Clinical Considerations for Patients with Excessive Daytime Sleepiness due to Obstructive Sleep Apnea:

Novel Strategies for Improved Management

sleep360

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Faculty Disclosures

- **Dr. Chepke:** Advisory Board—Abbvie, Acadia, Alkermes, Corium, Eisai, Idorsia, Intracellular, Ironshore, Janssen, Jazz, Karuna, Lundbeck, Neurocrine, Noven, Otsuka, Takeda, Teva; Advisory Board (Spouse)—Otsuka; Consultant—AbbVie, Alkermes, Corium, Eisai, Intracellular, Janssen, Jazz, Karuna, Lundbeck, Neurocrine, Noven, Otsuka, Takeda, Teva; Grant Research/Support—Acadia, Axsome, Biohaven, Harmony, Neurocrine, Teva; Speaker's Bureau—AbbVie, Acadia, Alkermes, Eisai, Intracellular, Ironshore, Janssen, Jazz, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sunovion, Takeda, Teva.

- **Dr. Doghramji:** Consultant—Eisai, Harmony, Jazz, Merck, Pfizer; Educational/Research Grant—Eisai, Harmony, Inspire, Jazz; Stock—Merck; Stock (Spouse)—Merck.

Disclosures

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

Learning Objectives

- Assess the burden, incidence, and psychopathology of EDS due to OSA
- Diagnose EDS due to OSA in patients using clinical guidance and evidence-based diagnostic tools
- Describe the limitations of conventional treatment strategies for patients with EDS due to OSA
- Evaluate current clinical data associated with novel pharmacologic agents for the treatment of EDS due to OSA
- Implement shared decision-making strategies with patients and their care partners in the management of EDS due to OSA which incorporate novel pharmacologic agents and personalized care

What is Excessive Daytime Sleepiness?

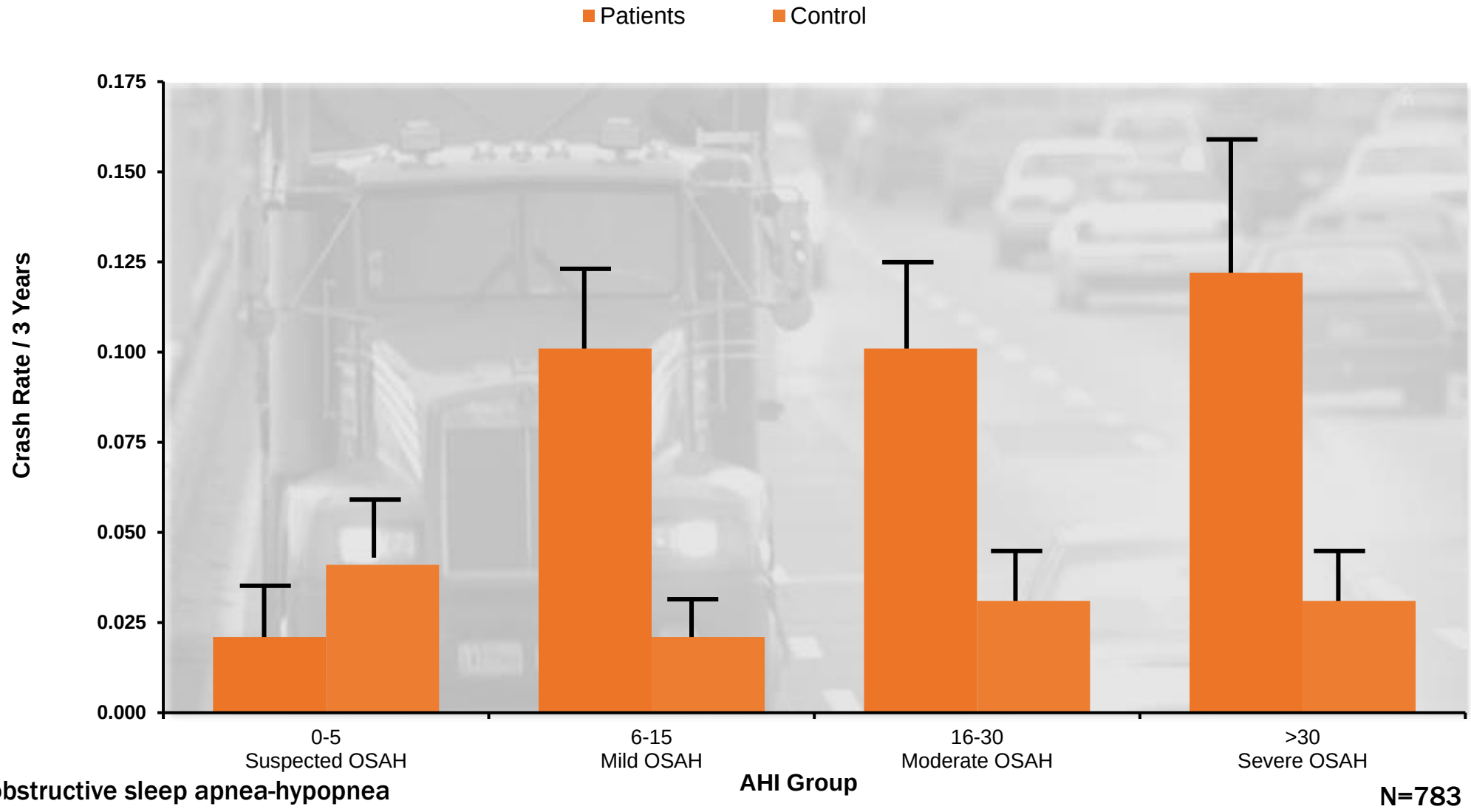
- ***Sleepiness***: Increased likelihood of falling asleep
  - A normal biologic drive
  - Sleep is to sleepiness as eating is to hunger
- ***Hypersomnia***: Prolonged sleep times
- ***Excessive daytime sleepiness***: Sleepiness that occurs in a situation when an individual would usually be expected to be awake and alert
- ***Tiredness and fatigue***: Sensation of weariness, exhaustion, loss of energy; the desire to rest – not necessarily sleepiness

Impact of Excessive Daytime Sleepiness

- Slower response time
- Instability of attention
- Cognitive slowing with rapid deterioration of performance
- Increased cognitive errors with increased time pressure
- Decline in short-term recall and working memory performance
- Reduced learning of cognitive tasks
- Drowsy driving (collisions and near misses)
- Diminished motivation
- Depression and anxiety
- Elevated sympathetic activity
- Insulin resistance
- Impaired immune function
- Hypoxemia
- Impaired quality of life
- Increased mortality

Lockley SW, et al. *N Engl J Med*. 2004;351(18):1829-1837. Zohar D, et al. *Sleep*. 2005;28(1):47-54. Philibert I. *Sleep*. 2005;28(11):1392-1402. Banks S, et al. *J Clin Sleep Med*. 2007;3(5):519-528. Hall MH, et al. *Sleep*. 2017;40(1):zsw003. Bhatia R, et al. Examining excessive daytime sleepiness in psychiatric patients. *Current Psychiatry*. 2017;16(7):27-32.

Automobile Accidents Associated With Injuries



OSAH=obstructive sleep apnea-hypopnea

Mulgrew AT, et al. *Thorax*. 2008;63:536-541.

N=783

Sleepiness Scales

Epworth Sleepiness Scale

(*recent times*)

Situation	Chance of Dozing			
Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting inactive in a public place (eg, a theater or a 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 to 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

An ESS score >10 suggests EDS. An ESS score ≥16 suggests a high level of EDS. Scores within this range are generally associated with significant sleep disorders, including narcolepsy.

Stanford Sleepiness Scale

(*now*)

Degree of Sleepiness	Scale Rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not fully alert	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fight sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

Respondents use a scale from 1 to 7 to indicate their current level of sleepiness. Scores can then be compared longitudinally across different times of day, seasons, and stages of treatment.

Johns MW. *Sleep*. 1991;14(6):540-545. Hoddes E, et al. The development and use of the Stanford Sleepiness Scale (SSS). *Psychophysiology*. 1972;9:150.

Causes of Excessive Daytime Sleepiness

Insufficient sleep (quantity and quality)	Acute Chronic
Circadian rhythm sleep-wake disorders	
Sleep disordered breathing (eg, obstructive sleep apnea)	
Disorders of central hypersomnia	Idiopathic hypersomnia Narcolepsy
Medication or substance use effects	
Hypersomnia associated with psychiatric disorder (HAPD)	
Insomnia?	

