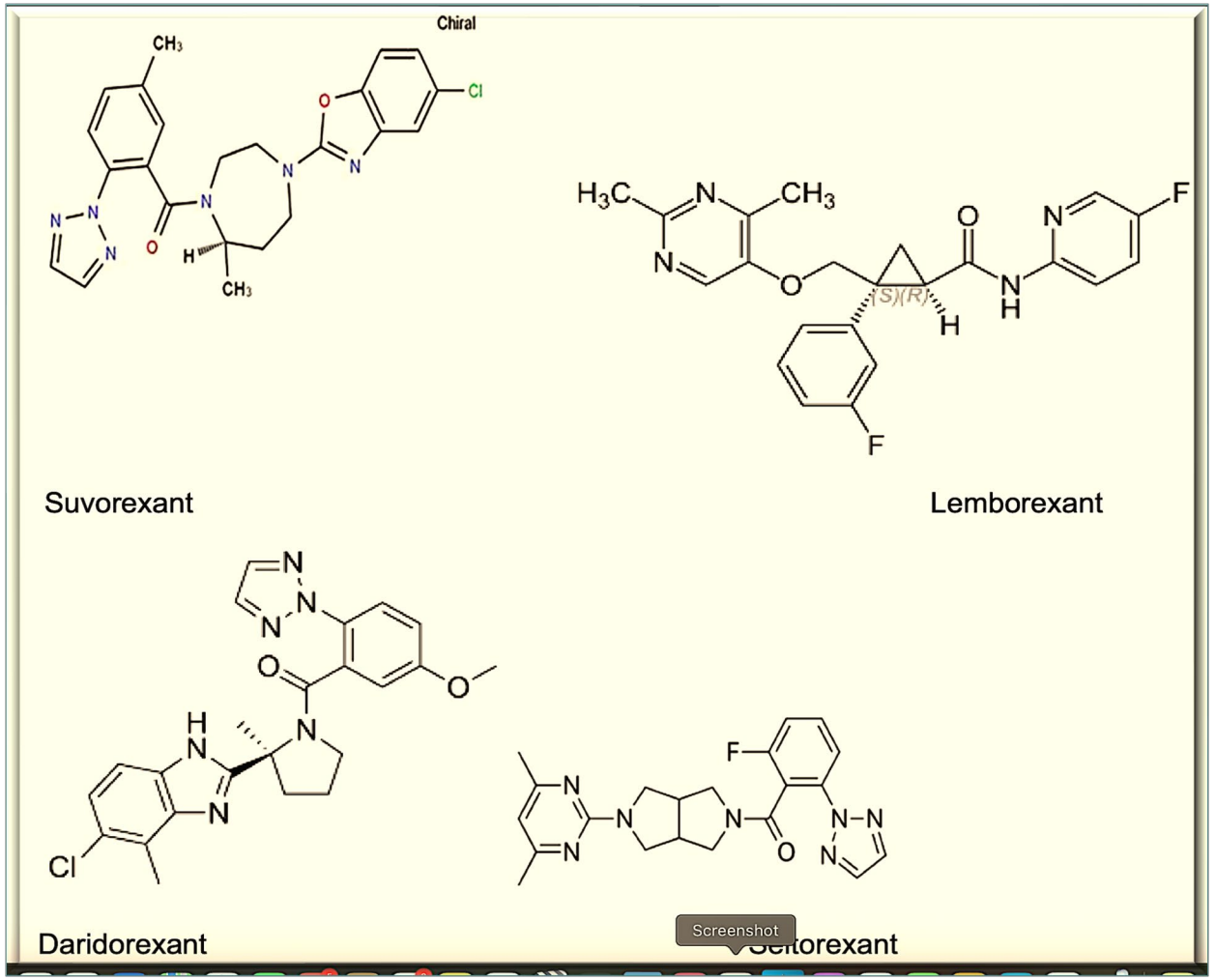
1. Orexin-containing neurons project neurofibers to the dopaminergic ventral tegmental nucleus and substantia nigra, which are important regulators of emotional activity, suggesting that the orexin/receptor system is involved in the pathophysiology of depression.

