Psych Congress MasterClass

IN PARTNERSHIP WITH Sleep Research Society Foundation

New Solutions for Excessive Daytime Sleepiness and Obstructive Sleep Apnea:

The Silent Killer of Better Outcomes in Psychiatric Practice

Supported by an independent educational grant from Axsome Therapeutics, Inc.

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Faculty Disclosures

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

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- **Nick Hunter:** Has disclosed no relevant financial relationship with any ineligible company (commercial interest)

Disclosures

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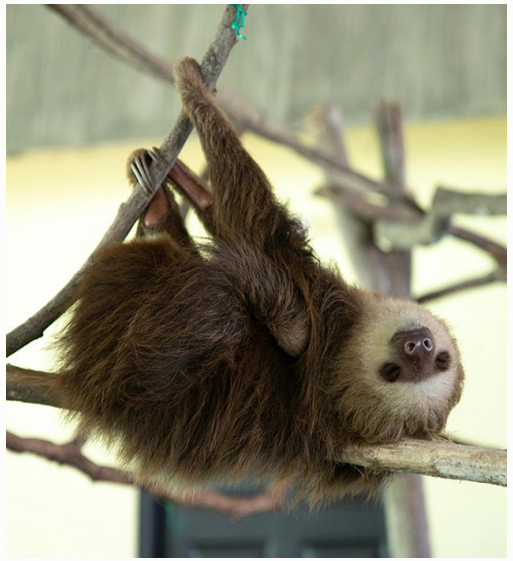
Learning Objectives

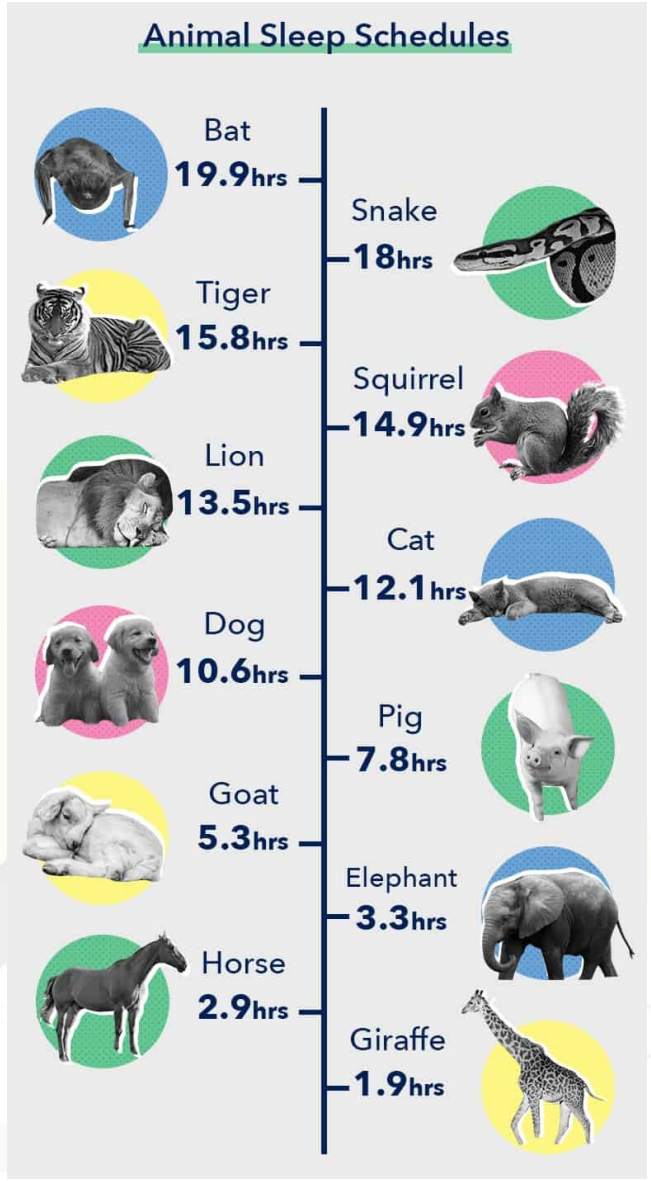
1. Describe the prevalence and major psychiatric comorbidities of EDS and the role of psychiatry clinicians in addressing EDS
2. Apply strategies to improve recognition of EDS in patients with mental illness, detect underlying OSA, and refer appropriate patients to sleep specialists for further testing
3. Evaluate the latest clinical evidence and implications associated with novel/investigational treatments for EDS and OSA in comparison to traditional/off-label treatments

UNDERSTANDING EDS & OSA

In the Context of Mental Illness

Who Sleeps the Longest ?





What Is Excessive Daytime Sleepiness (EDS) ?

Excessive Daytime Sleepiness

Inability **to maintain wakefulness** or alertness during the wake portion of the sleep-wake cycle (> 3 mos & > normal biologic drive to sleep)

Key point: Patients with fatigue **can typically stay awake** despite lack of physical/mental energy, while patients with **EDS simply cannot**

EDS = excessive daytime sleepiness.

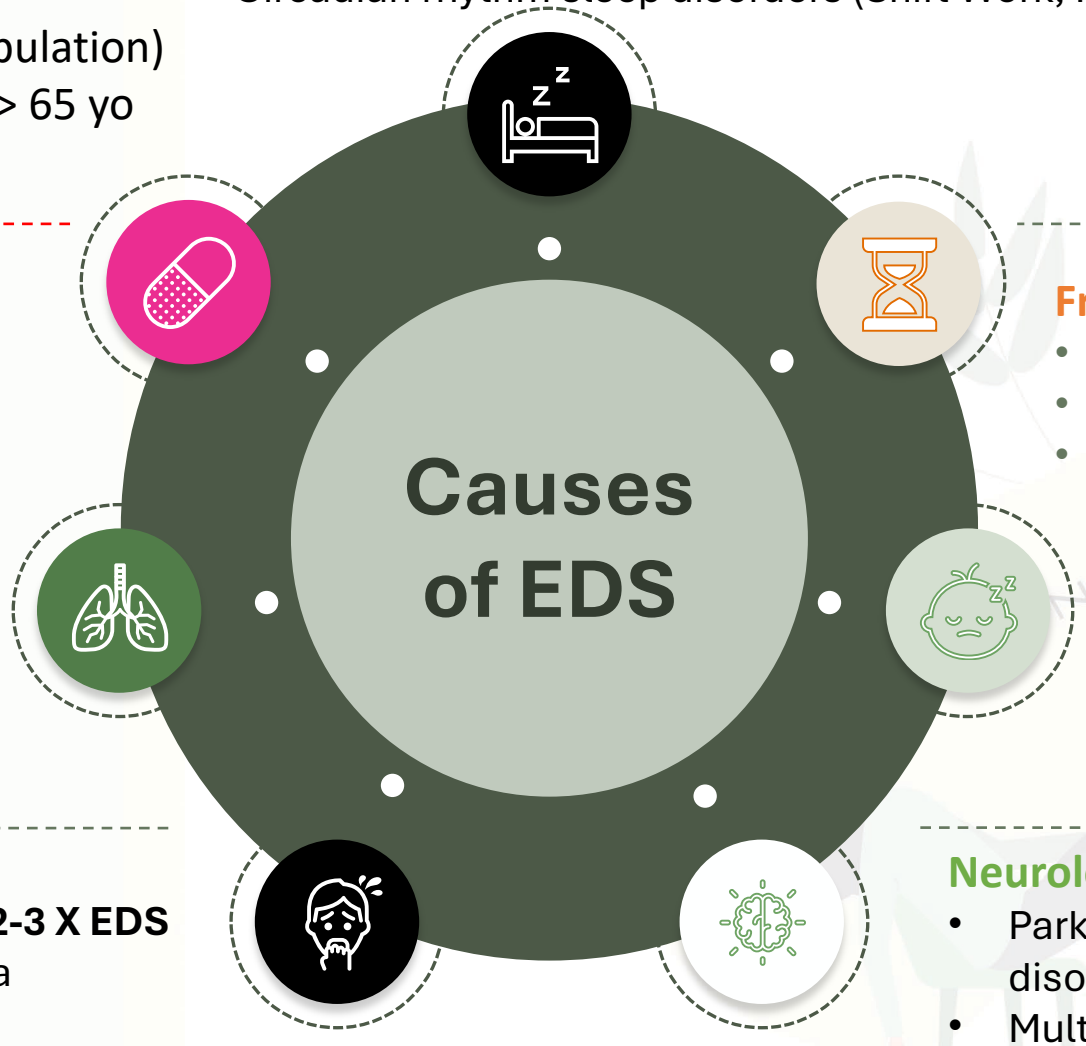
Shen J, et al. *Sleep Med Rev*. 2006;10(1):63-76. Tenor. GIFs. Accessed September 2025. https://tenor.com/.

Sleep deprivation

- Behavioural (Insufficient Sleep)
- Circadian rhythm sleep disorders (Shift Work, Irregular Schedules)

Prevalence of EDS

- **18%-25%** of adults (general population)
- **Age Association:** EDS > **30%** in > 65 yo



Medications

- CNS Depressants
- Benzodiazepines
- Polypharmacy

Other organic disease

- Congestive heart failure
- Chronic renal failure
- Anemia, Thyroid

Psychiatric (HAPD)

- Mood Disorders MDD, GAD; **2-3 X EDS**
- ADHD, Bipolar, Schizophrenia
- Alcohol & Substance Abuse

Fragmentation of sleep

- **Obstructive sleep apnea**
- Restless legs syndrome, PLMD
- RBD

Primary CNS hypersomnias

- Narcolepsy Type 1 / Type 2
- Idiopathic hypersomnia

Neurological

- Parkinson's disease & neurodegenerative disorders, Dementia
- Multiple sclerosis

RBD = REM sleep behavior disorder; PLMD = periodic limb movement disorder; CNS = central nervous system; MDD = major depressive disorder; GAD = generalized anxiety disorder; ADHD = attention-deficit/hyperactivity disorder.

Slater G, et al. *J Thorac Dis*. 2012;4(6):608-616. Wanberg LJ, et al. *J Clin Sleep Med*. 2021;17(12):2363-2372. Bock JM, et al. *Heart*. 2022;108(22):1761-1766. Gooneratne NS, et al. *J Am Geriatr Soc*. 2003;51(5):642-649. Kerner NA, et al. *Am J Geriatr Psychiatry*. 2016;24(6):496-508.

Obstructive Sleep Apnea (OSA)

He SNORES, I am Exhausted

Best Treatments for OSA

Obstructive Sleep Apnea

Snoring

- Posterior airway vibration **(60-70 db)**
- Whisper 20 db, Conversation 30 db,
- Vaccuum Cleaner 70db

Mild OSA	**AHI=5-15/hr of Sleep.**
Mod OSA	**AHI=15-30/hr of Sleep.**
Severe OSA	**AHI = 30/hr of Sleep.**

AHI = APNEA HYPOPNEA INDEX Breathing Pauses / per hour of Sleep

AHI = apnea hypopnea index.

Risk Factors and Clinical Symptoms of OSA

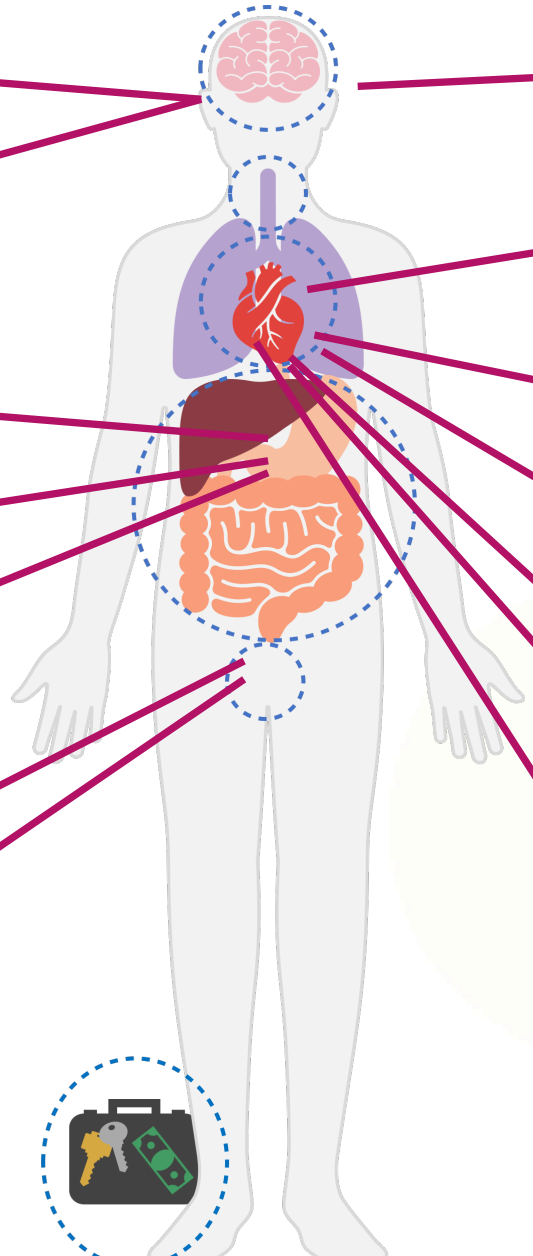
Risk Factors	Odds Ratio
Weight	
Overweight vs Normal Weight	2.3-3.4
Obese vs Normal Weight	4.0-10.5
Male Sex (vs female)	1.7-3.0
Age (per 1—year increment)	1.4-3.2
Postmenopausal state in women	2.8-4.3
Enlarged Upper Airway Soft Tissues (eg, tonsils, adenoids, tongue)	Unknown
Craniofacial Abnormalities (eg, retrognathia, micrognathia)	Unknown

Clinical Symptoms and Signs	Prevalence, %
Excessive Sleepiness, Fatigue, or Unrefreshing Sleep	73-90 %
Snoring Most Nights	50-60
Witnessed Breathing Pauses, Choking, or Gasping During Sleep	10-15
Nocturia (≥2 times per night)	30
Nocturnal Gastroesophageal Reflux	50-75
Morning Headache	12-18

Gottlieb DJ, et al. *JAMA*. 2020;323(14):1389-1400.

OSA – The Greatest Hits Album

- Daytime Sleepiness
- Mood Disorders
- Heart Burn
- Obesity
- Diabetes
- Sexual Dysfunction
- Nocturia



- Stroke
- Hypertension
- Irregular Heart Rhythms
- Coronary Artery Disease
- Heart Failure
- Blood Clots
- Sudden Cardiac Death

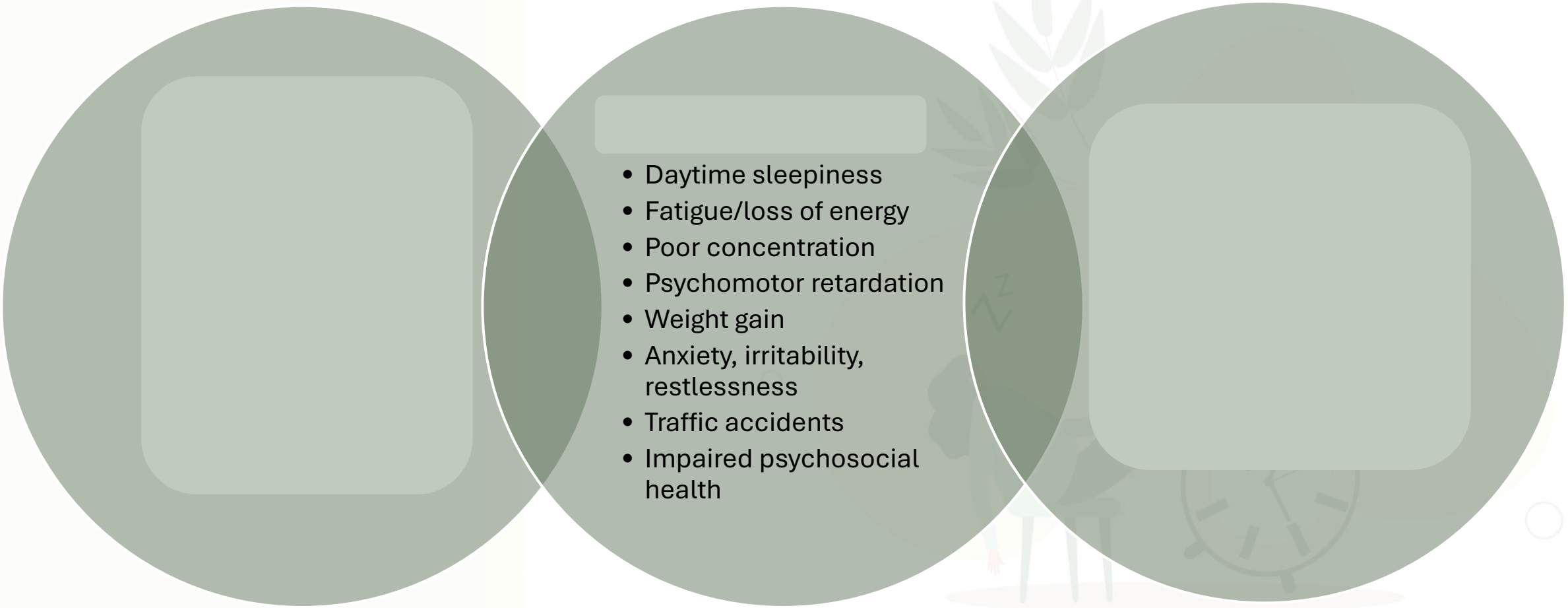
Prevalence of Excessive Daytime Sleepiness in Comorbid Psychiatric Disorders

Depression (MDD)	• Sleep difficulty in up to 90% with MDD; **1 in 3** will describe EDS
Bipolar Disorder	• **Manic phase:** Decreased need for sleep, less EDS manifestation • **Depressed phase:** EDS
Anxiety (GAD)	• **> 50%** experience sleep difficulties and subsequent **EDS**
PTSD	• Difficulty initiating and maintaining sleep, nightmares = less sleep **= EDS**
Schizophrenia	• Shifts in circadian rhythm = EDS
Alcoholism	• Poor sleep quality/fragmentations/deprivation = EDS

PTSD = posttraumatic stress disorder.