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* American Psychiatric Association Publishing; 2013. American Academy of Sleep Medicine. *International Classification of Sleep Disorders, Third Edition.* American Academy of Sleep Medicine; 2014.

Excessive Daytime Sleepiness and Psychiatric Disorders

Depression (MDD)	• Sleep difficulty occurs in up to 90% of those with MDD during episodes • Hypersomnia is reported in ~30% of those with MDD and 50% with SAD
Bipolar Disorder	• Manic phase: Decreased "need" for sleep • Depressed phase: Hypersomnia
Anxiety (GAD)	• >50% experience sleep difficulties and daytime fatigue
PTSD	• Difficulty initiating and maintaining sleep, vivid nightmares, panic awakenings, all leading to daytime fatigue
Schizophrenia	• Shifts in circadian rhythm ("day-night reversal") – 15% at risk for SDB
Alcohol Use Disorder	• Poor sleep quality, EDS

GAD = generalized anxiety disorder; MDD = major depressive disorder; SAD = seasonal affective disorder; SDB = sleep disordered breathing. Krystal AD. *Neurol Clin*. 2012;30(4):1389-1413.

Hypersomnia Associated with a Psychiatric Disorder

ICSD-3 Criteria

1) Daytime sleepiness for at least 3 months
2) A concurrent psychiatric disorder
3) Sleepiness is not better explained by another untreated sleep, medical, or neurological disorder or from the effects of medication

- HAPD accounts for 5%–7% of hypersomnia cases
- Women > Men
- Age of onset: 20–50 years
- Those with insomnia and hypersomnia are 10× more likely to have MDD
- Severe sleep disturbances often occur prior to episodes of acute psychotic decompensation in those with schizophrenia

ICSD-3 = *International Classification of Sleep Disorders, Third Edition.*

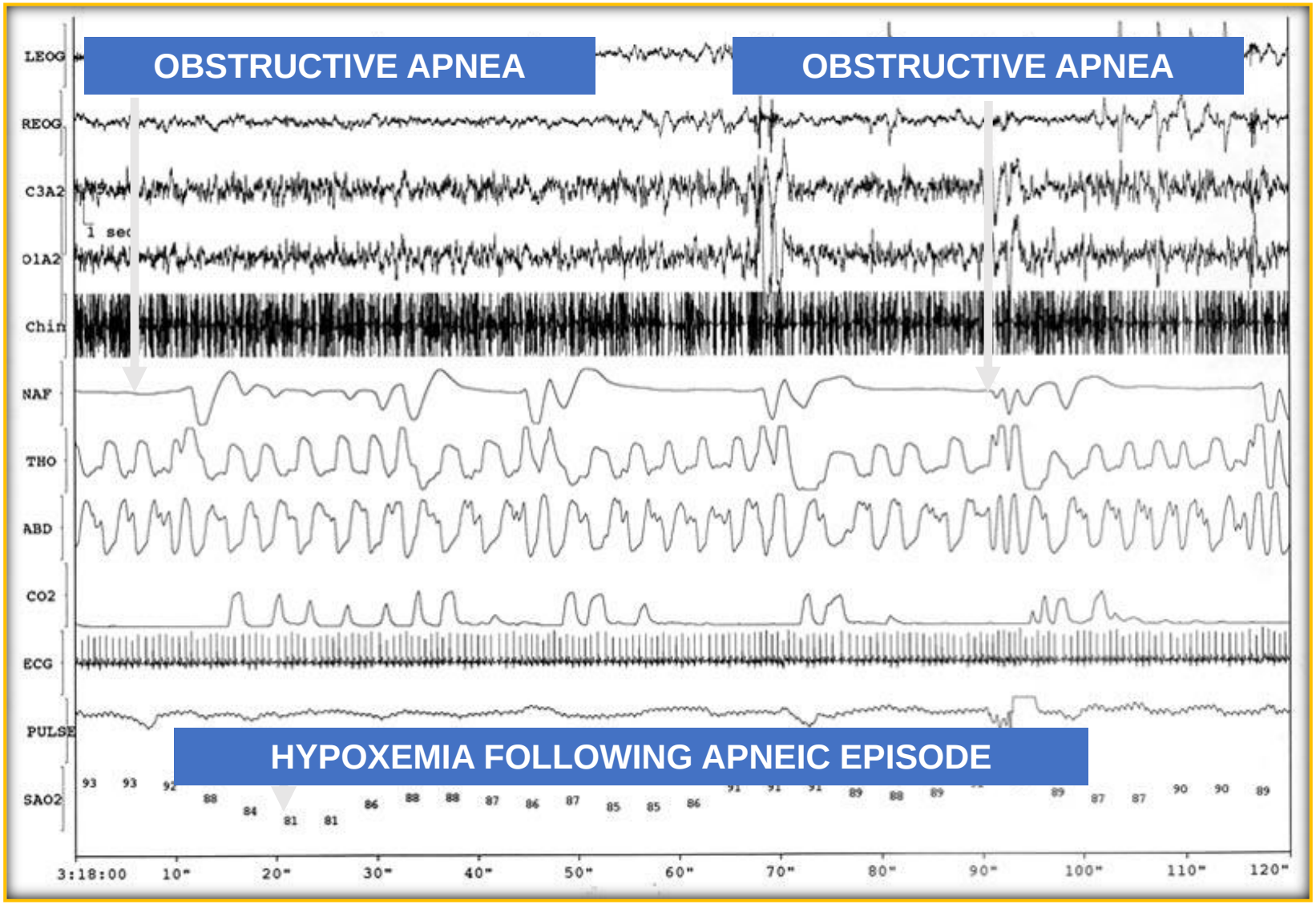
Berry RB, et al. *Sleep Medicine Pearls*. Third Edition. Saunders; 2015.

Overview of Obstructive Sleep Apnea

- Sleep-related breathing disorder
  - Muscles relax and soft tissue collapses
  - Repetitive blockage of the upper airway
  - Decrease or complete halt in airflow
  - Intermittent episodic hypoxia and impaired ventilation
- Diagnosis
  - Laboratory polysomnography (AHI)
  - Home sleep apnea test (REI)
  - Diagnostic criteria (AHI or REI)
    - ≥5 episodes/hour in combination with excessive daytime sleepiness, insomnia, hypertension, mood disorder, cognitive impairment, ischemic heart disease or prior stroke
    - ≥15 episodes/hour
  - Severity Criteria (AHI or REI)
    - Mild: 5 – 15
    - Moderate: 16 – 30
    - Severe: > 30

AHI: Apnea hypopnea index. REI = respiratory event index.
aasm.org/resources/factsheets/sleepapnea.pdf. Benjafield. Lancet Respir Med. 2019;687. Javaheri. Chest. 2020;158:776. Lal. Ann Am Thorac Soc. 2021; 18:757. Rundo. Cleve Clin J Med. 2019;86:2.

Obstructive Apnea During Laboratory Polysomnography



STOP-BANG Inventory for OSA Detection

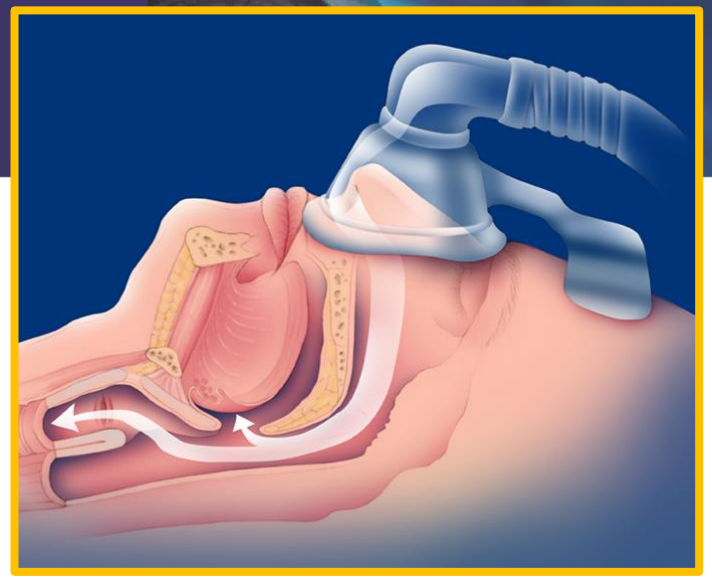
- Risk factors of OSA
  - **S**: Snoring
  - **T**: Tired (daytime fatigue, sleepiness)
  - **O**: Observed breathing pauses (choking, gasping)
  - **P**: Pressure (high blood pressure)
  - **B**: BMI >35
  - **A**: Age >50
  - **N**: Neck size large (>40 cm)
  - **G**: Gender = male
- Scoring: Risk for OSA
  - **High risk**: ≥ 3 items