2. Orexin receptors are also expressed outside the neuron systems; they are found on Astrocytes and Oligodendrocytes, both of which are implicated in the pathophysiology of depression.

Wang C, et al. *Front Mol Neurosci*. 2018;11:220.

Different Orexin Receptor Antagonist of Interest

- Suvorexant, Lemborexant, and Daridorexant are all DORAs and FDA-approved for Insomnia Disorder
- Seltorexant is a SORA-2 and is being developed as an adjunct treatment of MDD in patients with Insomnia symptoms
- The emerging term for this is – MDDIS (Major Depressive Disorder with Insomnia Symptoms)



DORA = dual orexin receptor antagonist; SORA = selective orexin receptor antagonist; MDDIS = major depressive disorder with insomnia symptoms.

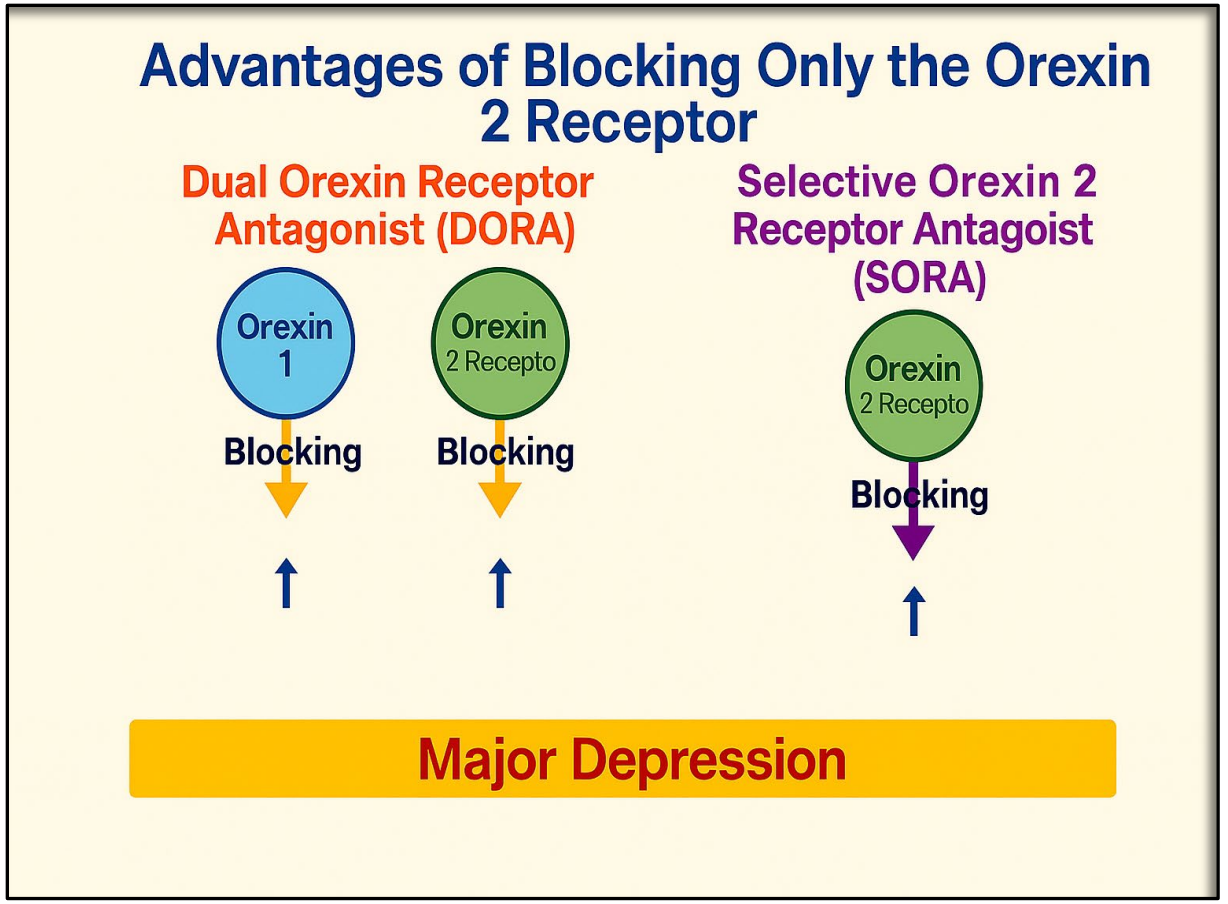
Shigetsura Y, et al. *Clin Neuropharmacol*. 2022;45(3):52-60. Thase ME. *Eur Arch Psychiatry Clin Neurosci*. 2025 [Epub ahead of print].