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

Is it OSA or is it Depression?



Jehan S, et al. *Sleep Med Disord*. 2017;1(3):00012. Ejaz SM, et al. *Innov Clin Neurosci*. 2011;8(8):17-25.

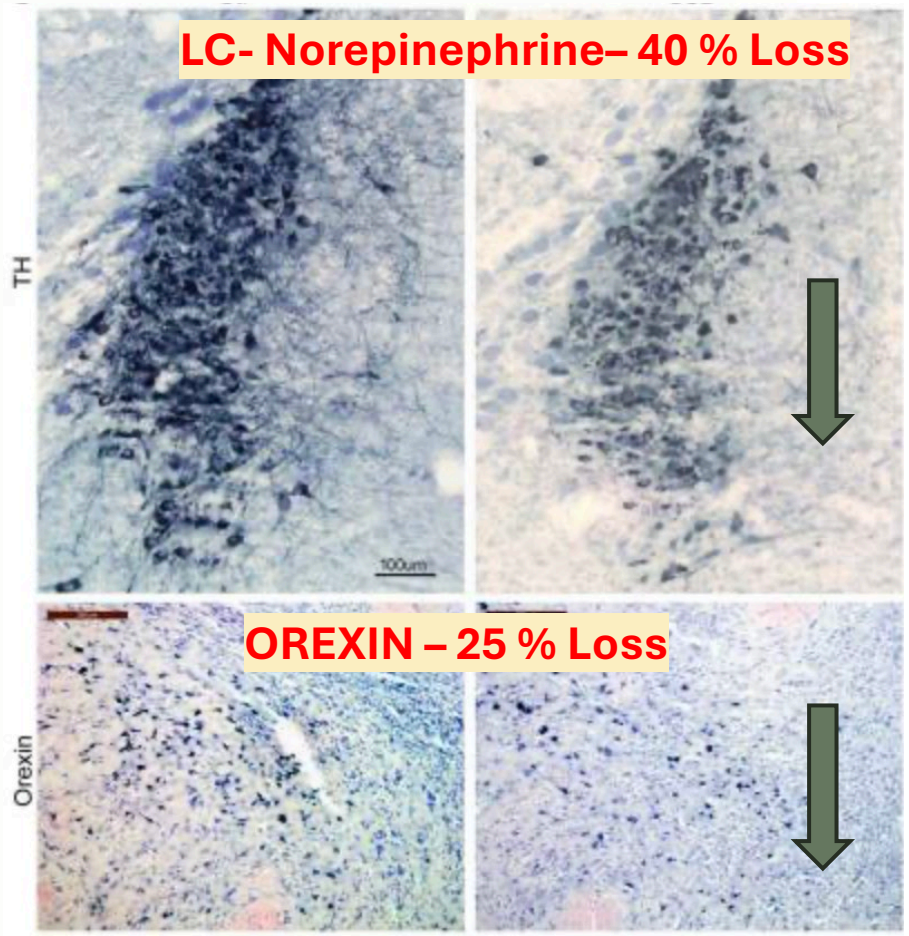
Psychiatric Symptoms + OSA "Driving with Hand Brakes up"

Psychiatric Symptom	Absence of OSA (Prevalence/Severity)	Presence of OSA (Prevalence/Severity)
Depression	Lower prevalence (General population: **5%-10%)**	Higher prevalence **(22%-63%)**
Anxiety	General adult population: **18%-20%**	Higher prevalence **(24%-44%)**
Cognitive Impairment	Less common/severe, especially in younger adults	Marked deficits (≈**25%** or more)
Fatigue/EDS	Occasional; less severe, not OSA-associated	Nearly universal in moderate–severe OSA
Emotional Lability	Less frequent/severe	Frequently reported, often significant
Irritability	Less reported; often due to other causes	More common with OSA & sleep fragmentation
Libido Disorder	Less common, unless other illnesses are present	More common, especially with comorbidities

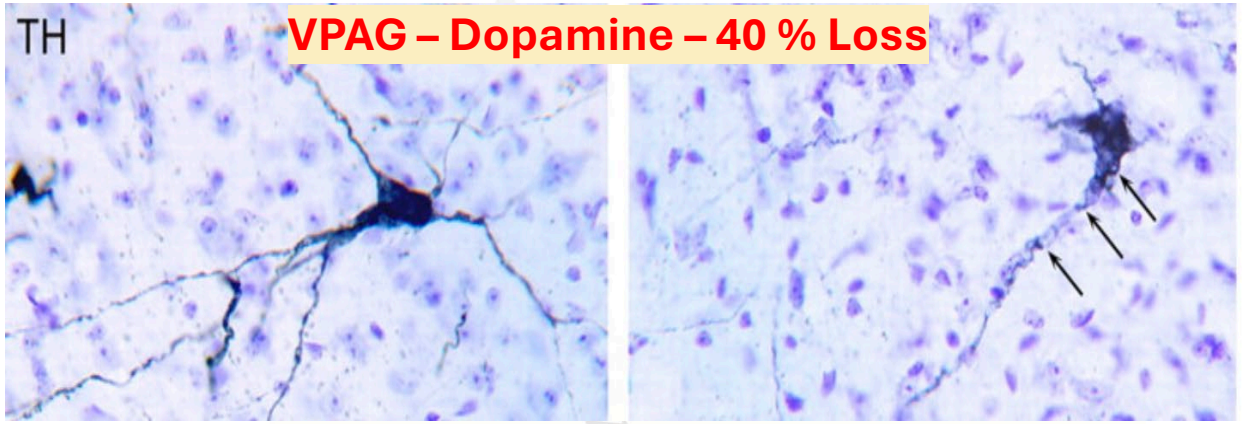
Gharsalli H, et al. *Tunis Med*. 2022;100(7):525-533. Sharafkhaneh A, et al. *Sleep*. 2005;28(11):1405-1411. Beebe DW, et al. *Sleep*. 2003;26(3):298-307. Lal C, et al. *Ann Am Thorac Soc*. 2022;19(8):1245-1256. Krysta K, et al. *J Neural Transm (Vienna)*. 2016;124(suppl 1):187-201.

Possible OSA-Related Neuronal Damage – Brain Injury Mechanisms

CHRONIC SLEEP FRAGMENTATION 14 weeks



INTERMITTENT HYPOXIA 8 weeks

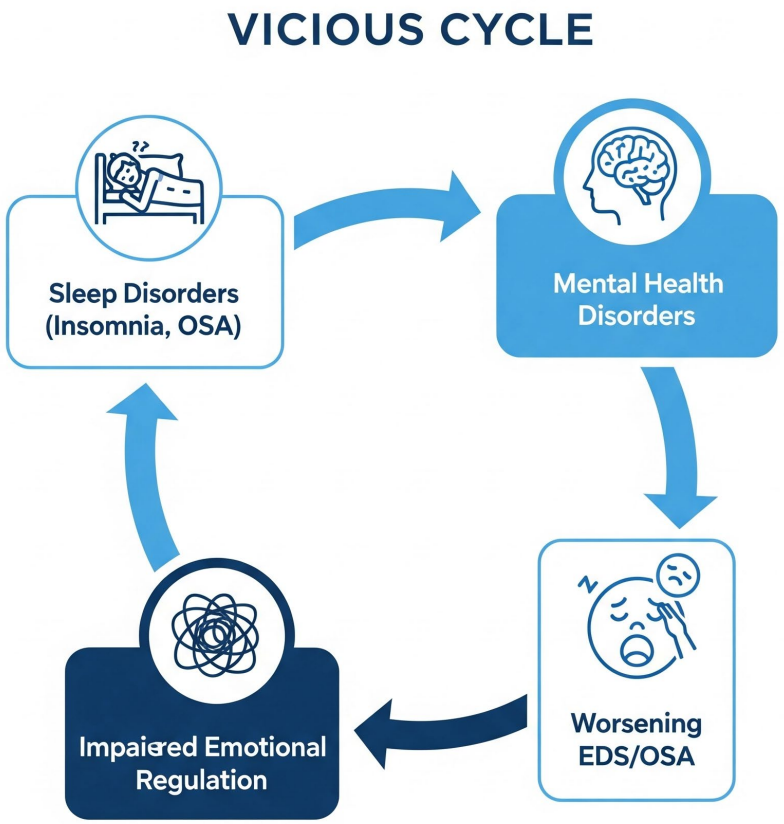


Wake remained Impaired – 6 months of Normoxemia

LC = locus ceruleus; VPAG = ventral periaqueductal gray.

Zhu Y, et al. *Front Neurol*. 2015;6:109. Zhu Y, et al. *Neurosci*. 2007;27(37):10060-10071.

Key Learning Points



- OSA – Grossly Underdiagnosed
- OSA Prevalence > Major Depression
- OSA – Broad Impact – More than meets the Ear
- Neuronal damage may be partly **irreversible –** Time is Tissue!
- OSA/EDS are *Hand Brakes* to Mental Health Therapy Outcomes

Assessing Patients for EDS and OSA

In the Context of Mental Illness

Sleep History/Logs, Partner Report, Wearables

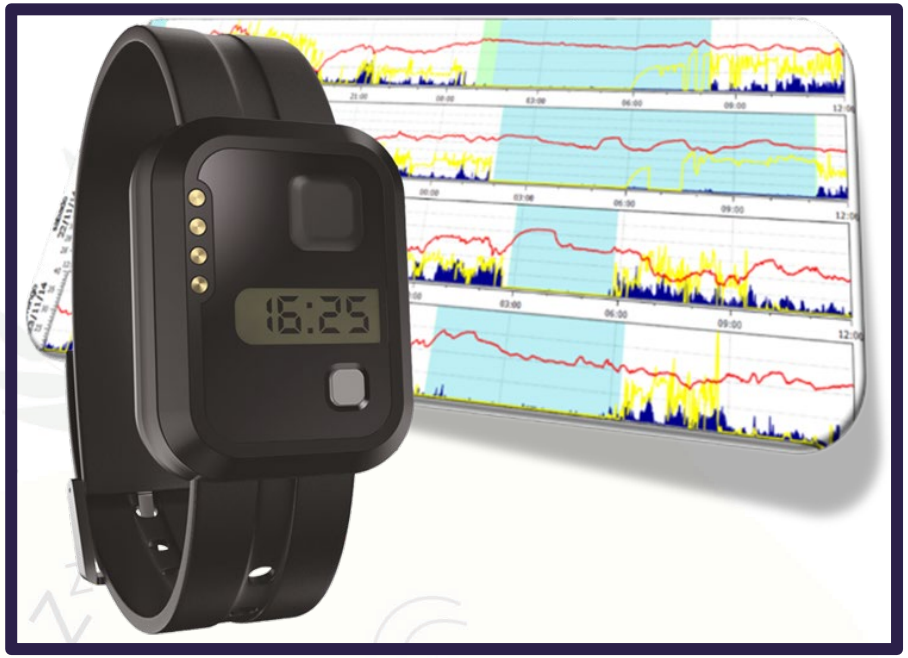
TWO WEEK SLEEP DIARY

AASM | SLEEP EDUCATION

INSTRUCTIONS:
(1) Write the date, day of the week, and type of day: Work, School, Day Off, or Vacation. **(2)** Put the letter "C" in the box when you have coffee, cola or tea. Put "M" when you take any medicine. Put "A" when you drink alcohol. Put "E" when you exercise. **(3)** Put a "B" in the box to show when you go to bed. Put a "Z" in the box that shows when you think you fell asleep. **(4)** Put a "Z" in all the boxes that show when you are asleep at night or when you take a nap during the day. **(5)** Leave boxes empty to show when you wake up at night and when you are awake during the day.

SAMPLE ENTRY BELOW: On a Monday when I worked, I jogged on my lunch break at 1 PM, had a glass of wine with dinner at 6 PM, fell asleep watching TV from 7 to 8 PM, went to bed at 10:30 PM, fell asleep around Midnight, woke up and couldn't got back to sleep at about 4 AM, went back to sleep from 5 to 7 AM, and had coffee and medicine at 7 AM.

Date	Day of the week	Type of Day (Work, School, Day Off, Vacation)	Noon	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	Midnight	1 AM	2 AM	3 AM	4 AM	5 AM	6 AM	7 AM	8 AM	9 AM	10 AM	11 AM
sample	Mon.	Work		E					A	Z			B		Z	Z	Z	Z		Z	Z	C M				
week 1																										
week 2																										



STOP BANG Questionnaire

High risk of OSA: Yes 5 - 8
Intermediate risk of OSA: Yes 3 - 4
Low risk of OSA: Yes 0 - 2

STOP

Do you **SNORE** loudly (louder than talking or loud enough to be heard through closed doors)?	Yes	No
Do you often feel **TIRED**, fatigued, or sleepy during daytime?	Yes	No
Has anyone **OBSERVED** you stop breathing during your sleep?	Yes	No
Do you have or are you being treated for high blood **PRESSURE**?	Yes	No

BANG

BMI > 35kg/m2?	Yes	No
AGE 50 years old?	Yes	No
NECK circ > 16 inches (40cm)?	Yes	No
GENDER: Male?	Yes	No

Specificity – 40 %
Sensitivity – 90 %

Chung F, et al. *Anesthesiology*. 2008;108:812-821.

Epworth Sleepiness Scale

ESS: USED TO MEASURE EXCESSIVE DAYTIME SLEEPINESS (EDS) IN ADULTS

0 Would *never* doze | **1** *Slight* chance of "dozing" | **2** *Moderate* chance of "dozing" | **3** *High* chance of "dozing"

SITUATION	CHANCE OF DOZING			
Sitting and reading	0	1	2	3
Watching TV	0	1	2	3
Sitting inactive in a public place (eg, a theater or meeting)	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon when circumstances permit	0	1	2	3
Sitting and talking with someone	0	1	2	3
Sitting quietly after a lunch without alcohol	0	1	2	3
In a car, while stopped for a few minutes in traffic	0	1	2	3

Max Score – 24

- **10** Abnormal
- **16** VERY SLEEPY

Johns MW. *Sleep*. 1991;14(6):540-545.

Sleep Testing – Mic Check 1,2,3

➢Polysomnography – In lab ~ 8 hr

- ✓ EEG (# 8)
- ✓ EOG
- ✓ EKG
- ✓ Leg
- ✓ Flow x2
- ✓ Pulse Ox
- ✓ Effort x 2
- ✓ Video Cam.
- ✓ ETCO2

➢Home Sleep Apnea Test

- ✓ Pulse Ox
- ✓ Effort belt up to 2 ; Flow x 1
- ✓ +/- Position
- ✓ TRUE SLEEP – Not measured

EEG = electroencephalogram; EOG = electrooculogram; EKG = electrocardiogram; ETCO2 = end-tidal carbon dioxide.