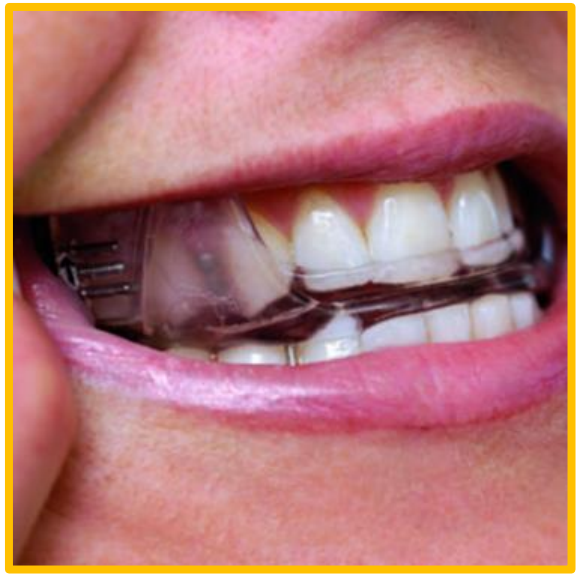
BMI = body mass index.

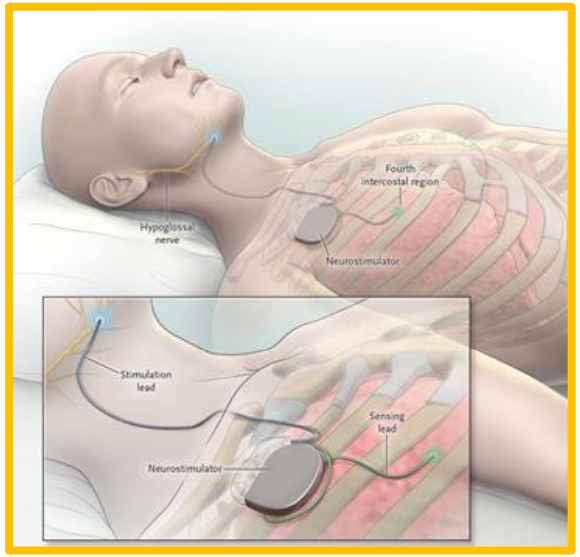
Chung F, et al. *Anesthesiology*. 2008;108(5):812-821. Nagappa M, et al. *PLoS One*. 2015;10(12):e0143697.

Treatments for OSA

- Continuous positive airway pressure
- Upper airway surgery
- Oral appliances
- Body positioning devices
- Nasal EPAP devices
- Nasal insufflation
- Upper airway muscle strengthening
- Medications
- Bariatric surgery
- Hypoglossal nerve stimulator







Residual EDS in OSA

- 9%-22% of OSA patients have persistent EDS despite adherence to PAP treatment and AHI normalization
- These patients are at risk for impairments associated with EDS
- Etiology unclear; may be a result of hypoxic brain damage

Dongol EM, et al. Curr Opin Pulm Med. 2016;22(6):589-594. Gasa M, et al. *J Sleep Res.* (2013) 22, 389–397. Pépin J-L, et al. *Eur Respir J.* 2009;33(5):1062-1067. Weaver TE, et al. *Sleep*. 2007;30(6):711-719. Weaver EM, et al.. 2004;130(4):453-458. Antic NA, et al. *Sleep*. 2011;34(1):111-119. Koutsourelakis I, et al. *Eur Respir J.* 2009;34(3):687-693. Weaver EM, et al. 2005;132(2):255-262

Management of Residual EDS in OSA

- Optimize PAP adherence
  - Minimum adherence generally regarded as PAP use ≥ 4 hours per night for ≥ 70% of days over a 30-day period[1]
  - Greater adherence rates are related to lower residual EDS[2]
- Consider treatment alternatives for OSA
- Lifestyle modifications
- Treat comorbid causes of EDS
- Direct treatment of residual sleepiness despite above
  - Modafinil
  - Armodafinil
  - Solriamfetol

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

Strategies to Improve PAP Adherence

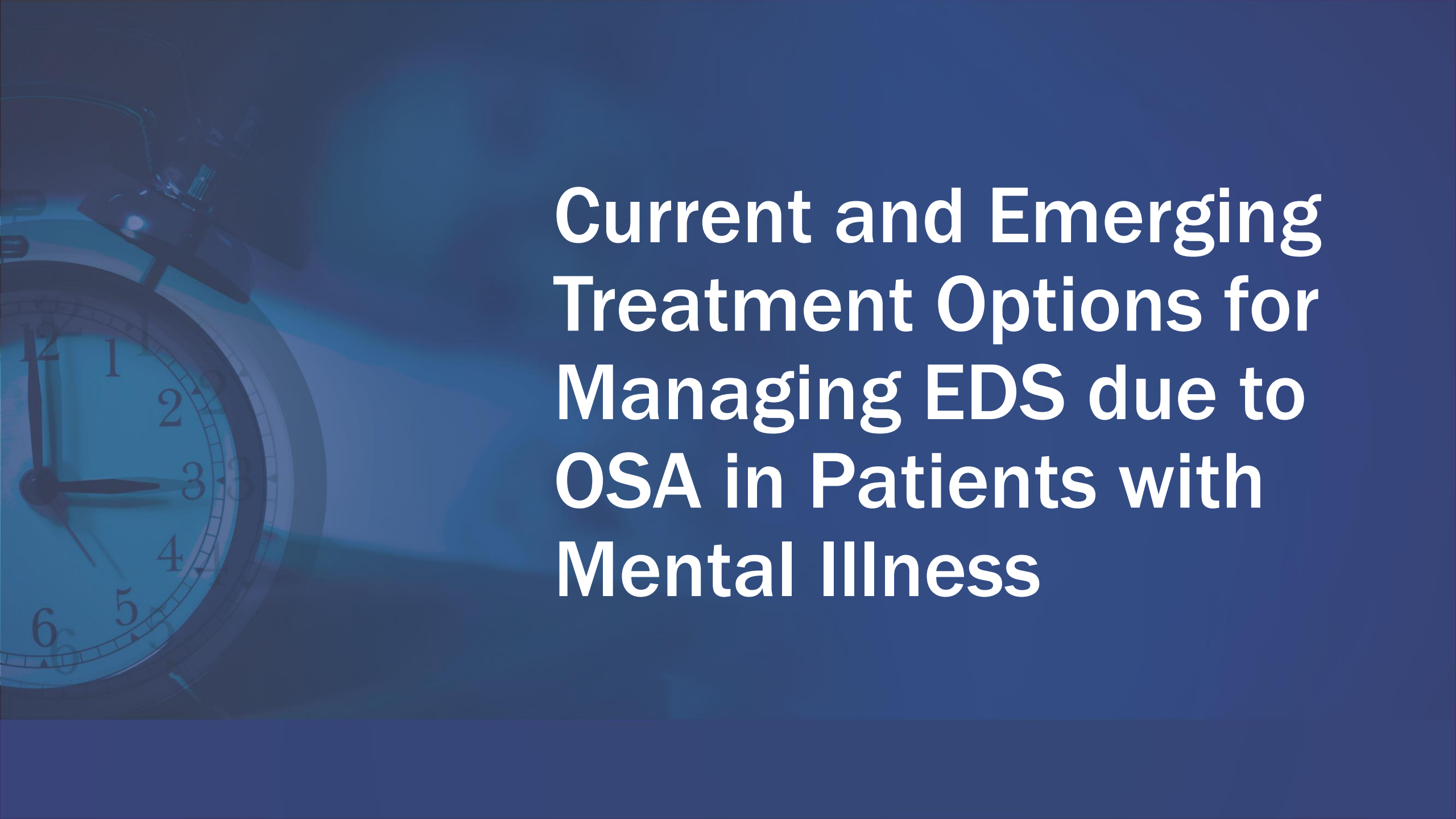
- Early follow up critical!
- Machine-patient interfaces
  - Masks
  - Nasal pillows
  - Chin straps
- Humidifiers
- Ramp
- Desensitization
- Bi-level pressure

Strollo PJ Jr., Sanders MH, Stiller RA. *COMS* 1995;7:221-30.