There Are Two Types of Orexin Receptor Antagonists – DORAs and SORAs

DORAs = Dual Orexin Receptor Antagonists

SORAs = Selective Orexin Receptor Antagonist
(They can be selective for Orexin 1 or 2)

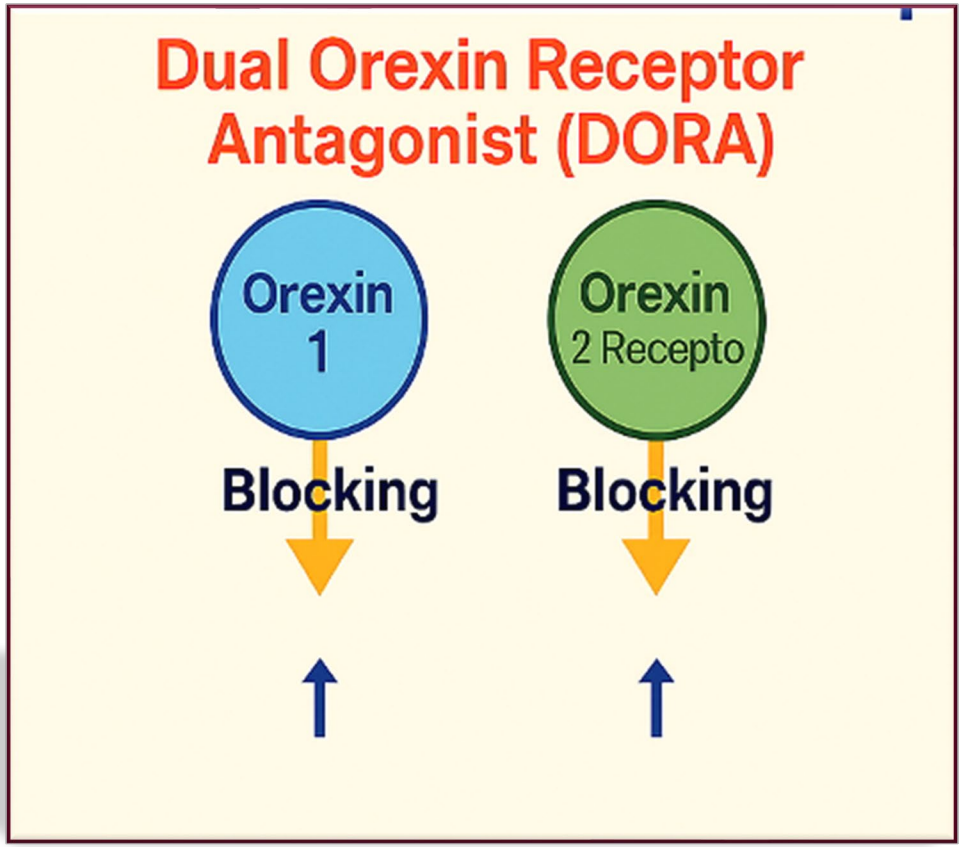
In Major Depression – It is the SORAs on Orexin Receptor 2 that are being developed



Shigetsura Y, et al. *Clin Neuropharmacol*. 2022;45(3):52-60. Thase ME. *Eur Arch Psychiatry Clin Neurosci*. 2025 [Epub ahead of print].