Recognizing Compensatory Behaviors

Often describe it as “Fatigued”

Tired is a TROPHY

Sleepy is a SIN!

Referring Patients to Sleep Specialists

High-Risk Patients

Intolerant of OSA therapies

Sleepy despite compliance with PAP therapies

Sleepy despite adequate quantity of sleep & absence of OSA

Sleepiness not explained by other etiologies

Psychiatric disorders not responding to therapies (think of the sleep disorder **hand brake**!)

PAP = positive airway pressure.

Differential Diagnoses of EDS

OSA	EDS	Disturbed Nocturnal Sleep	Snoring / Airway obstructions	Morning Headaches, Unrefreshing Sleep
MDD	EDS	**Co Occurs with** fatigue, low energy, & motivation.	Sleep Problems tied to mood symptoms.	
IH	Persistent EDS despite **adequate sleep** duration	CONSLIDATED **sleep** duration	Sleep Inertia, LONG Unrefreshing NAPS	**No Cataplexy**
ADHD	Atypical EDS	Coupled with focus, attention & motivation issues		
NARCOLPESY	EDS	Sudden Sleep Attacks, Cataplexy TYPE 1	Fragmented night sleep, rapid onset of REM sleep in naps	

Key Learning Points

1 Billion affected with OSA worldwide

Untreated sleep disorders increase **precipitation** of mental health disorders

(**SHINGLES …PAIN – RASH – PAIN Cycle**)

High prevalence of **overlap of symptoms** OSA/mental health disorders makes OSA recognition challenging

Untreated/Sub-optimally treated OSA – **worsens** mental health conditions & **impairs** RESPONSE to treatments

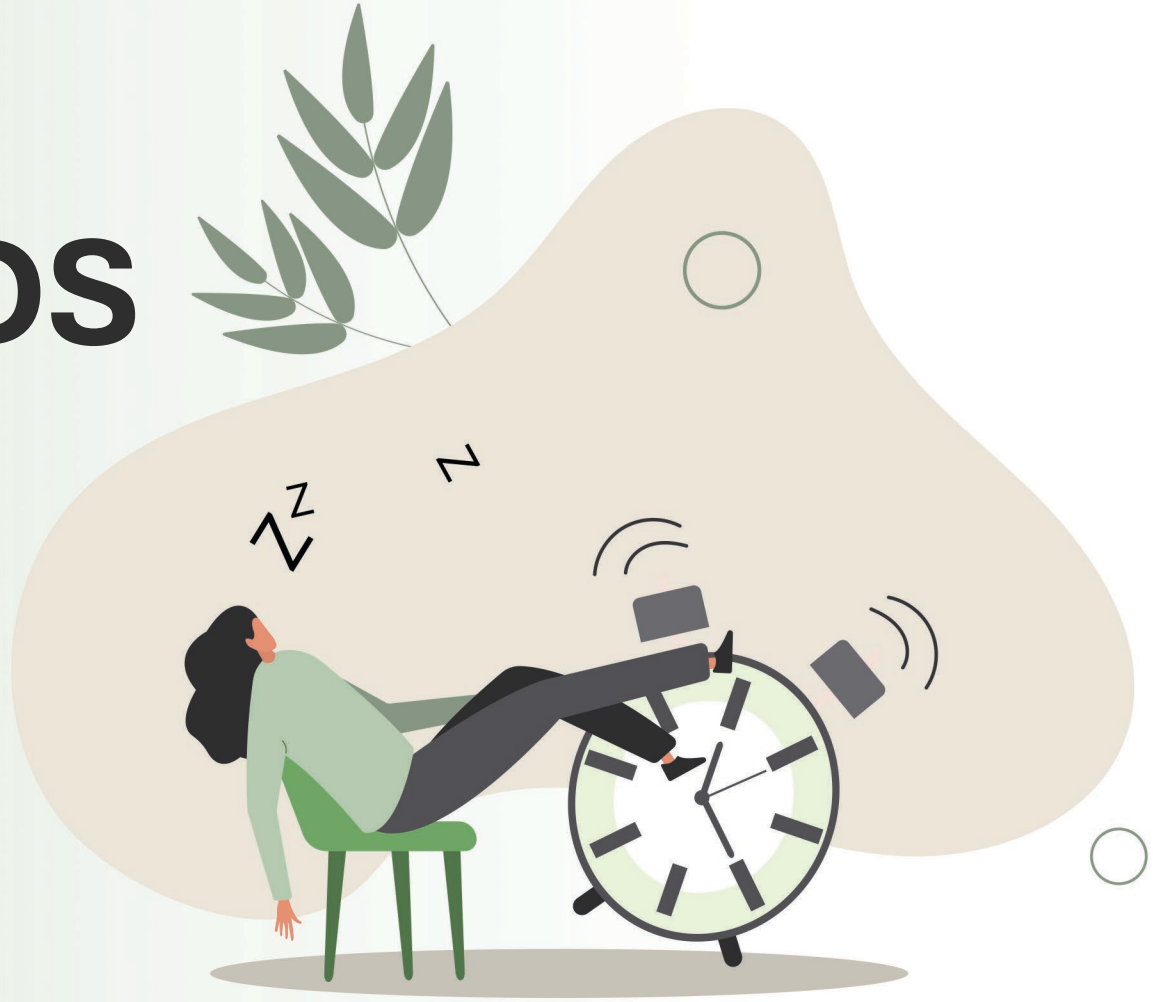
Don’t sleep on sleep disorders! (bidirectionality)

IGNORE THE SNORE NO MORE

Benca RM, et al. *J Clin Psychiatry*. 2023;84(2):22r14521.

Traditional Treatments for EDS and OSA

In the Context of Mental Illness



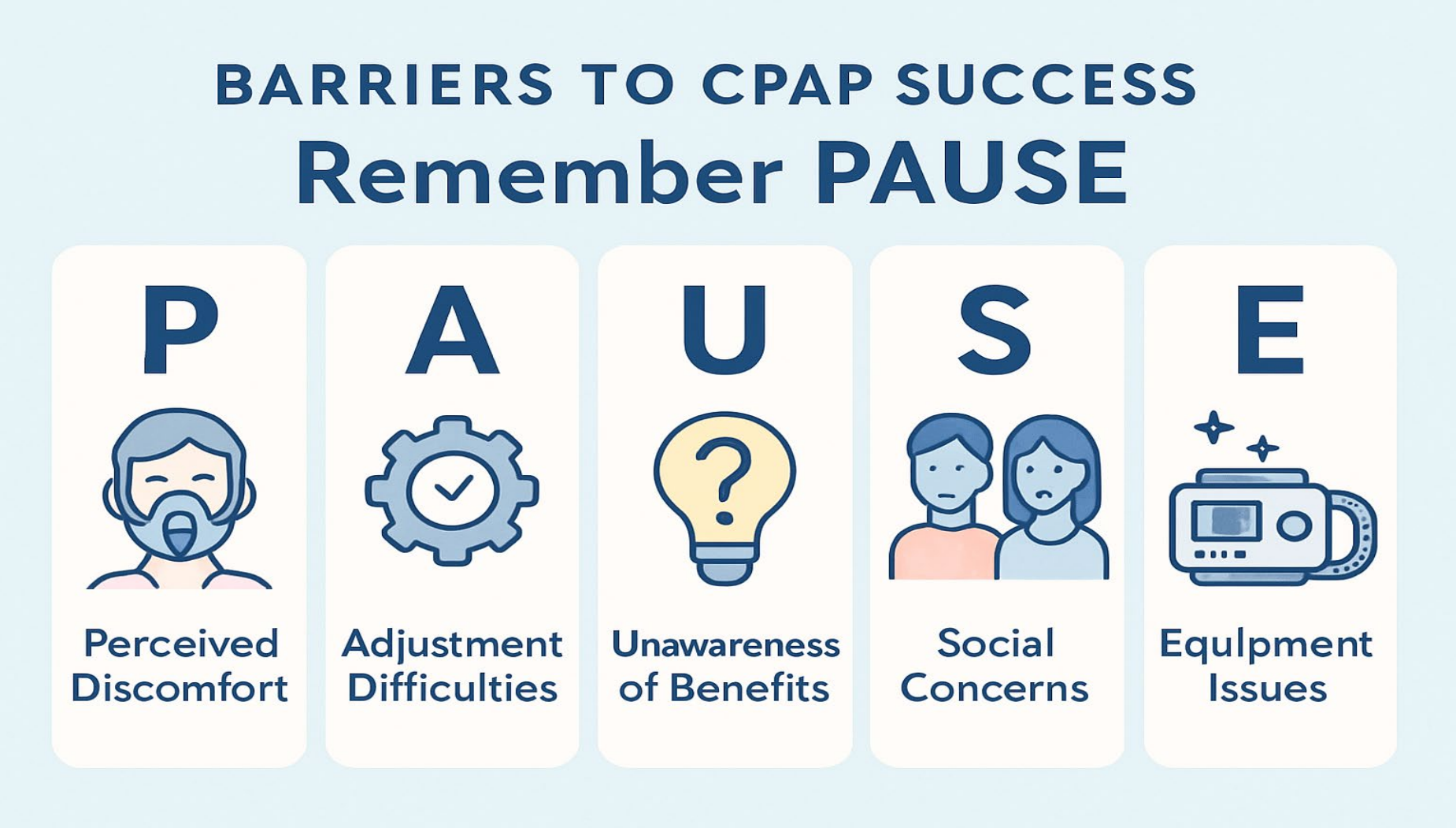
Positive Airway Pressure in 2025

Many, Many Flavors to Choose From

Resmed, Phillips, HDMZ

- 100 interfaces
- Downloadable
- Auto PAP / Humidity
- 40 years since invention

CPAP Adherence Issues Are Common

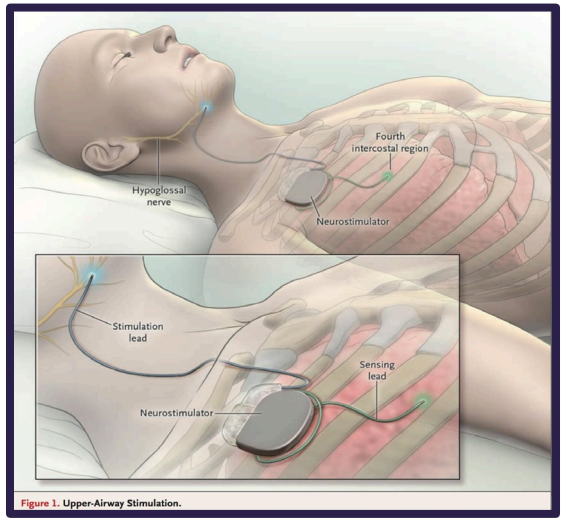


P A U S E and Troubleshoot one by one

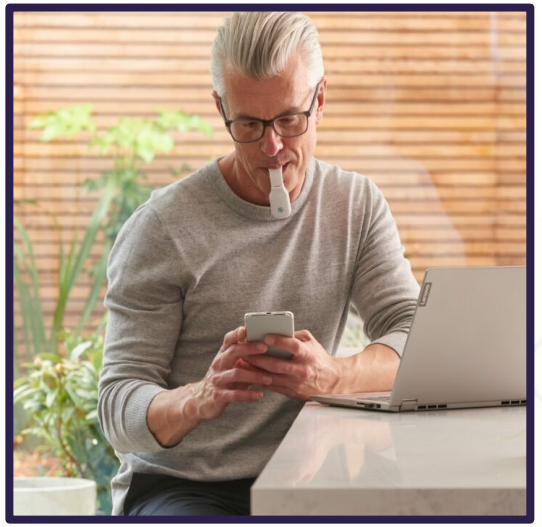
CPAP = continuous positive airway pressure.
Singh A, 2025 unpublished

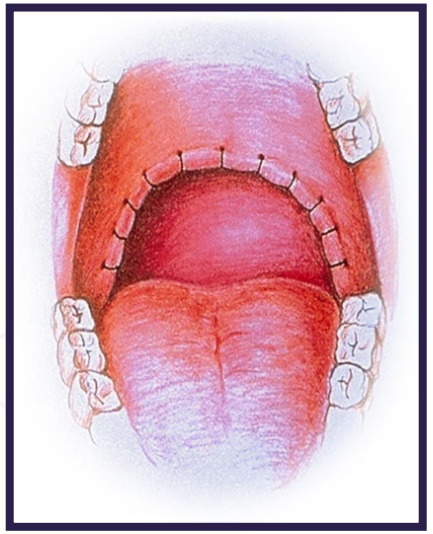
OSA Treatments: Non-PAP Options

Oral Appliance therapy



Hypoglossal Nerve Stim





Tongue Neuromodulation

- Weight Loss (20 % —> 50 %)
- ZEPBOUND® Approved for OSA Dec 2024 – GLP/GIP (Tirzepatide)

GLP = glucagon-like peptide; GIP = glucose-dependent insulinotropic polypeptide.

CPAP Reliably Resolves Snoring & Airway Obstruction ...BUT Sleepiness Can Persist Despite CPAP Usage

52%

of OSA patients on CPAP (2-7 hrs) still have EDS

34%

of OSA patients on CPAP ≥5 hrs/night still have EDS

EDS can persist even with airway therapy due to compromised neuronal activity.

Sleepiness is a critical patient-reported outcome.
- American Academy of Sleep Medicine

Antic NA, et al. *Sleep*. 2011;34(1):111-119.

Managing Residual EDS in OSA

Ensure **proper adherence** to sleep hygiene habits

Reduce sedating medications in the evening
which can worsen OSA

Optimize PAP adherence
(Minimum ≥4 hours/night for ≥70% of days)

~50% with OSA may have **residual EDS**
despite any amount of PAP use

When the above are insufficient,
a trial of **pharmacotherapy** may be considered!

Kribbs NB, et al. *Am Rev Respir Dis*. 1993;147(4):887-895. Gasa M, et al. *J Sleep Res*. 2013;22(4):389-397. Ballard RD. *J Fam Pract*. 2008;57(8 Suppl): S24-S30. Garnock-Jones KP, et al. *CNS Drugs*. 2009;23(9):793-803. Black JE, et al. *J Clin Sleep Med*. 2010;6(5):458-466. Antic NA, et al. *Sleep*. 2011;34(1):111-119.

Treatments for EDS – Journey Thus Far

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

SWSD = shift work sleep disorder.