Examples of Lifestyle Modifications

- Adequate amounts of sleep
- Judicious napping
- Get out of bed at the same time every morning
- Establish a daily activity routine
- Increase exposure to bright light during the day
- Exercise regularly in the morning and/or afternoon
- Avoid alcohol
- Judicious use of caffeine
- Implement behaviors that promote sleep quality

Ghandi. Mayo Clin Proc. 2021;96:1288. www.everydayhealth.com/narcolepsy/lifestyle-manage/.



Current and Emerging Treatment Options for Managing EDS due to OSA in Patients with Mental Illness

Traditional Pharmacotherapy Options for Excessive Daytime Sleepiness in OSA

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

SWSD = shift work sleep disorder.

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

The Most Common Pharmacotherapy for EDS in OSA?

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

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

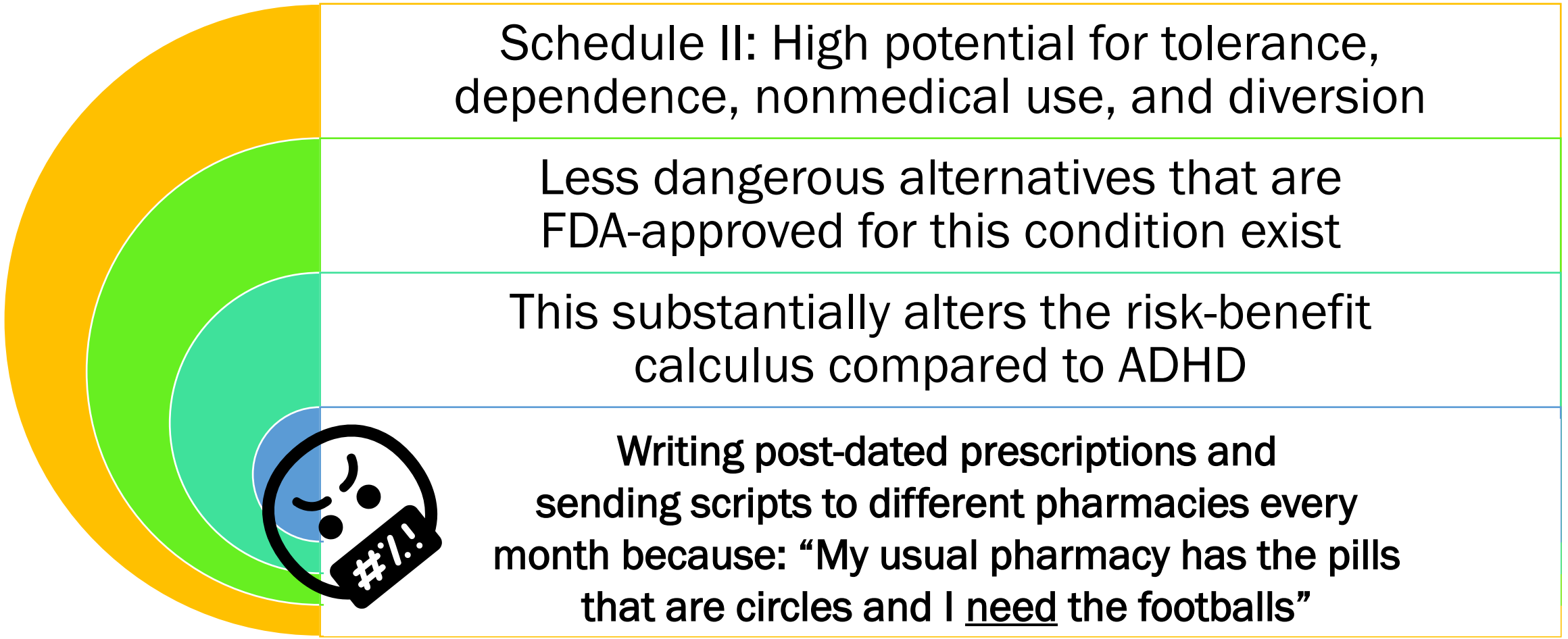
Limitations of Modafinil / Armodafinil

- Common Adverse Effects (≥5%): headache, nausea, dizziness, and insomnia
- Inhibits CYP2C19 and induces CYP3A4/5
- Effectiveness of steroidal contraceptives may be reduced
- Potential for serious rashes, such as SJS

AE = Adverse Effects; CY = Cytochrome P450; SJS = Stevens-Johnson Syndrome.

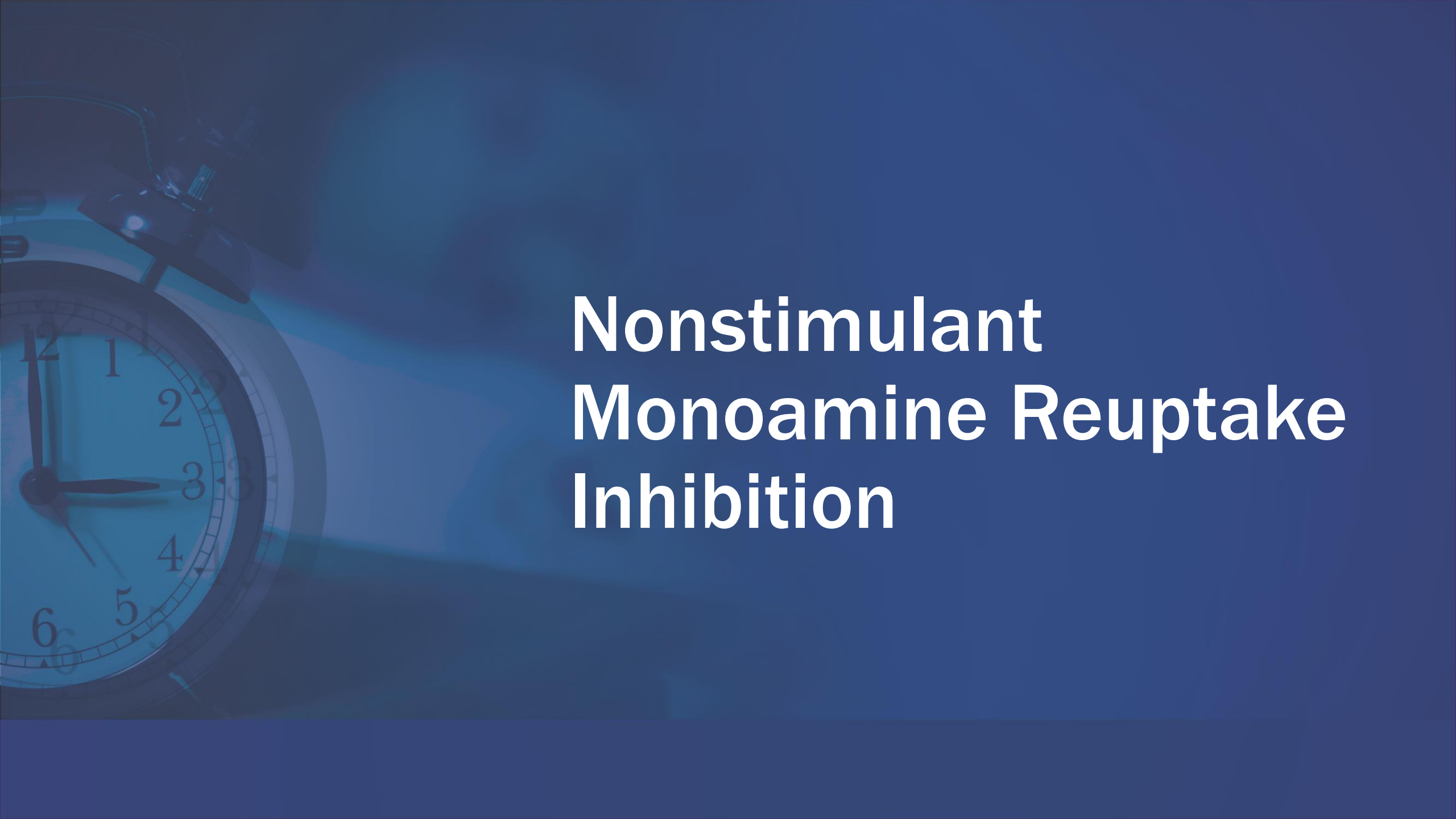
Modafinil Prescribing information. Cephalon;2015. Armodafinil Prescribing information. Cephalon; 201. Holfinger S, et al. *Journal of Clinical Sleep Medicine.* 2018;14(5):885-887.