DORAs Have a Sparse Track Record in MDD

- Evidence for DORAs as augmentation therapy is "surprisingly sparse." A single small (n=18) RCT of suvorexant was the only published study identified of any of the approved DORAs conducted in patients with MDD
- Avoiding blocking the Orexin 1 receptor may be of benefit, as blocking ORX1R in some contexts might interfere with adaptive arousal or reward-related signaling, and could dampen positive affect
- This is why a SELECTIVE Orexin 2 antagonist may be the preferred option in a patient with Major Depression



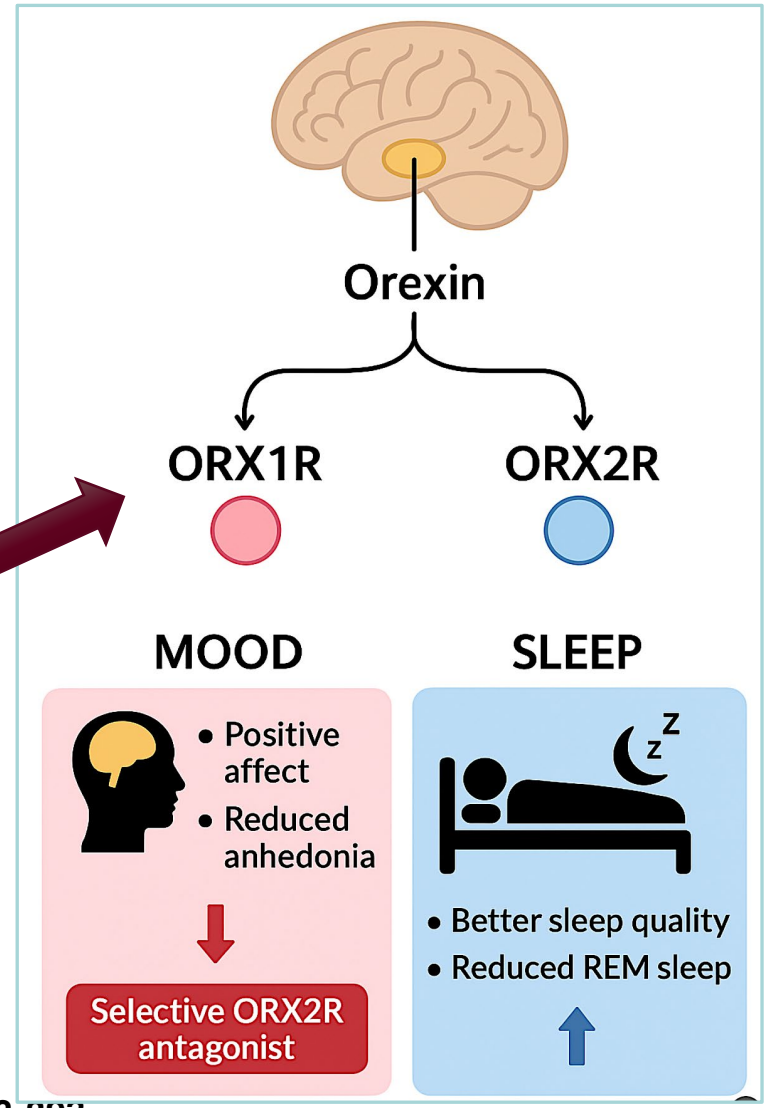
RCT = randomized controlled trial.

Shigetsura Y, et al. *Clin Neuropharmacol*. 2022;45(3):52-60. Thase ME. *Eur Arch Psychiatry Clin Neurosci*. 2025 [Epub ahead of print].