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

Psychostimulants for EDS in OSA

Amphetamines and Methylphenidate

1. Off-Label
2. Schedule II Drug, Habit-Forming
3. Diversion Potential
4. Need for Controlled Substance Agreements
5. Medication Shortages
6. Withdrawal Risks
7. Less Addictive, Safer Alternatives Exist

The Daffodils: Modafinil/Armodafinil

FDA-Approved Indication: EDS Due to Narcolepsy/SWSD/OSA

The Daffodils

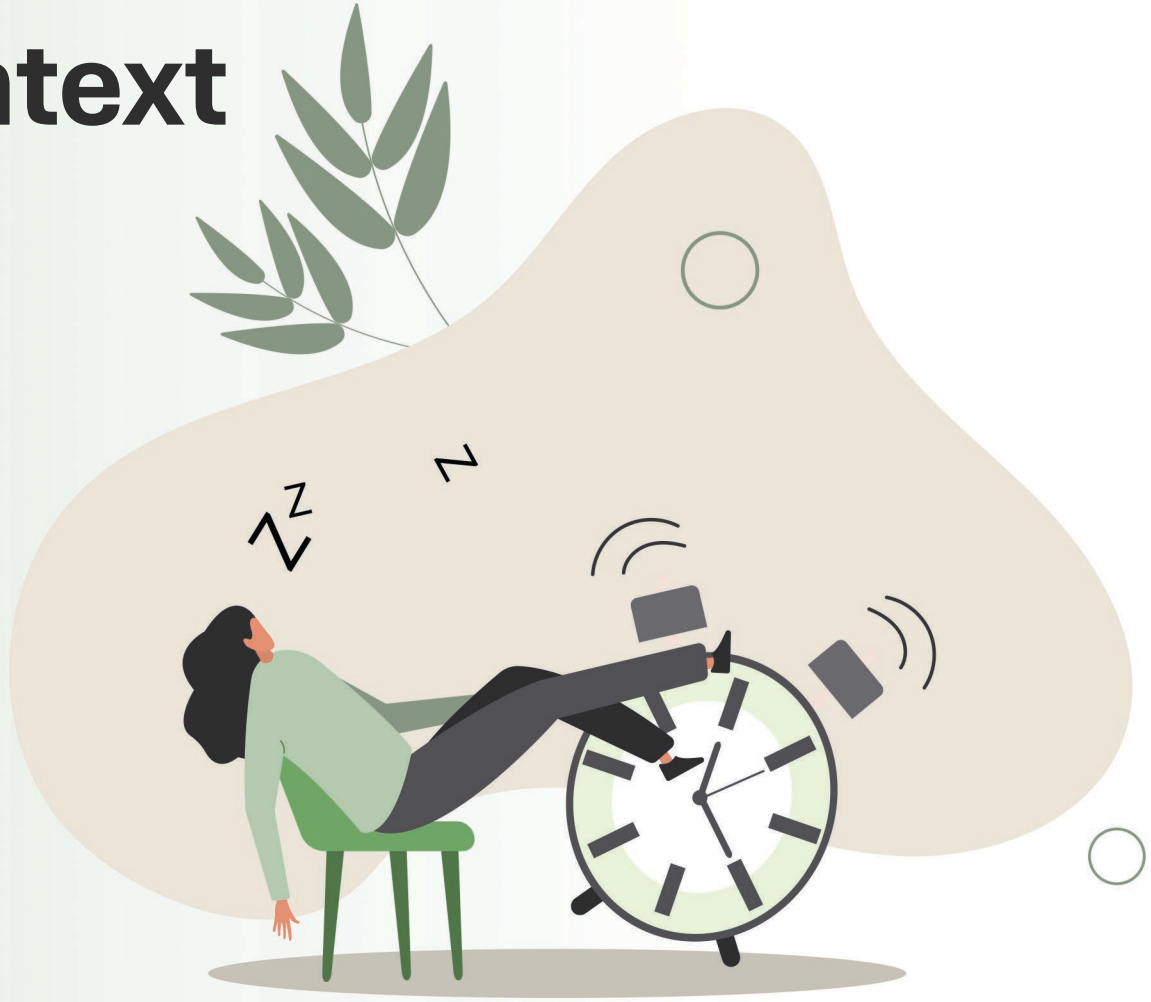
- Common adverse effects (≥5%): headache, nausea, dizziness, and insomnia
- Inhibits CYP2C19 & Induces CYP3A4/5
- Effectiveness of steroidal contraceptives may be reduced
- Potential for rare but serious rashes, such as Stevens-Johnson Syndrome

CYP = Cytochrome P450.

Modafinil and Armodafinil Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed January 10, 2023. www.accessdata.fda.gov/scripts/cder/daf/. Holfinger S, et al. *Journal of Clinical Sleep Medicine*. 2018;14(5):885-887

Novel Treatments for EDS Due to OSA in the Context of Mental Health Conditions

Nonstimulant Monoamine Reuptake Inhibition



Introduction to Solriamfetol

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

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

t_{max}=2 hrs
$t_{½}$=7 hrs

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

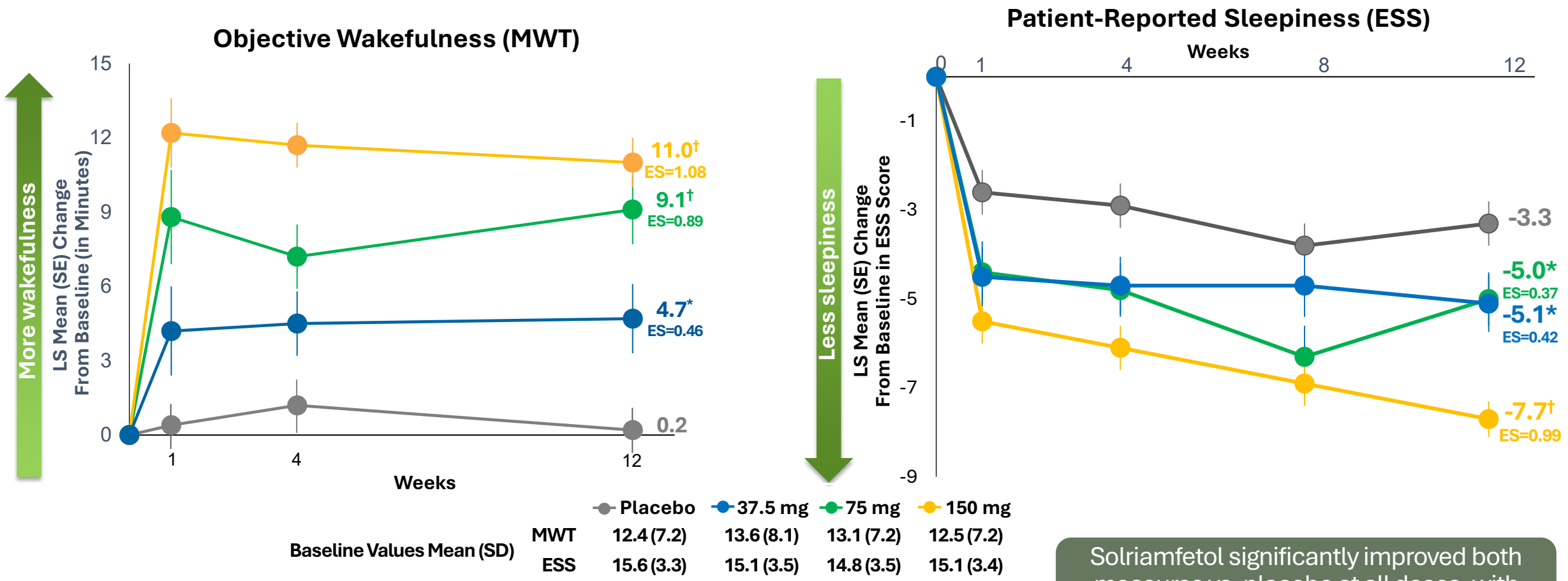
Predominantly excreted unchanged in the urine; No hepatic metabolism; No induction or inhibition of CYP or other metabolic enzymes

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

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

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

Solriamfetol Improves Wakefulness and Reduces Sleepiness



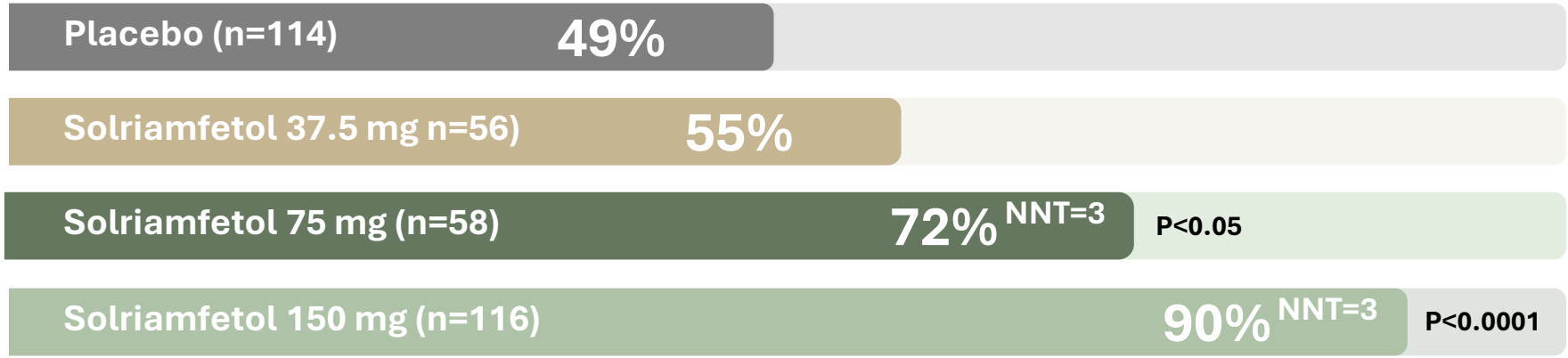
Baseline Values Mean (SD)	Placebo	37.5 mg	75 mg	150 mg
MWT	12.4 (7.2)	13.6 (8.1)	13.1 (7.2)	12.5 (7.2)
ESS	15.6 (3.3)	15.1 (3.5)	14.8 (3.5)	15.1 (3.4)

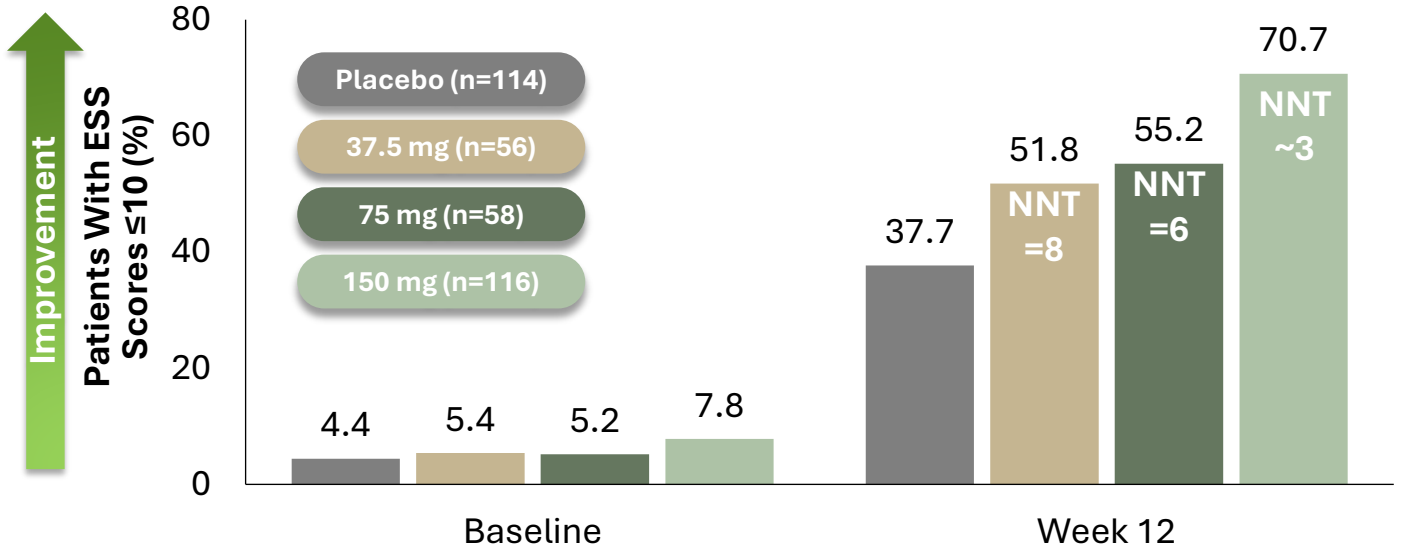
Solriamfetol significantly improved both measures vs. placebo at all doses, with large effect sizes at the 150 mg dose

*P<0.05 versus placebo; †P<0.0001 versus placebo.
MWT = maintenance of wakefulness; ESS = Epworth Sleepiness Scale; LS = least squares; SE = standard error.
Solriamfetol Prescribing Information. Jazz Pharmaceuticals 2021. Schweitzer PK, et al. *Am J Respir Crit Care Med*. 2019;199(11):1421-1431.

Additional Measures of Solriamfetol Efficacy

Percent of patients who reported feeling better on the PGI-C





Percentage of patients with ESS scores within normal range (post-hoc analysis)

PGI-C = Patient Global Impression of Change; NNT = number needed to treat.

Chepke C. et al. Solriamfetol for Excessive Sleepiness in Narcolepsy and Obstructive Sleep Apnea: Effect Sizes and Numbers Needed to Treat or Harm. Poster Presented at Psych Congress 2023; September 6–10, 2023; Nashville, TN, USA. Schweitzer PK, et al. *Am J Respir Crit Care Med*. 2019;199(11):1421-1431.

Tolerability of Solriamfetol in Pooled 12-Week OSA Studies

Adverse Reactions ≥2% and ≥Placebo

	Placebo (%)	Solriamfetol (%) (all doses)
Nausea	6%	8%
Decreased appetite	1%	6%
Diarrhea	1%	4%
Anxiety	1%	4%
Irritability	0	3%
Palpitations	0	3%
Abdominal pain	2%	3%
Dry mouth	2%	3%
Feeling jittery	0	3%
Chest discomfort	0	2%
Hyperhidrosis	0	2%
Dizziness	1%	2%

Discontinuation due to adverse reactions (all doses)

Solriamfetol	Placebo
3% (n=11)	<1% (n=1)

No effect on QTc;
May increase BP and HR

Mean (95% CI)	Placebo	37.5 mg	75 mg	150 mg
ΔSBP	**1.7** (-1.4, 4.9)	**4.6** (-1.1, 10.2)	**3.8** (1.2, 6.4)	**2.4** (0.4, 4.4)
ΔDBP	**1.4** (-0.1, 2.9)	**1.9** (-2.3, 6.0)	**3.2** (-0.9, 7.3)	**1.8** (0.4, 3.2)
ΔHR	**1.7** (0.1, 3.3)	**1.9** (-1.9, 5.7)	**3.3** (0.6, 6.0)	**2.9** (1.4, 4.4)

BP = blood pressure; HR = heart rate; CI = confidence interval; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Solriamfetol Prescribing Information. Jazz Pharmaceuticals. 2021.

In Addition to DA and NE Reuptake Agonism, Solriamfetol Shows TAAR1 Agonism in Preclinical Studies

Solriamfetol activates TAAR1 in vitro, at clinically relevant plasma concentrations

	DAT IC_{50} µM	NET IC_{50} µM	TAAR1 EC_{50} µM (E_{max})	5-HT_{1A} IC_{50} µM
WPA or DAT/NET inhibitor				
Solriamfetol	3.21	14.4	10-16 (100%)	25
Modafinil	2.8	>100	No dose response	Unknown
Bupropion	0.26	2.79	No dose response	No functional activity
Stimulants				
(+) Amphetamine	0.041	0.023	2.8 (91%)	Unknown

Solriamfetol is a weak DA and NE reuptake inhibitor, but TAAR1 agonism can also internalize DA and NE transporters

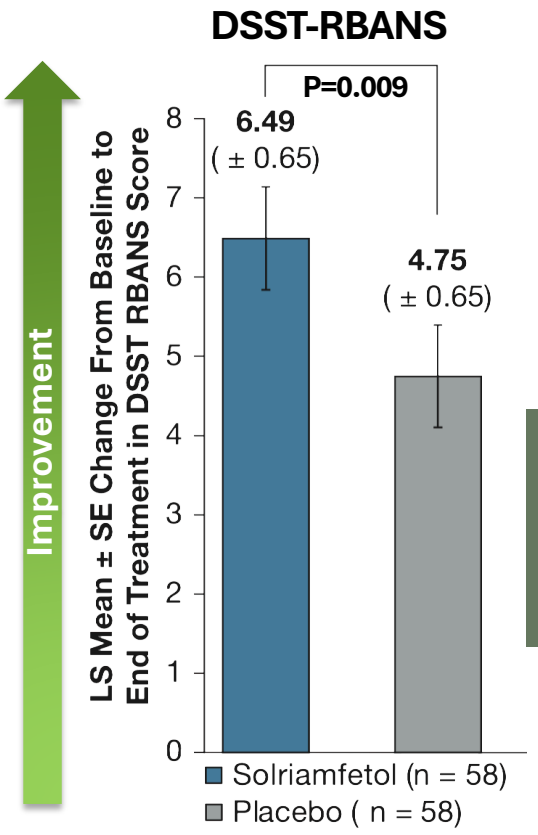
TAAR1 agonism influences wake-promoting monoamine nuclei, and enhances glutamatergic output in the PFC to increase arousal, vigilance, and attention

TAAR1 forms functional complexes with D_2 receptors and can rebalance dopaminergic tone implicated in impulsivity

TAAR = trace amine-associated receptor; 5-HT = serotonin; EC50 = half maximal effective concentration; Emax = maximal effect; DA = dopamine; NE = norepinephrine; T = transporter; IC50 = half maximal inhibitory concentration; WPA = wake-promoting agent; PFC = prefrontal cortex.