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



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

Novel Pharmacologic Strategies for EDS Associated with OSA



Nonstimulant Monoamine Reuptake Inhibition

Solriamfetol Basic Information

DNRI indicated for adults with EDS associated with OSA or narcolepsy

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

t_{max} 2 hours, $t_{½}$ = 7 hours;
Efficacy established to at least 9h in trials

No hepatic metabolism; predominantly excreted unchanged in the urine

No induction or inhibition of CYP or other metabolic enzymes

Not a stimulant:
a schedule IV medication with lower abuse/dependence liability

Abuse potential at 8x maximum recommended dose was similar to or lower than that of phentermine

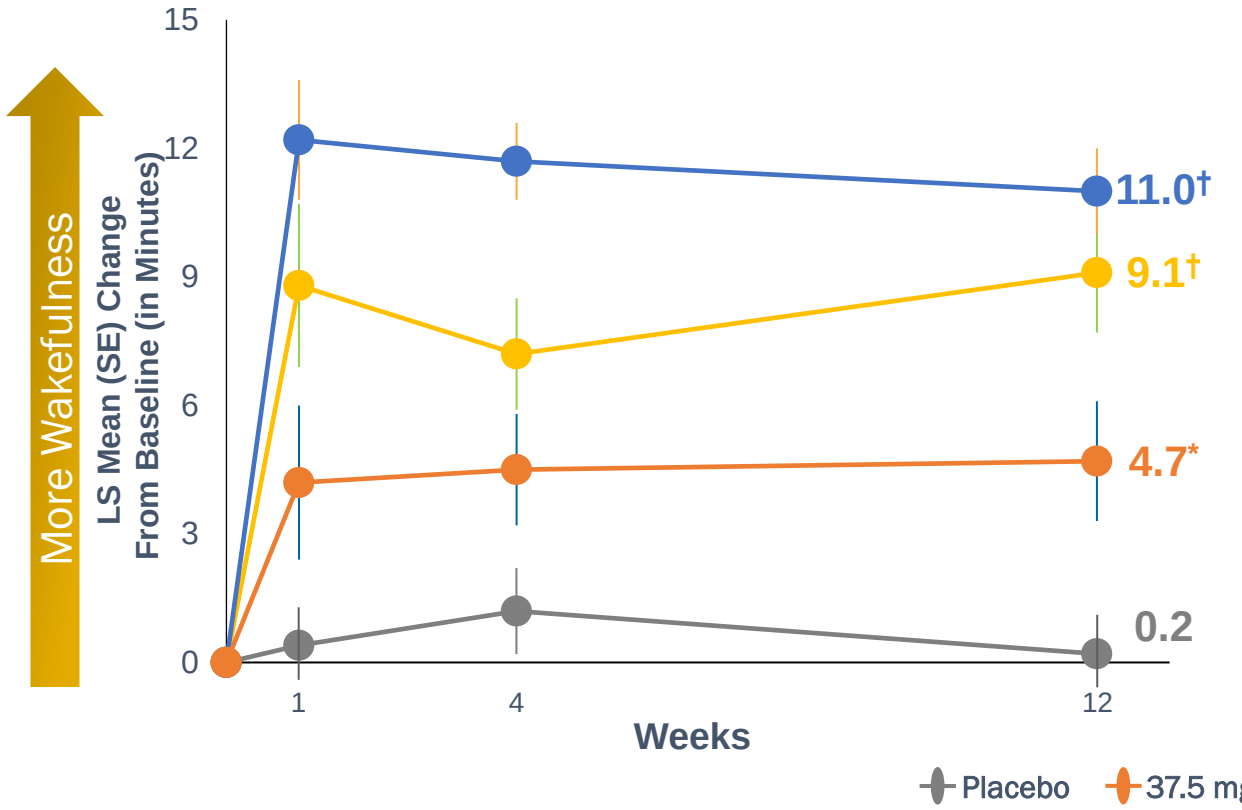
No evidence of tolerance, withdrawal, or dependence in clinical trials

DNRI = dopamine-norepinephrine reuptake inhibitor; EDS = excessive daytime sleepiness; OSA = Obstructive Sleep Apnea; CYP = cytochrome P450.

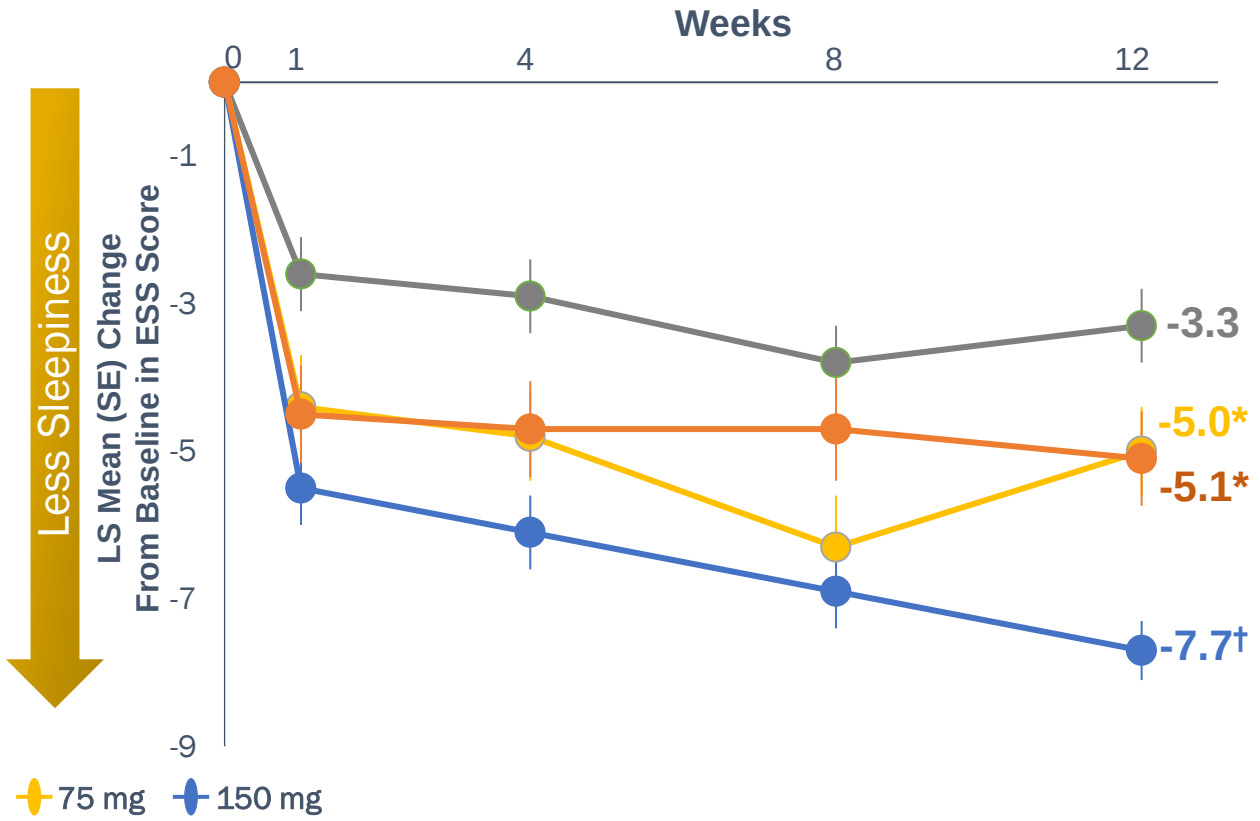
Solriamfetol Prescribing Information. Jazz Pharmaceuticals 2021. Carter, LP, et al. *Journal of Psychopharmacology*. 2018;32(12): 1351-1361.