Take Home Message on Why Selectivity Matters in the Orexin System –

Blocking OX1R may impair natural reward circuits, arousal, and stress coping mechanisms, which supports the idea that **SORAs that spare OX1R (while antagonizing OX2R) might preserve positive affect and motivation**—a potentially important benefit in treating depression.

This is why avoiding blocking the Orexin 1 Receptor is better than blocking both in MDD



Kim W-J, Kim HS. *Transl Clin Pharmacol*. 2024;32(1):1-17. Ji M-J. et al. *Mol Psychiatry*. 2018;24(2):282-293.

Role of Orexin in the Regulation of Mood, Affect, Motivation, And Reward

Orexin and Emotions: A Tight, Bi-Directional Relationship

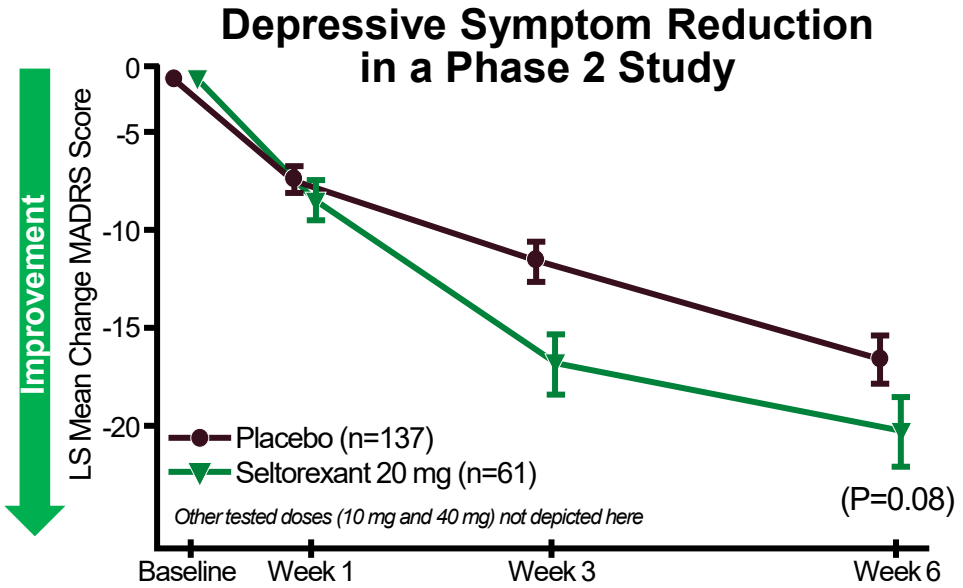
1. Orexin-producing neurons have been shown to receive input from neurons in the limbic system, including the amygdala, the nucleus of the tegmental striatum, and the nucleus accumbens

2. Orexin neurons receiving input from the limbic system are involved in the regulation of the autonomic nervous system and the maintenance of arousal levels associated with emotion

Saitoh T, Sakurai T. *Peptides*. 2023;167:171051.

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



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		

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)

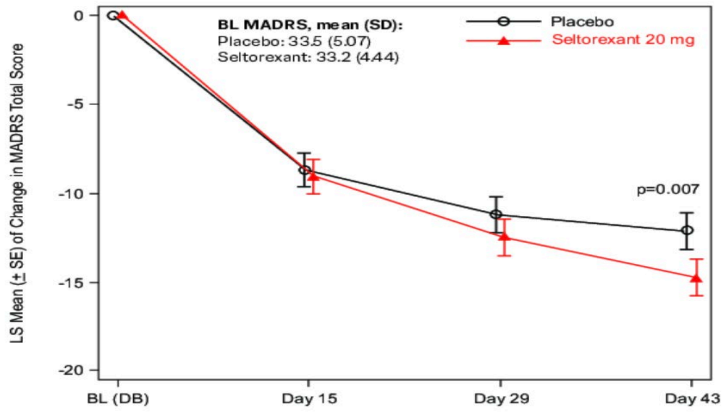
LS = least squares; ISI = Insomnia Severity Index; D/C = discontinuation.