Gursahani H, et al. Preclinical Pharmacology of Solriamfetol: Potential Mechanisms for Wake Promotion. Poster Presented at Psych Congress. New Orleans, LA. Sept 17-20, 2022. Park, S et al. International Journal of Molecular Sciences 25.21 (2024): 11351. Raony Í, et al. Prog Neuropsychopharmacol Biol Psychiatry. 2022;117:110555.

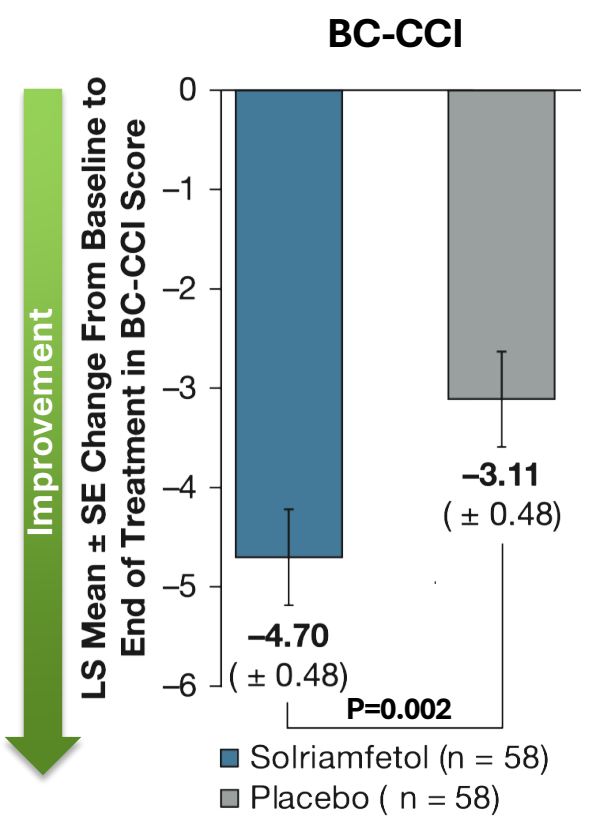
Solriamfetol May Improve Measures of Cognition in People with OSA



Solriamfetol's Effect on Cognitive Health in Apnea Participants
Randomized, Double-Blind, Crossover Study of Adults with OSA and Impaired Cognitive Function

Increases in DSST-RBANS indicate improvements in attention, processing speed, and working memory.

Decreases in BC-CCI indicate **fewer** self-reported problems with expressing thoughts, word finding, thinking, and solving problems

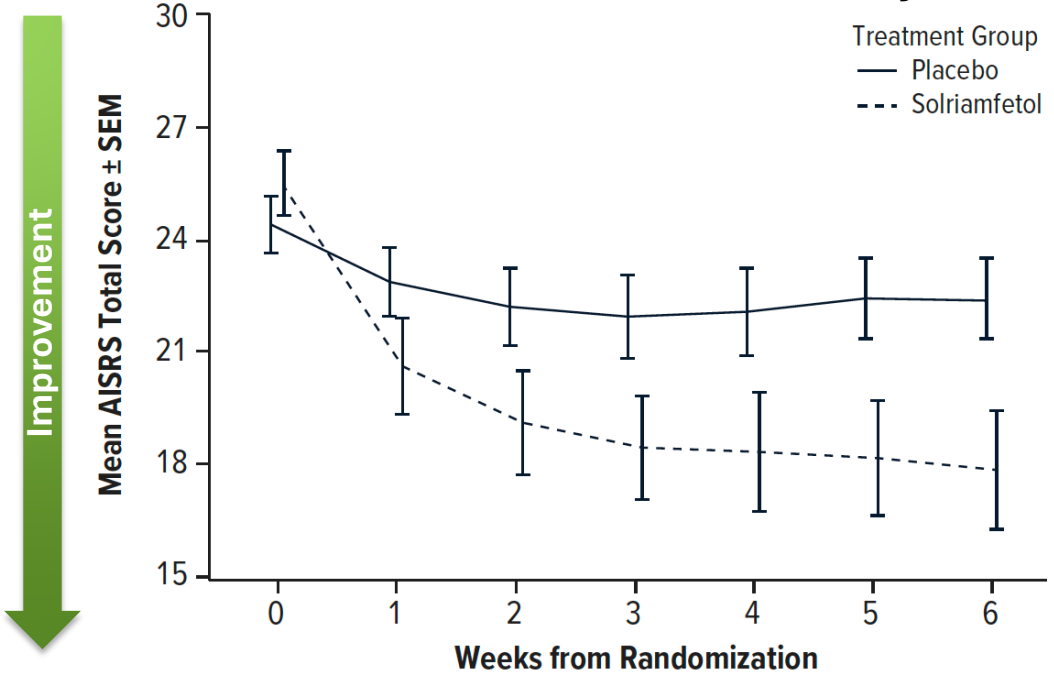


DSST RBANS = Digit Symbol Substitution Test subtest of the Repeatable Battery for the Assessment of Neuropsychological Status; BC-CCI = British Columbia Cognitive Complaints Inventory.

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

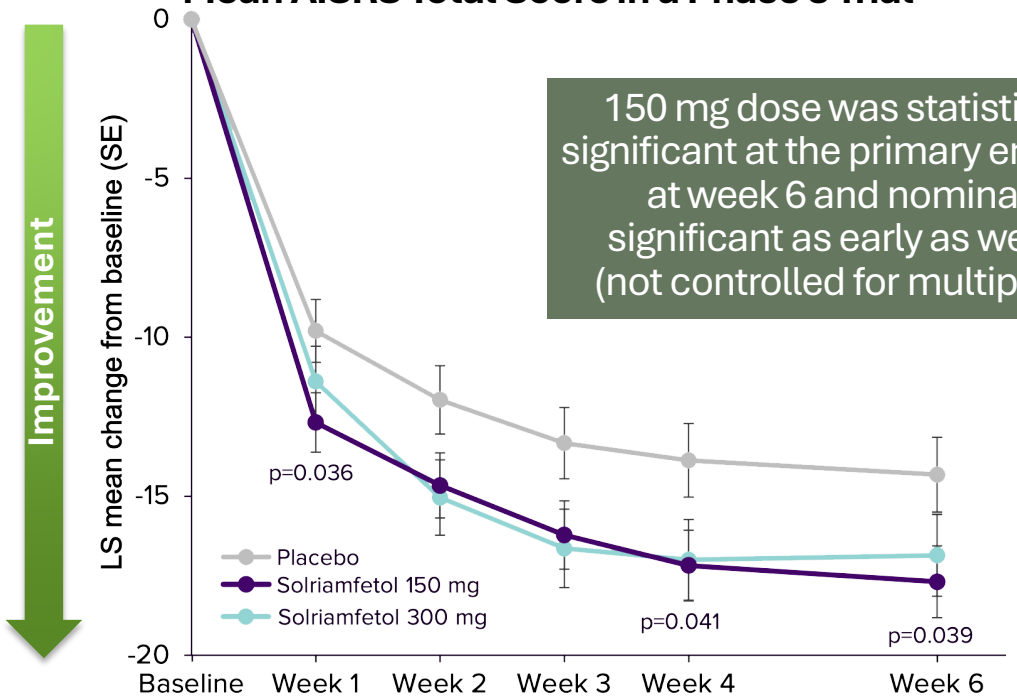
Solriamfetol Improved ADHD in Adults in Two Trials

Mean AISRS Total Score in a Pilot Study



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

Mean AISRS Total Score in a Phase 3 Trial



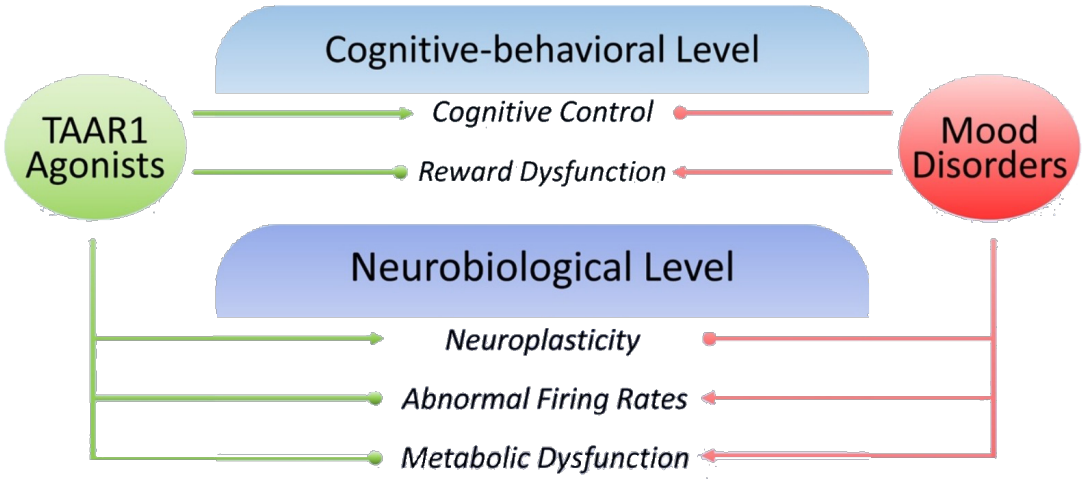
150 mg dose was statistically significant at the primary endpoint at week 6 and nominally significant as early as week 1 (not controlled for multiplicity)

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

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

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

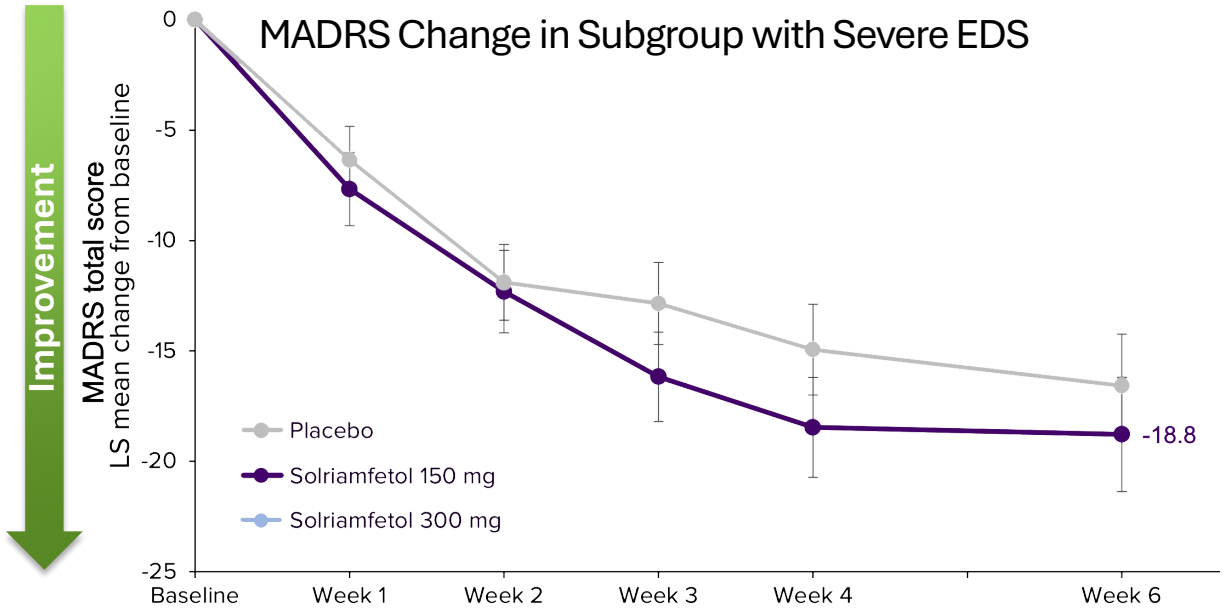
Solriamfetol May Also Have Benefits in MDD



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

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

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



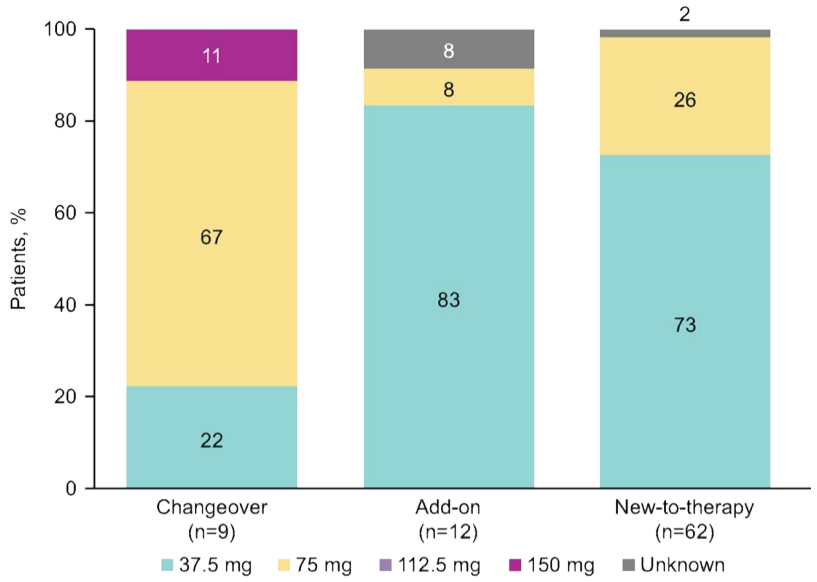
Further studies are planned in a population of MDD with EDS

MADRS = Montgomery-Åsberg Depression Rating Scale

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

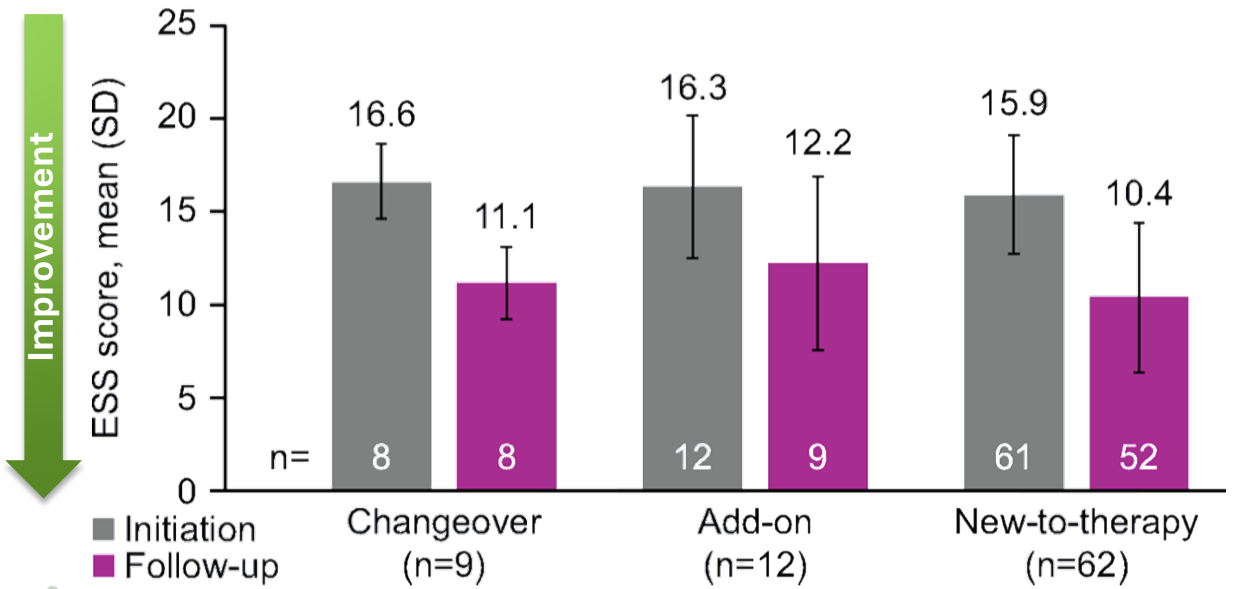
SURWEY Real-World Study of Solriamfetol for Individuals with Obstructive Sleep Apnea in Germany

Starting Doses of Solriamfetol



A dose of 37.5mg was used in most new starts or when used adjunctively, but at higher doses with switches (off-label in US)