Solriamfetol Improves Wakefulness and Reduces Sleepiness

Objective Wakefulness (MWT)



Patient-Reported Sleepiness (ESS)



Placebo | 37.5 mg | 75 mg | 150 mg

Significant improvements vs. placebo at all doses in both measures

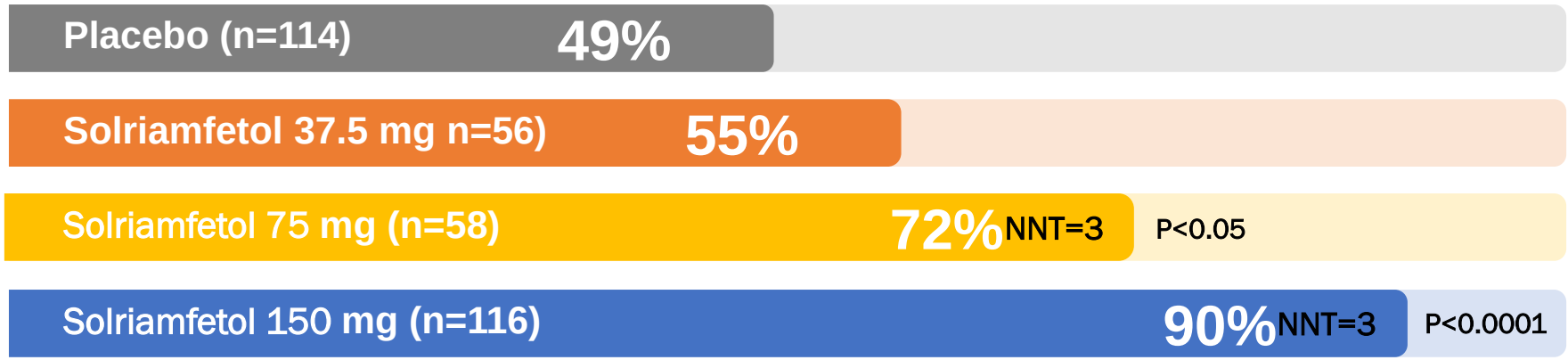
*P<0.05 versus placebo. †P<0.0001 versus placebo.

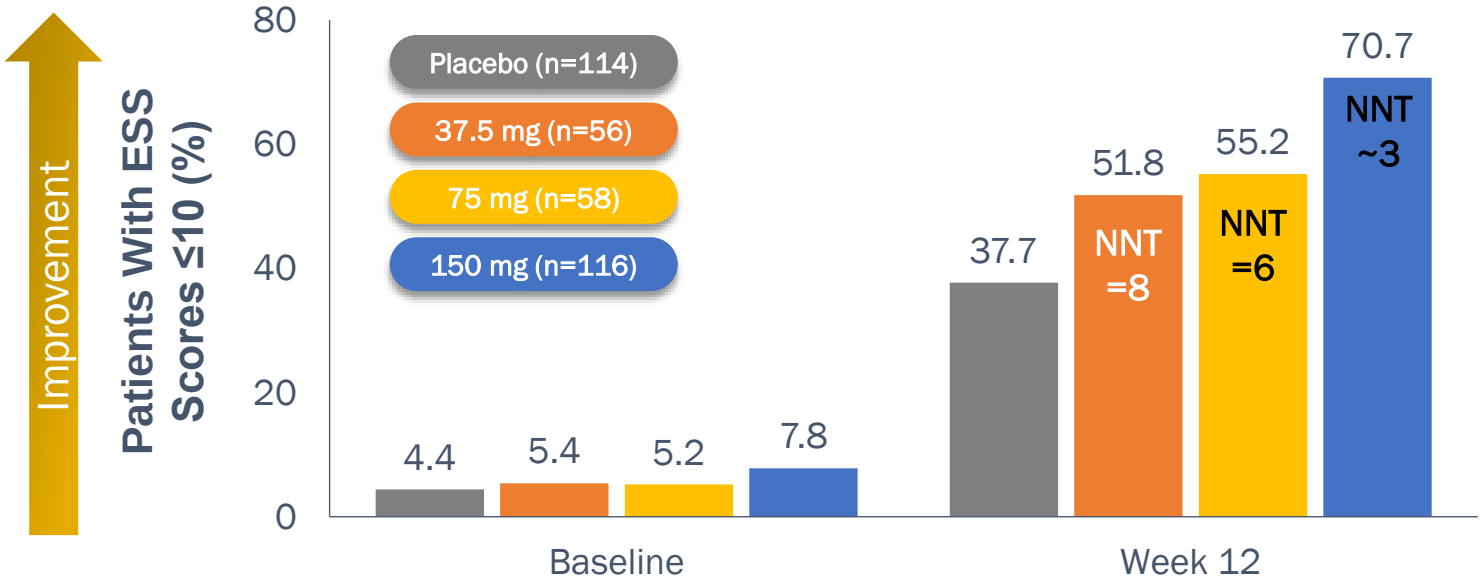
MWT=Maintenance of Wakefulness; ESS=Epworth Sleepiness Scale; LS=least squares; OSA=obstructive sleep apnea; SE=standard error.

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; ESS = Epworth Sleepiness Scale; NNT = Number Needed to Treat.

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)

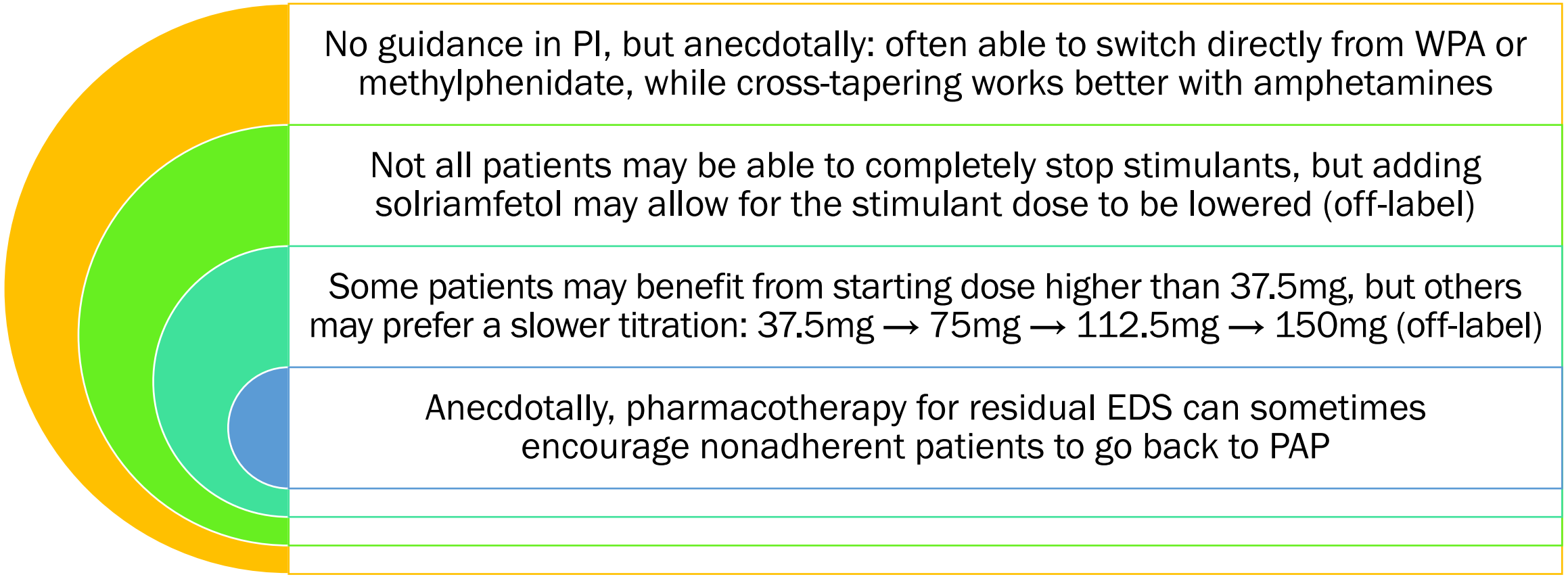
Solriamfetol	Placebo
3% (n=11)	<1% (n=1)

No effect on QTc;
May cause increased 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)

Solriamfetol Prescribing Information. Jazz Pharmaceuticals. 2021.

Lessons Learned from >3 Years of Clinical Experience with Solriamfetol



PI = prescribing information; WPA=Wake-Promoting Agent.