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.

Orexin-Based Innovation: Seltorexant – SORAs in Mood Disorders

Seltorexant is a first-in-class, potent, selective orexin-2 receptor antagonist. Phase 3, 6-week, multicenter, international, double-blind (DB), randomized, placebo-controlled trial (Figure 1) • Eligible participants with MDD (with or without insomnia) were randomized 1:1 to receive seltorexant 20 mg or a matching placebo for 6 weeks, while continuing their baseline SSRI/SNRI

FIGURE 2: LS mean (± SE) change from baseline over time[a] in MADRS total score



[a]Mixed effects model for repeated measures observed case.
BL, baseline; DB, double-blind; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; SE, standard error

TABLE 2: Safety summary (N=586[a])

TEAEs, n (%)	Placebo (n=303)	Seltorexant 20 mg (n=283)
Participants with ≥1 TEAE	122 (40.3%)	102 (36.0%)
TEAEs occurring in ≥5% of participants		
Headache	27 (8.9%)	24 (8.5%)
Related TEAEs[b]	51 (16.8%)	34 (12.0%)
TEAEs leading to discontinuation of study treatment	7 (2.3%)	6 (2.1%)
Related TEAEs leading to discontinuation of study treatment[b]	5 (1.7%)	3 (1.1%)
TEAEs of special interest	7 (2.3%)	5 (1.8%)
Serious TEAEs	1 (0.3%)	1 (0.4%)
Related serious TEAEs[b]	0	0

[a]Participants with MDD who received ≥1 dose of study drug. [b]TEAEs are assessed by the investigator as related to study agent.
TEAE, treatment-emergent adverse event

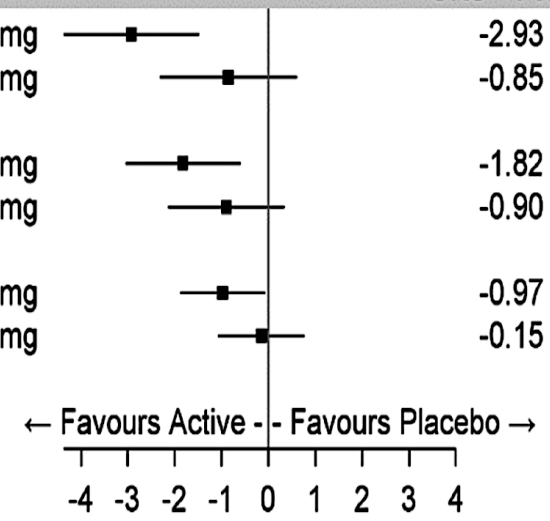
DB = double-blind.

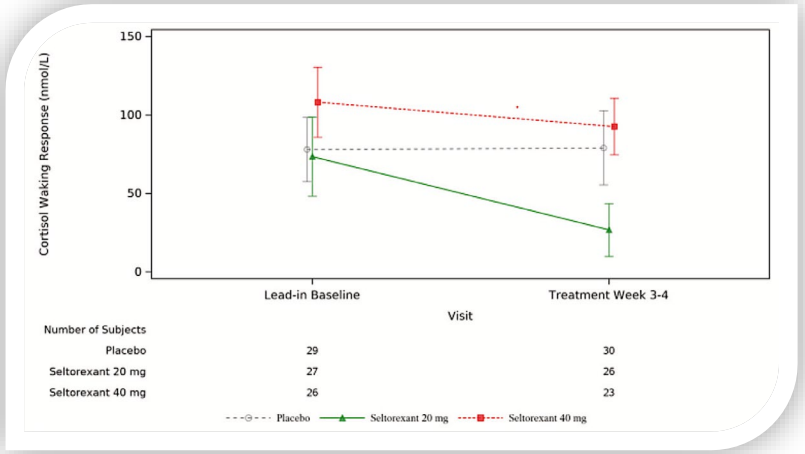
Thase ME, et al. Presented at: American Society of Clinical Psychopharmacology; May 28-30, 2024; Miami Beach, FL.