Mean Decreases in ESS Scores With Solriamfetol



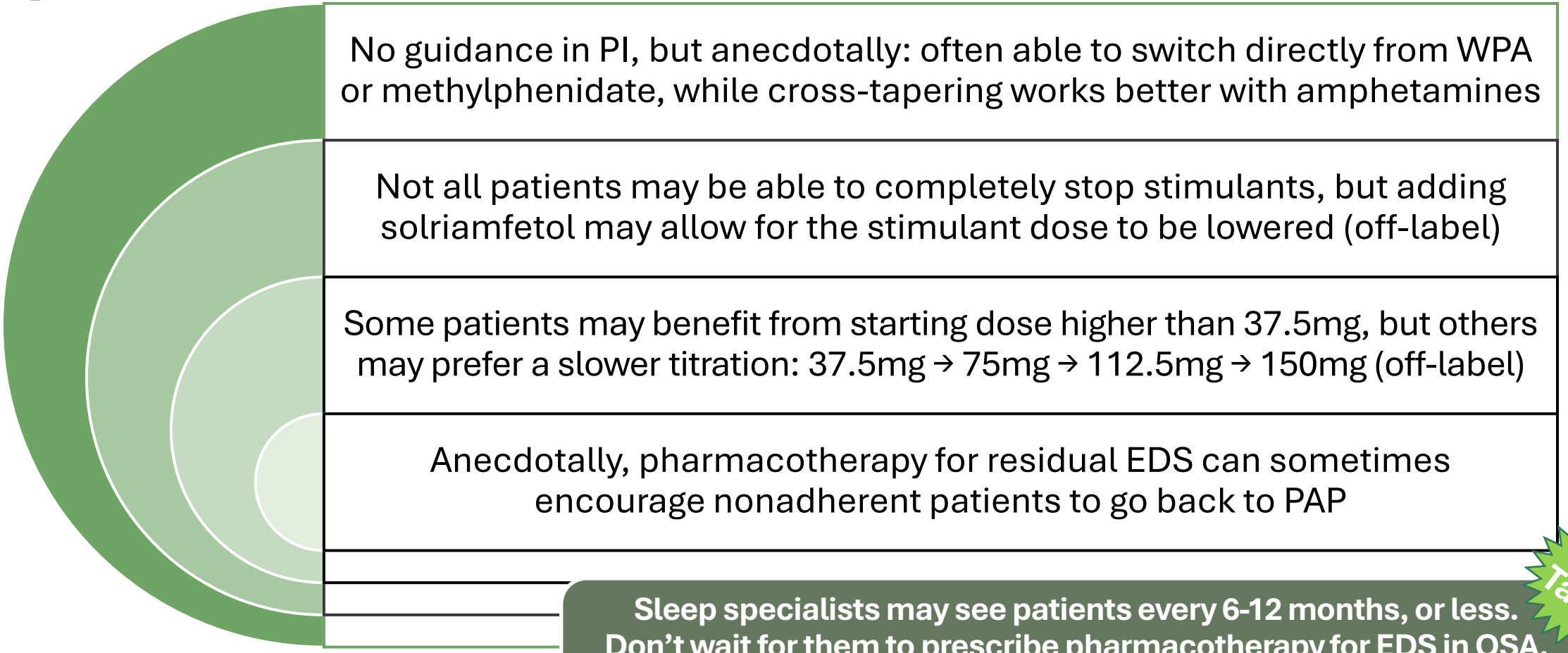
Decrease in ESS was comparable with solriamfetol used as first-line treatment, a switch, or added-on

Most common AEs: headache 9%, decreased appetite 7%, insomnia 6% (insomnia reported only in new-to-therapy subgroup)

AE = adverse event.

Winter Y, et al. *Sleep Breath*. 2025;29(1):112.

Lessons Learned from >5 Years of Clinical Experience with Solriamfetol



PI = prescribing information.

Novel Treatments for EDS due to OSA in the Context of Mental Health Conditions

Histamine-3 Receptor Inverse Agonism

Histamine-3 Receptor Inverse Agonism Is a Wake-Promoting Mechanism

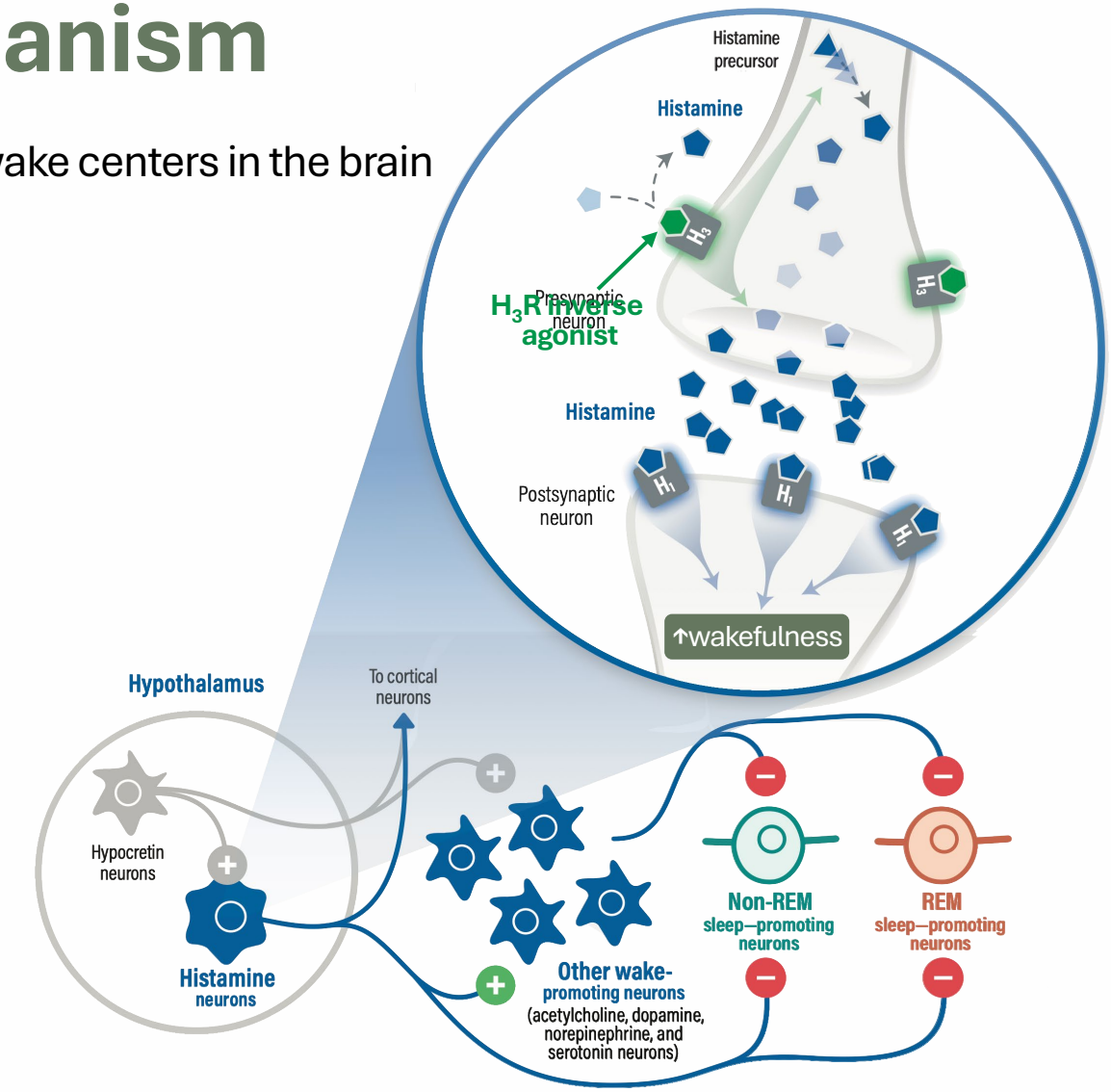
Histamine neurons from the hypothalamus project to major sleep/wake centers in the brain

H_3 presynaptic autoreceptors are found predominantly in the central nervous system

Stimulation of H_3Rs inhibit the synthesis and release of histamine

H_3R inverse agonists disinhibit these processes, enhancing histamine release

This activates postsynaptic H_1 receptors, which **promotes** wakefulness



H_3R = Histamine-3 Receptor.

Lin J-S, et al. *JPET.* 2011;336(1):17-23. Schwartz J-C. *Br J Pharmacol.* 2011;163(4):713-721. Harwell V, et al. *Medicines* 2020;7(9):55. Benarroch EE. *Neurology.* 2010;75(16):1472-1479.

Currently Available H_3R Inverse Agonist: Pitolisant

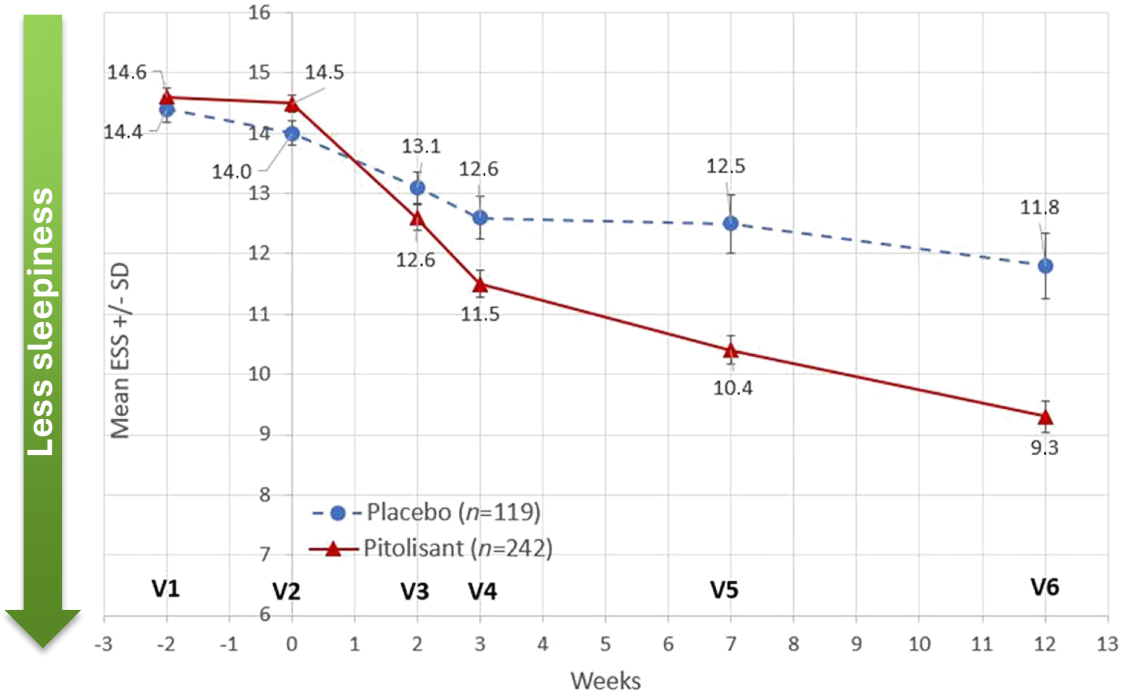
Currently approved for adults with narcolepsy in the US; Not a scheduled medication

Common adverse reactions (≥5% and 2x placebo): insomnia, nausea, anxiety

Centrally acting antihistamines reduce effectiveness

Multiple positive ph 2 /3 studies in EDS d/t OSA globally, and Pitolisant is approved for EDS d/t OSA in Europe

Pitolisant in EDS due to OSA



Pipeline Preview!

Samelisant (SUVN-G3031)

- Positive phase 2 for narcolepsy types I and II
- Phase 2 studies for cognitive disorders are planned

d/t=due to.

Pitolisant PI. Harmony Biosciences, 2021. Dauvilliers Y, et al. *Am J Respir Crit Care Med*. 2020;201(9):1135-1145. Dauvilliers, Y, et al. *J Sleep Res*. 2025;34(3):e14373. Nirogi, R, et al. *J Psychopharmacol*. 2021;35(6):713-729.

Novel Treatments for EDS due to OSA in the Context of Mental Health Conditions

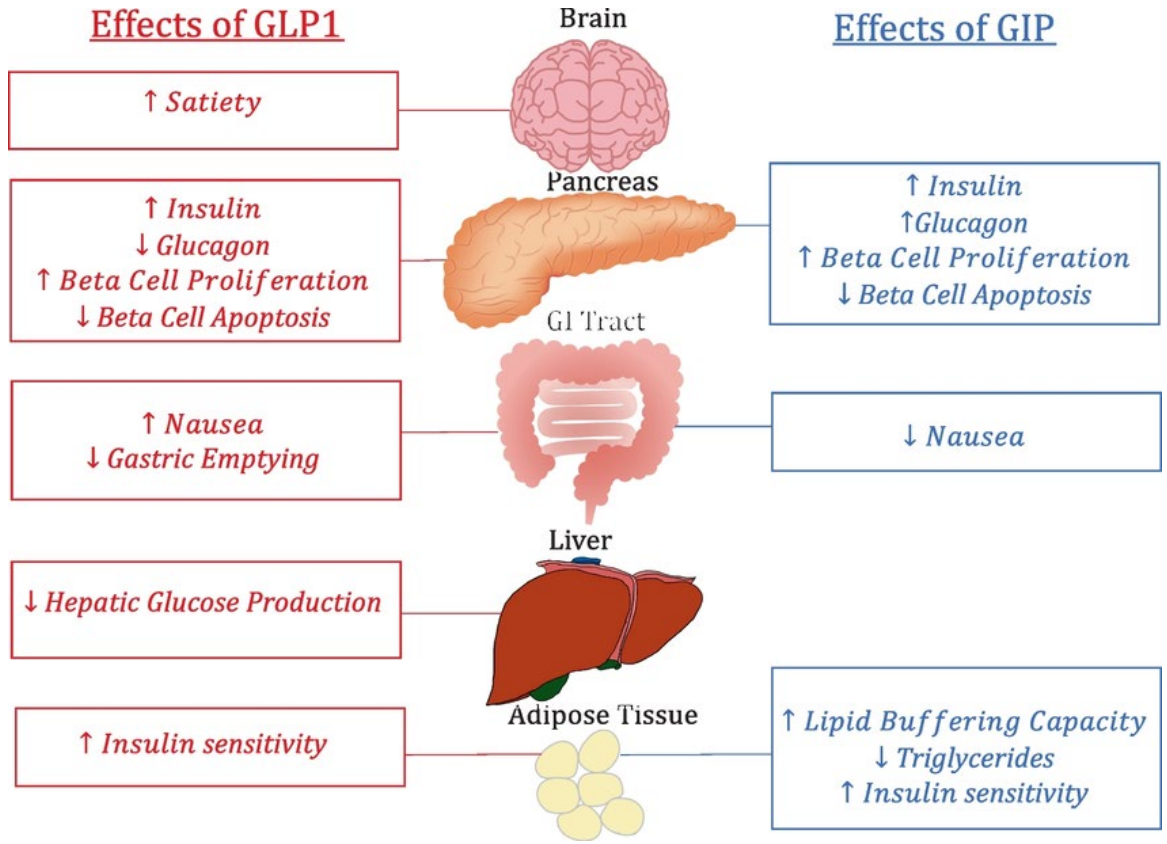
Incretin-Based Treatments

Tirzepatide Is the First Medication Approved for the Treatment of Obstructive Sleep Apnea

Tirzepatide is a **GLP-1** and **GIP** receptor agonist approved to treat moderate to severe OSA in adults with obesity

Both GIP receptors and GLP-1 receptors are found in areas of the brain involved in appetite regulation.

Animal studies show that tirzepatide distributes to and activates neurons in brain regions involved in regulation of appetite and food intake.