START Your Engines: Solriamfetol Titration and Administration Study

Design

Descriptive study with retrospective patient chart review

24 clinicians (1/5th psychiatrists) provided data from 50 patients with EDS in OSA

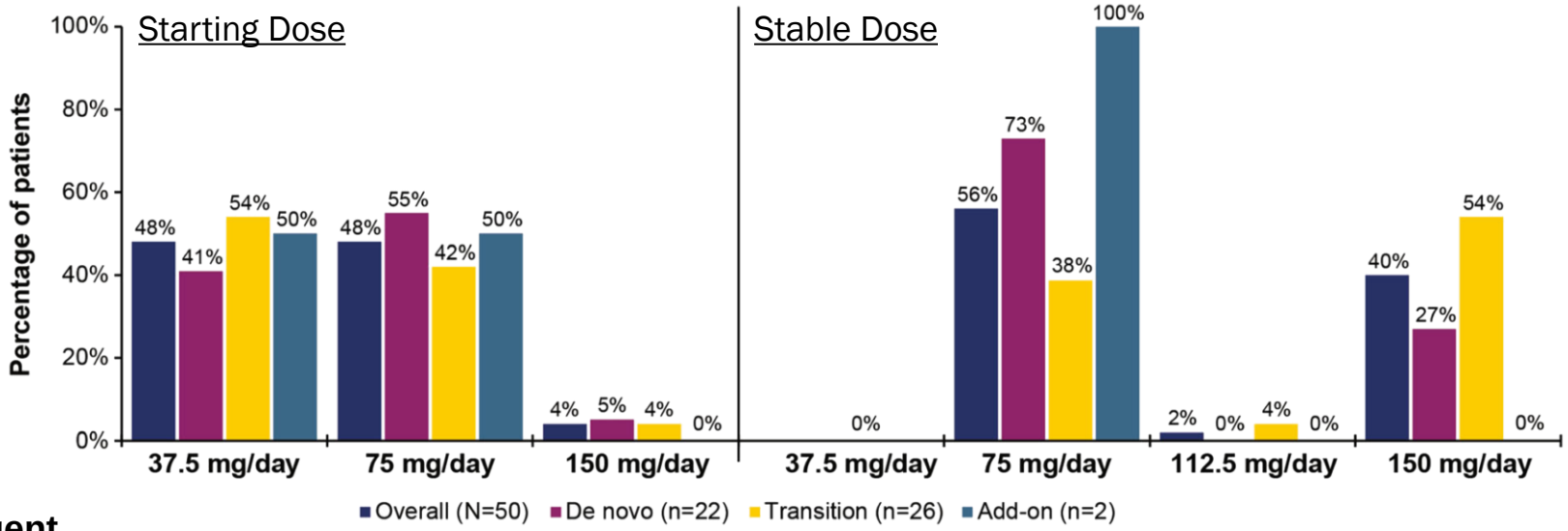
Transitions

52% were transitioned from another agent, 4% had it added to current WPA/stimulant

WPAs were abruptly discontinued for 94% and stimulants for 67% of transitioning patients

Titration

Median of 14 days to reach a stable dose indicates that clinicians generally titrate at intervals longer than the 3 days the label suggests as the minimum.



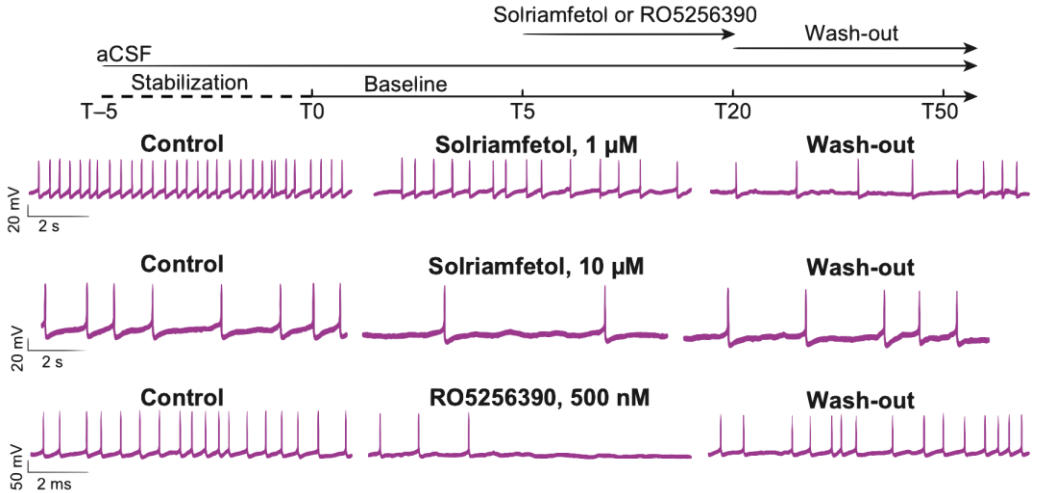
WPA = wake-promoting agent

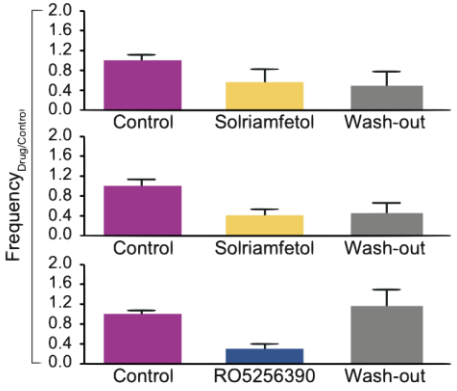
Singh, H, et al. Advances in Therapy(2022): 1-15.

Solriamfetol Shows TAAR1 Agonism in Preclinical Studies

Solriamfetol activates TAAR1, a component of the endogenous wake-promoting system, in vitro at potencies within the clinically relevant plasma concentration range

	DAT IC_{50} µM	NET IC_{50} µM	TAAR1 EC_{50} µM (E_{max})	5-HT_{1A} IC_{50} µM
WPA or hDAT/hNET 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
(+) Methamphetamine	0.082	0.0013	5.3 (70%)	Unknown





Solriamfetol inhibited firing frequency of VTA neurons in a D2-sensitive manner, similar to TAAR1 agonist RO5256390

TAAR, trace amine-associated receptor; 5-HT_{1A} , serotonin 1A receptor; EC_{50} , half maximal effective concentration; E_{max}, maximal effect; DAT, dopamine transporter; NET, norepinephrine transporter; IC_{50}, half maximal inhibitory concentration; WPA, wake-promoting agent; VTA = Ventral tegmental area

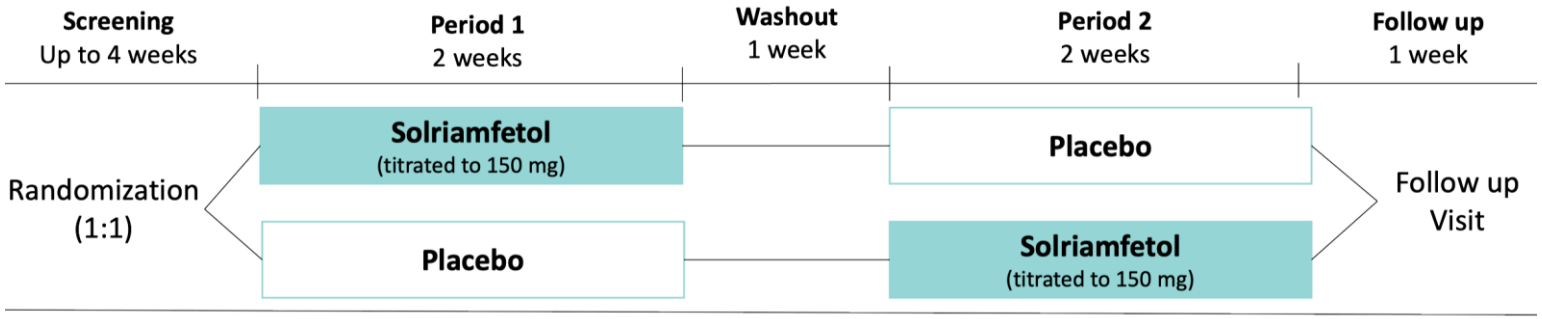
Gursahani, H, et al. Preclinical Pharmacology of Solriamfetol: Potential Mechanisms for Wake Promotion. Poster Presented at Psych Congress. New Orleans, LA. September 17-20, 2022.