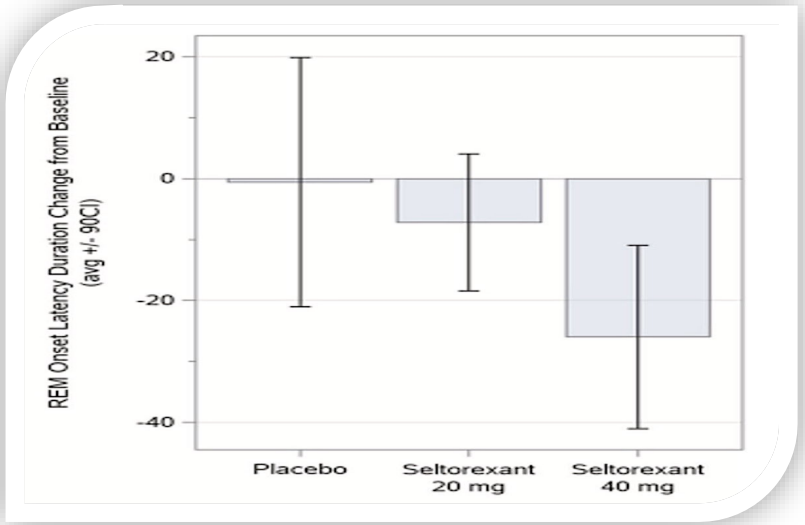
Seltorexant in MDD – More Than a Sleep Benefit

Seltorexant at 20 mg was effective as monotherapy for MDD.
The treatment benefit in the 20 mg arm remained significant even when removing the sleep items was removed from HDRS (nominal P=0.0289).

arameter	Treatment	LsMean Diff. (SE) JNJ - Placebo
HDRS17 Total Score	JNJ 20 mg	-2.93 (1.123)
	JNJ 40 mg	-0.85 (1.137)
HDRS17 Sleep Adjusted Total Score	JNJ 20 mg	-1.82 (0.953)
	JNJ 40 mg	-0.90 (0.967)
HAMD6 Subscale Score	JNJ 20 mg	-0.97 (0.706)
	JNJ 40 mg	-0.15 (0.717)







HDRS = Hamilton Depression Rating Scale.

Mesens S, et al. *Molecular Psychiatry*. 2025;30:2427-2435.

Concluding Thoughts on Seltorexant -

- A SORA may be a preferred agent (over DORAs) for the treatment of Depression and Insomnia in patients with Major Depression
- The emerging evidence shows a favorable efficacy-tolerability profile in MDDIS
- It appears that a SORA does not just improve sleep time, but sleep quality, and perhaps even positively modulate the HPA axis (cortisol levels)
- We await further data and eventual FDA approval

Faculty Discussion on Three “Hot Topics”

1.

Faculty Hot Topic Discussion:

Experience with the Clinical Utility of *"Using the Side Effect to Your Advantage"*

2.

Faculty Hot Topic Discussion:

Assessing Insomnia and EDS in Patients with MDD

3.

Faculty Hot Topic Discussion:

Individualizing Treatments for Individuals with MDD with Sleep/Wake Symptoms

Practical Take-Aways

- HCPs can tailor their clinical decision-making by understanding the differences in sleep/wake disorders and utilizing specifiers, as opposed to a "one-size-fits-all" approach in treating MDD
- Clinicians are equipped with the ability to use an algorithm-based approach paired with better alignment of pharmacological interventions to match sleep/wake phenotype, which can help patients
- It is ideal to target wake disorders when they are comorbid with psychiatric illnesses in order to achieve optimum outcomes with both conditions
- We clinicians should take full advantage of the currently available and emerging therapies to address sleep-wake disorders in our patients with concurrent psychiatric disorders

Q&A