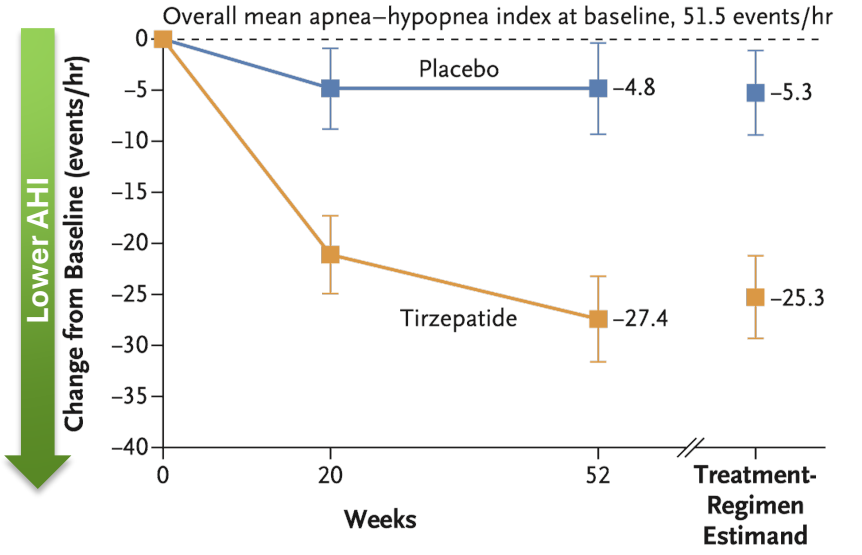


Coskun T, et al. *Mol Metab*. 2018;18:3-14. Andraos J, et al. *Rev Endocr Metab Disord*. 2023;24(6):1089-1101. Schneck K, Urva S. *CPT Pharmacometrics Syst Pharmacol*. 2024;13(3):494-503. Tirzepatide Prescribing Information. Drugs@FDA: Accessed 8.20.25. www.accessdata.fda.gov/scripts/cder/daf/.

Clinical Evidence for Tirzepatide in Two Samples of Adults with OSA and Obesity

Participants on PAP at Baseline

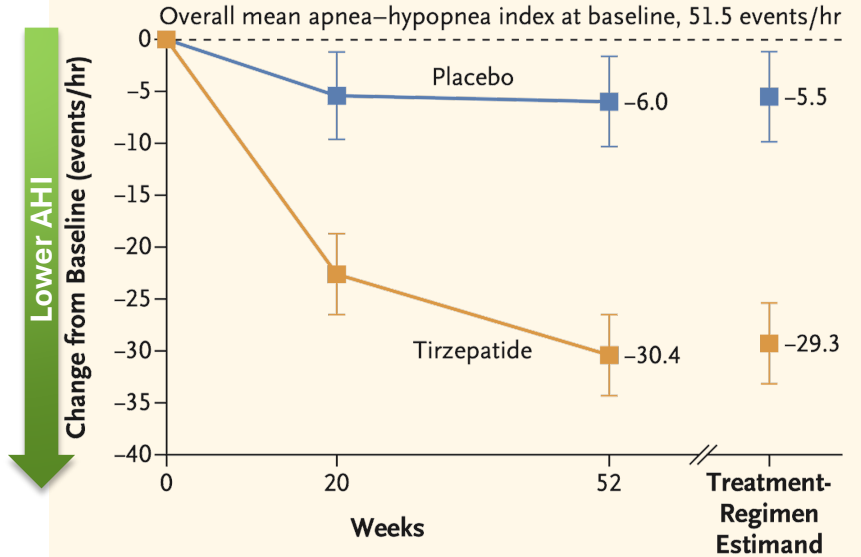
Change in Apnea–Hypopnea Index in Trial 1 (efficacy estimand)



	Tirzepatide	Placebo
% wt change	−17.7%	−1.6%
Remission or asymptomatic	42.2%	28.7%

Participants not on PAP at Baseline

Change in Apnea–Hypopnea Index in Trial 2 (efficacy estimand)



	Tirzepatide	Placebo
% wt change	−19.6%	−2.4%
Remission or asymptomatic	50.2%	33.2%

Positive secondary outcomes:

- Significant weight loss
- Less daytime sleepiness *(B/L ESS 10.5 study 1, 10.0 study 2)*
- Lower inflammation (hsCRP) and blood pressure
- Reduced hypoxic burden

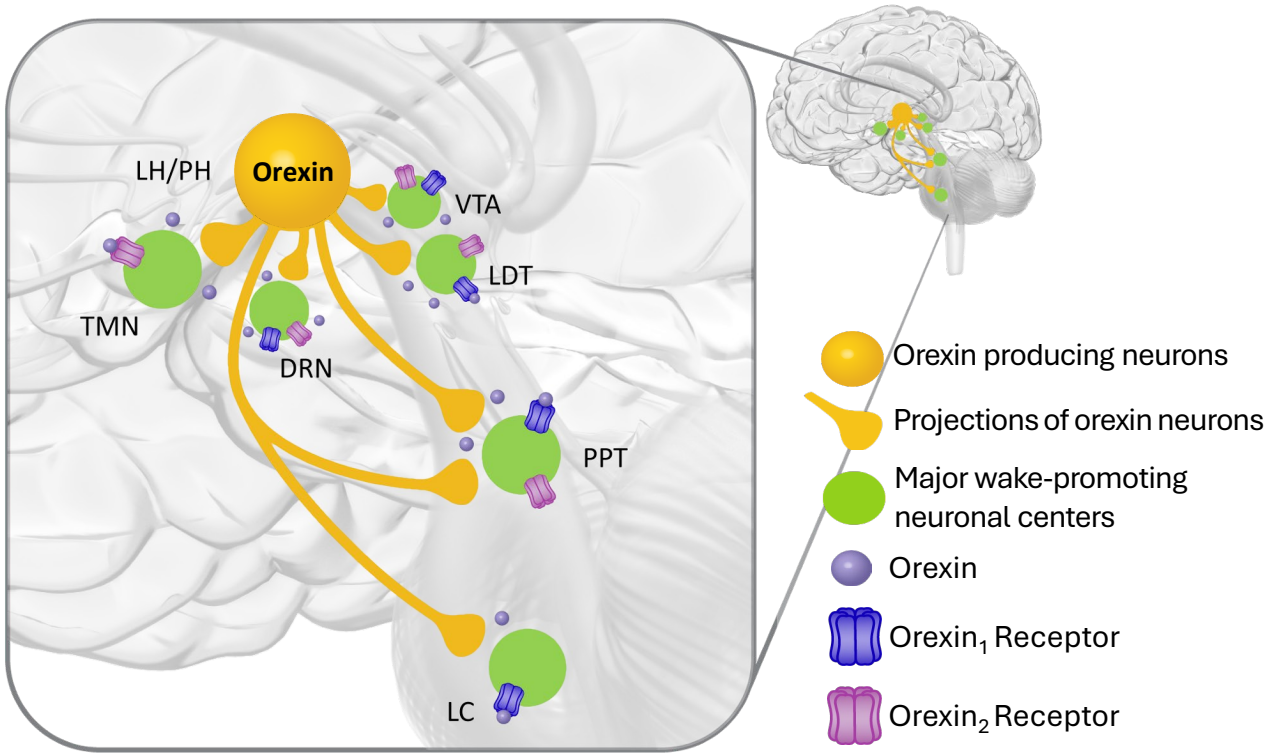
B/L = baseline; hsCRP = high-sensitivity C-reactive protein.

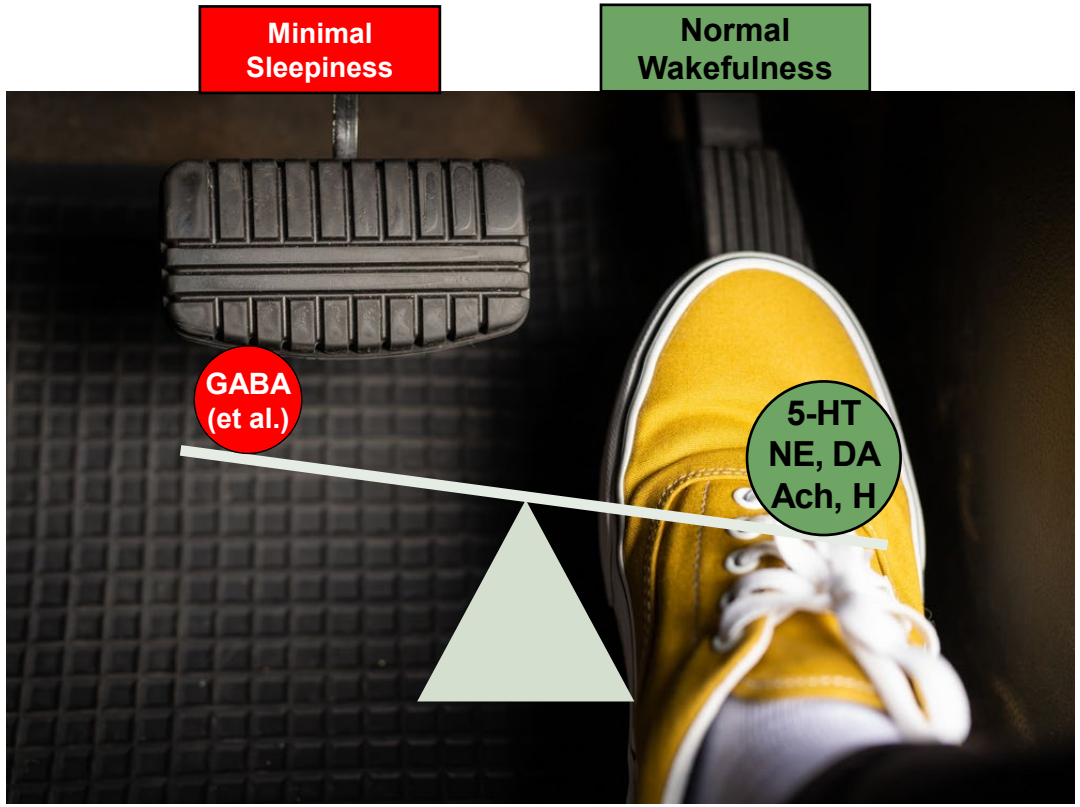
Malhotra A, et al. *N Engl J Med.* 2024;391:1193-1205.

Novel Treatments for EDS due to OSA in the Context of Mental Health Conditions

Orexin-2 Receptor Agonism

The Normal Orexin System



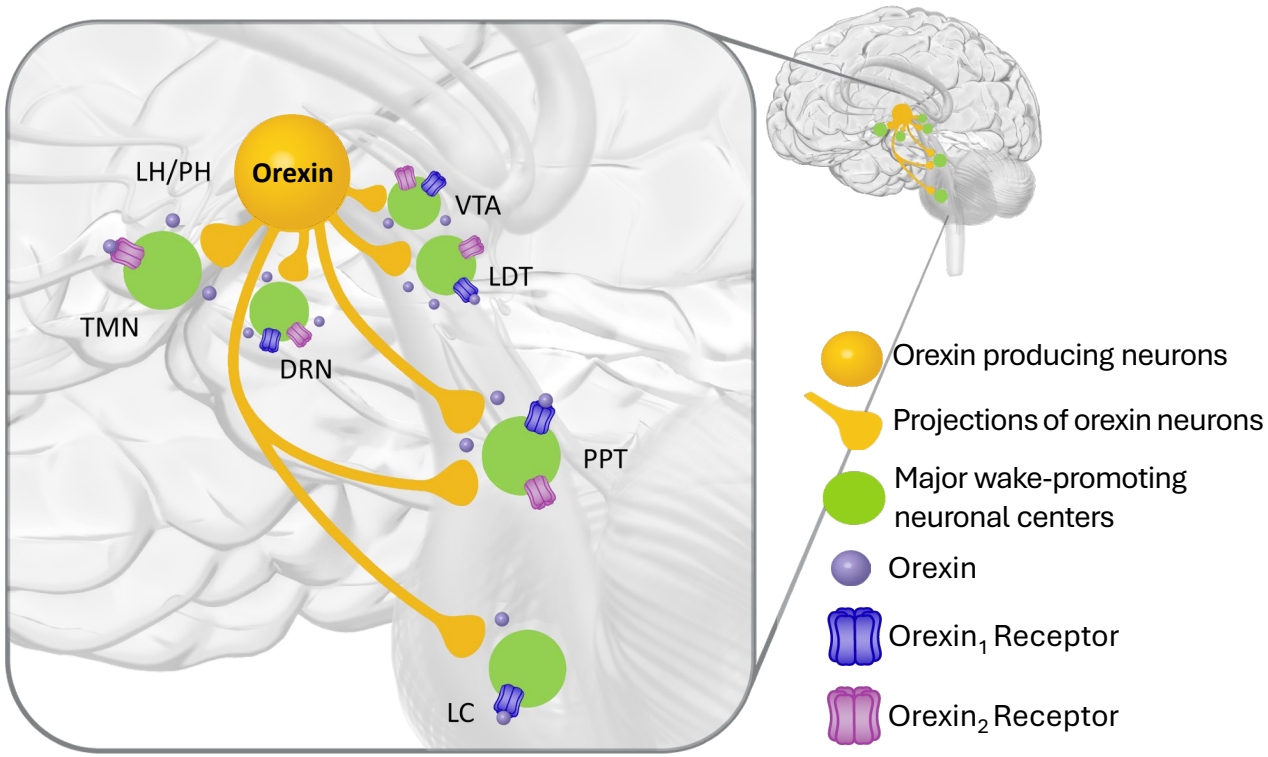


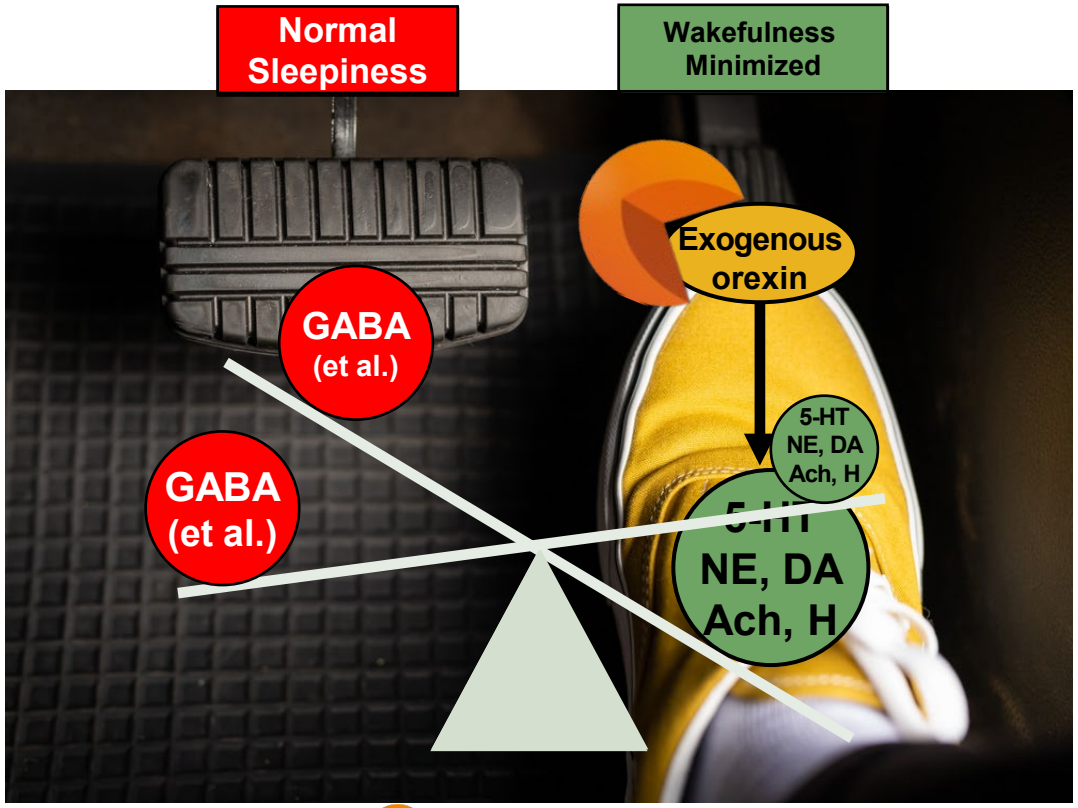
Orexin stabilizes the wake-promoting neurotransmitter centers of the brain to produce wakefulness

DRN = dorsal raphe nucleus; PPT = pedunculopontine tegmental nucleus; LDT = laterodorsal tegmental nucleus; LH/PH = lateral/posterior hypothalamus; TMN = tuberomammillary nucleus; VTA = ventral tegmental area.

Sakurai T. *Nat Rev Neurosci*. 2007;8(3):171-181. Marcus JN, et al. *J Comp Neurol*. 2001;435(1):6-25. Scammell TE, et al. *Annu Rev Pharmacol Toxicol*. 2011;51:243-266. Morin CM, et al. *Nat Rev Dis Primers*. 2015;1:15026.

Insomnia Disorder



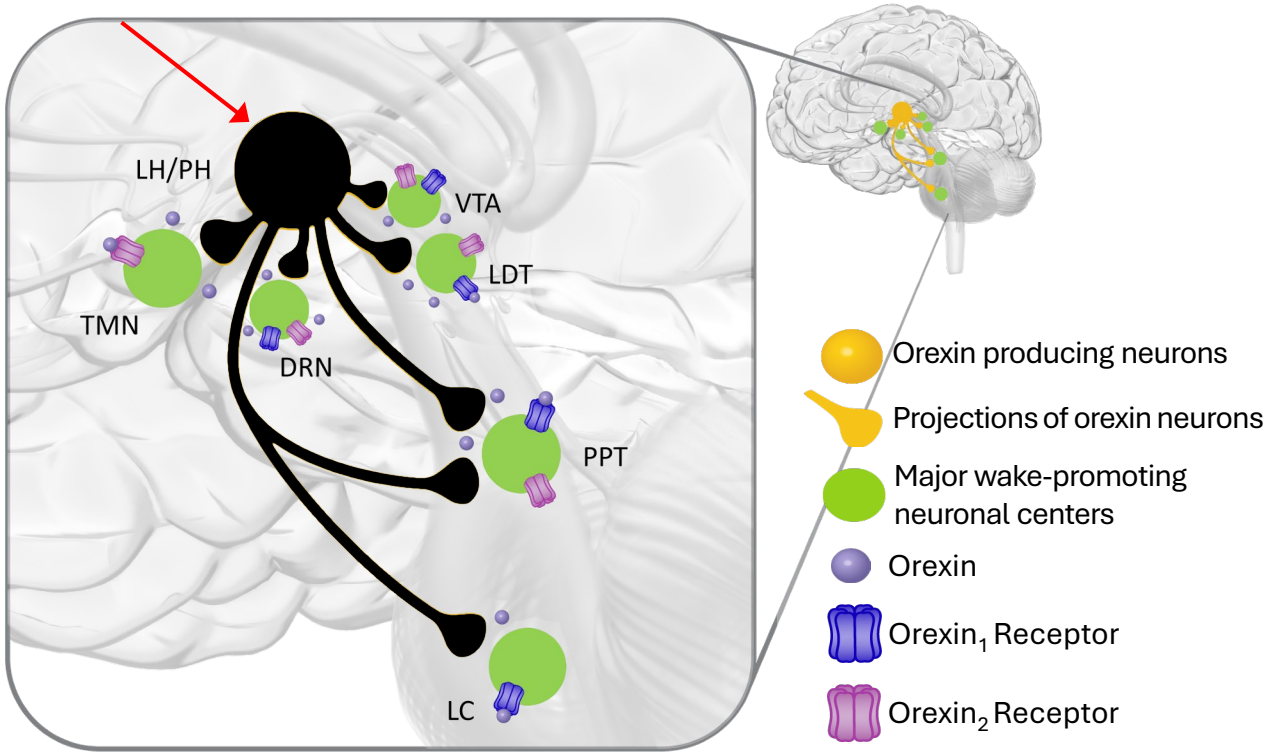


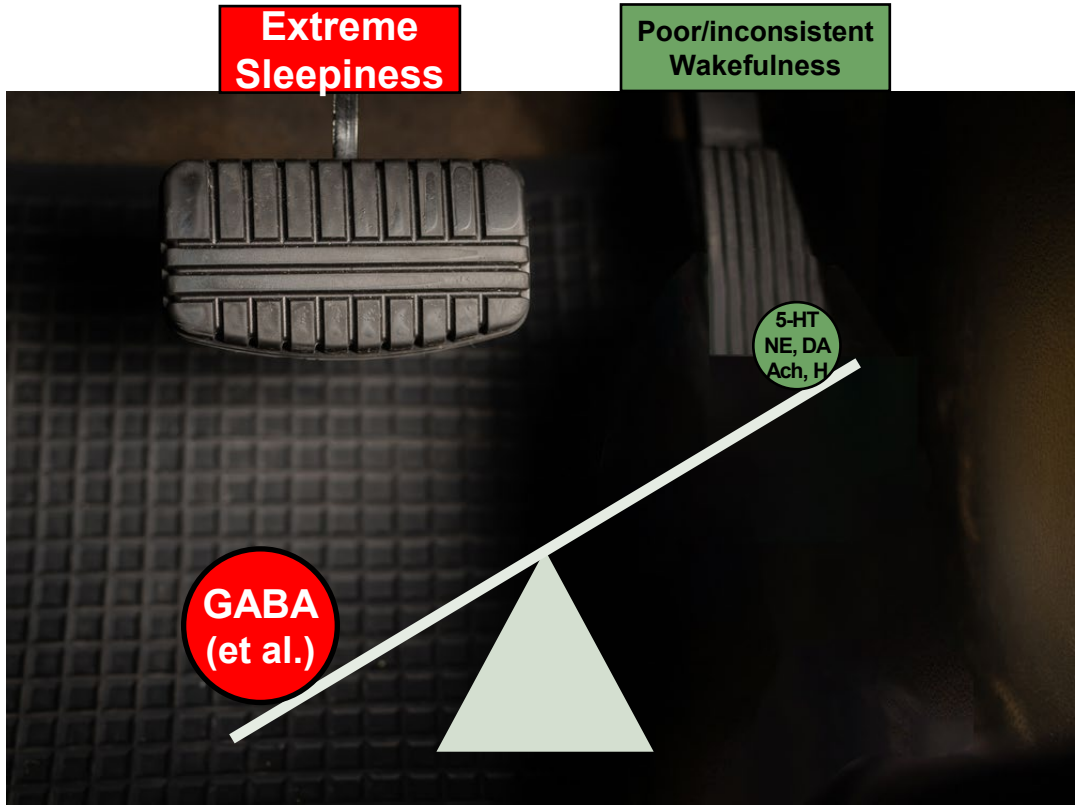
Orexin antagonists enable sleep by reducing excessive wakefulness

Sakurai T. *Nat Rev Neurosci*. 2007;8(3):171-181. Marcus JN, et al. *J Comp Neurol*. 2001;435(1):6-25. Scammell TE, et al. *Annu Rev Pharmacol Toxicol*. 2011;51:243-266. Morin CM, et al. *Nat Rev Dis Primers*. 2015;1:15026.

Narcolepsy Type 1

Deficiency of Orexin Neurons

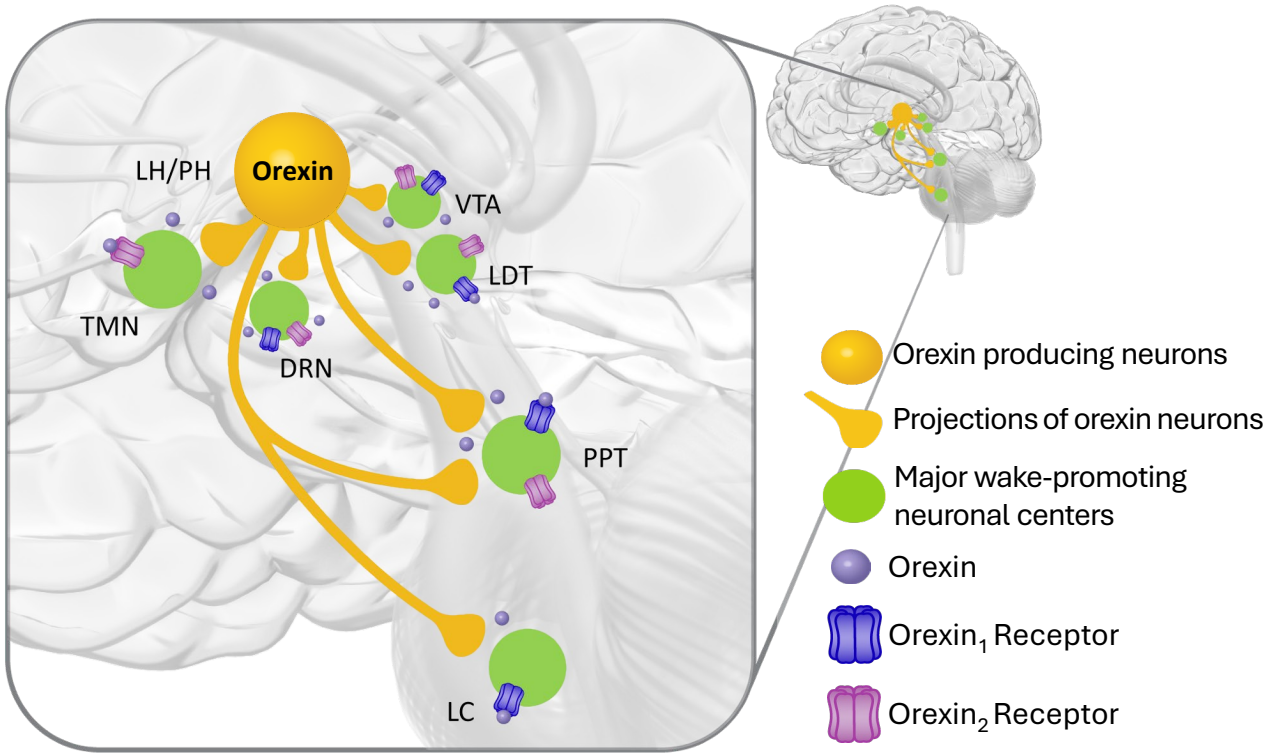


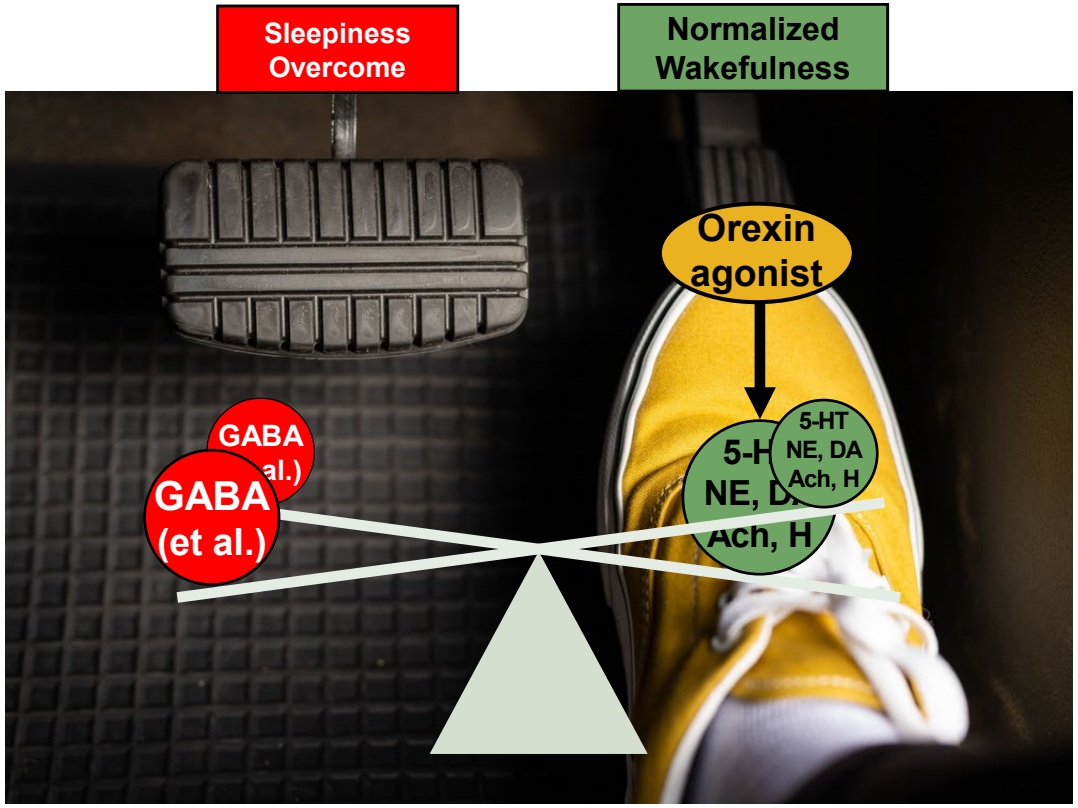


Deficiency of orexin neurons produces unrelenting sleepiness and intermittent cateplexy

Sakurai T. *Nat Rev Neurosci*. 2007;8(3):171-181. Marcus JN, et al. *J Comp Neurol*. 2001;435(1):6-25. Scammell TE, et al. *Annu Rev Pharmacol Toxicol*. 2011;51:243-266. Morin CM, et al. *Nat Rev Dis Primers*. 2015;1:15026.

Potential for Orexin Agonists in OSA?





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

Sakurai T. *Nat Rev Neurosci*. 2007;8(3):171-181. Marcus JN, et al. *J Comp Neurol*. 2001;435(1):6-25. Scammell TE, et al. *Annu Rev Pharmacol Toxicol*. 2011;51:243-266. Morin CM, et al. *Nat Rev Dis Primers*. 2015;1:15026.

Orexin Agonists in Development

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

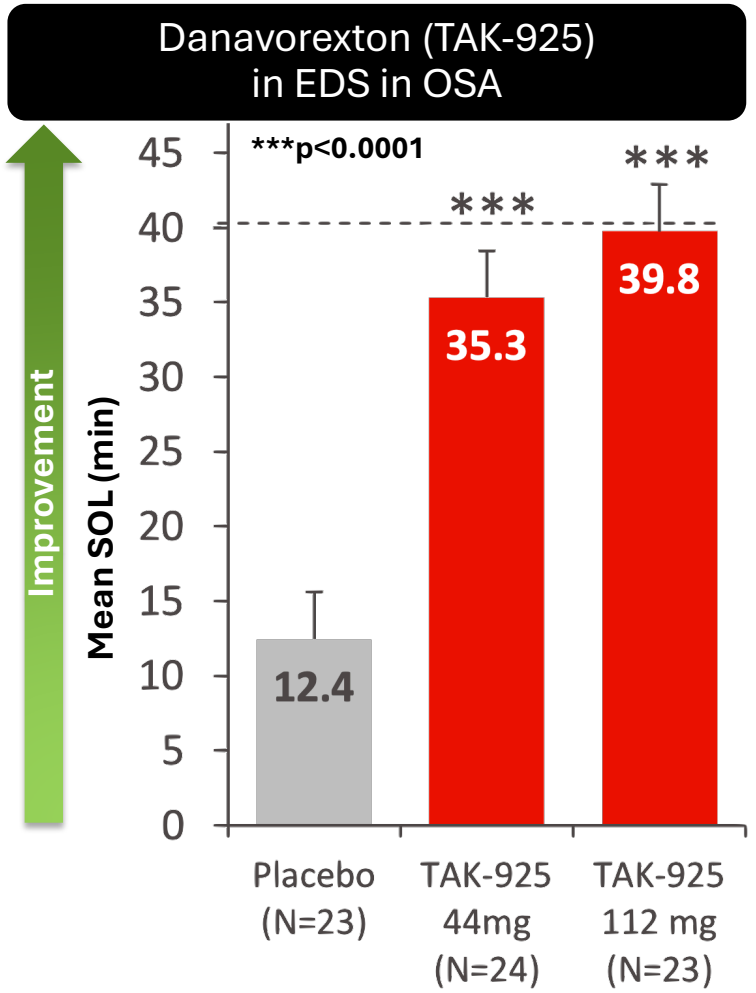
- Positive Phase Ib study in EDS in OSA
- No serious TEAEs or discontinuations due to TEAEs occurred

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

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

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

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



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

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

Key Learning Points

- Solriamfetol is a DNRI and TAAR1 agonist that reduces objective and subjective sleepiness with a large effect size
- Solriamfetol is a schedule IV medication with no evidence of tolerance, withdrawal, or dependence in clinical trials
- New mechanisms such as GLP-1/GIP receptor agonism, H_3 inverse agonism, and orexin agonism may provide other options

EDS due to OSA falls within our scope and responsibility to find and treat!

Panel Discussion

- Patient Advocate Experience with Diagnosis and Treatment of EDS Related to OSA
- Role of Psychiatry Clinicians in the Care of Patients with EDS Related to OSA
- Importance of Shared Decision-Making
- Building a Support Network with Sleep Specialists

Questions?