Solriamfetol May Have Potential for Cognitive Improvements

Randomized, double-blind, cross-over study assessing adults with OSA and impaired cognitive function

Primary endpoint is change in the Digit Symbol Substitution Test vs. placebo in each 2-week double-blind period

Data expected 3rd quarter 2022

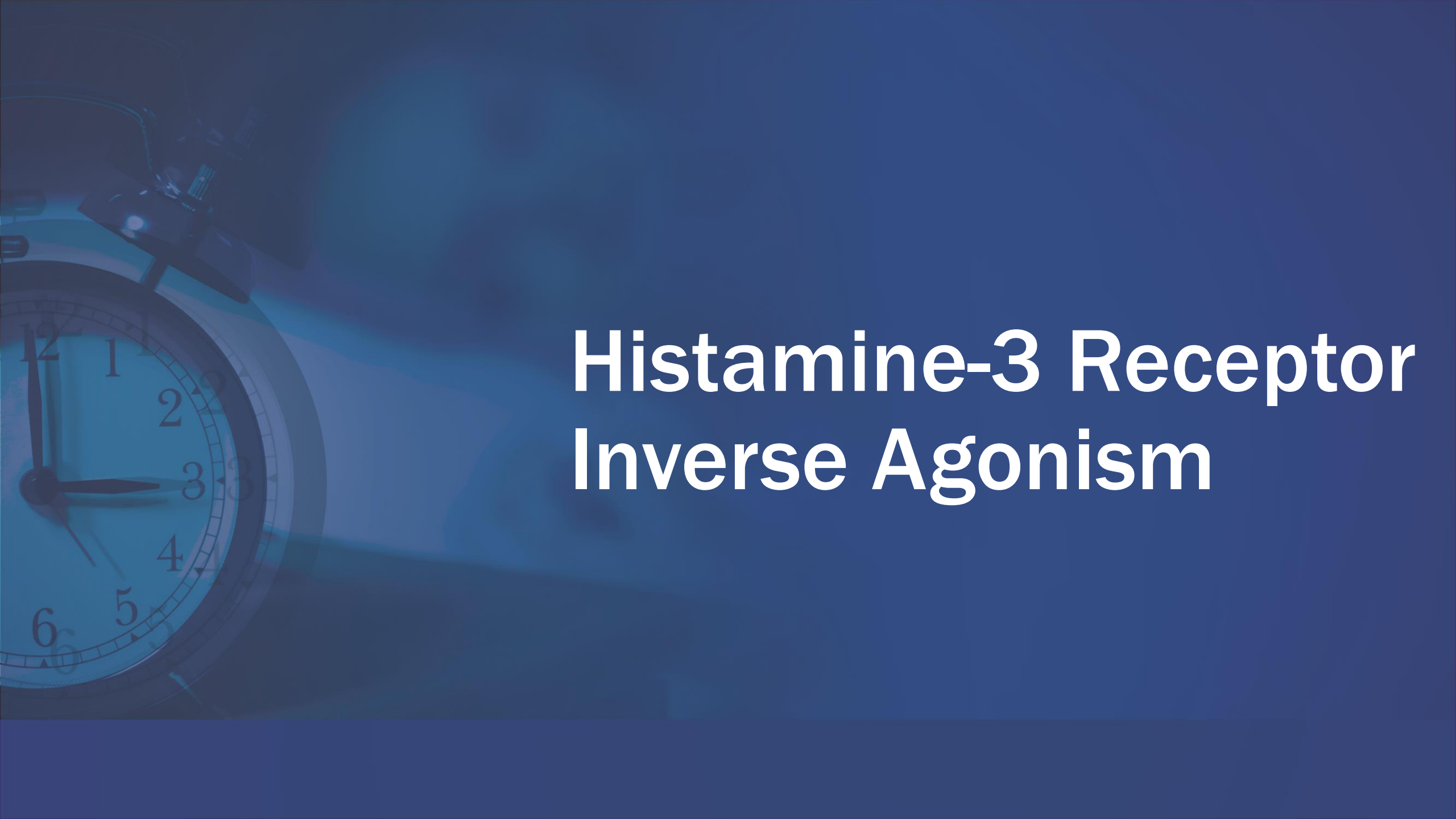


Pipeline Preview!

Phase 2/3 study in adults aged 18-55 years with ADHD beginning 4th quarter 2022

Results expected 2nd half of 2023; Future pediatric ADHD studies also planned

https://clinicaltrials.gov/show/NCT04789174. Leary, E, et al. Sleep Medicine 100 (2022): S285-S286. https://clinicaltrials.gov/show/NCT04839562. https://axsometherapeuticsinc.gcs-web.com/static-files/b6615d47-89c0-4ba7-b42e-eaa73b1bcc34. Accessed 9-4-2022.



Histamine-3 Receptor Inverse Agonism

Histamine-3 Receptor Inverse Agonism

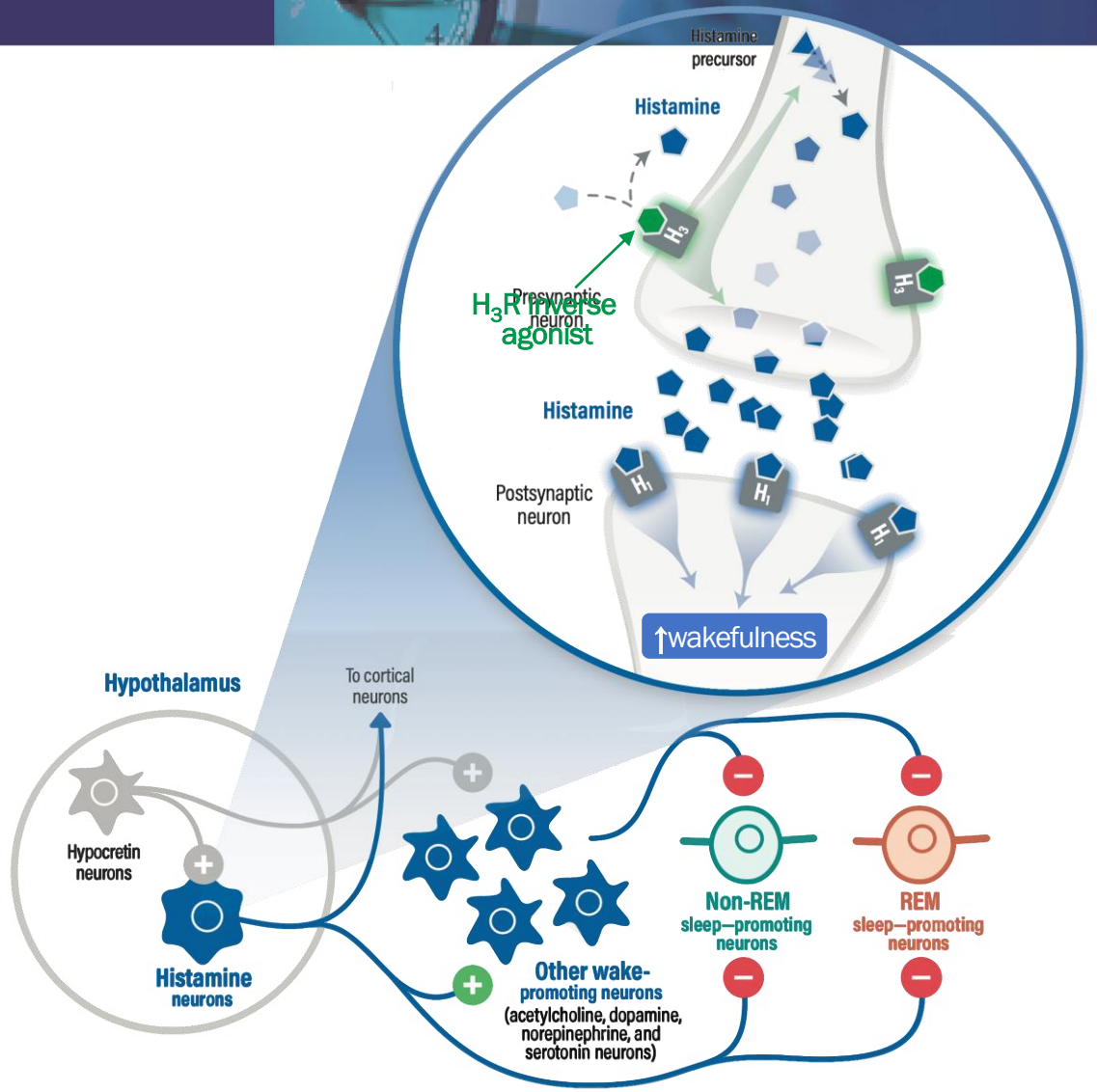
Histamine neurons originate in the hypothalamus and project to major sleep and wake centers

H_3 receptors are presynaptic autoreceptors found in only in the central nervous system

Stimulation of H_3Rs on histamine neurons inhibits firing frequency, histamine synthesis and release

H_3R inverse agonists disinhibit these processes, enhancing histamine release

This activates postsynaptic H_1 receptors and promote wakefulness



H_3R=Histamine-3 Receptor

Lin, J-S, et al. JPET 336.1 (2011): 17-23. Schwartz, J-C. British journal of pharmacology 163.4 (2011): 713-721. Harwell, V, and PS. Fasinu. Medicines7.9 (2020): 55. Benarroch, EE. Neurology 75.16 (2010): 1472-1479.

Currently Available H_3R Inverse Agonist: Pitolisant

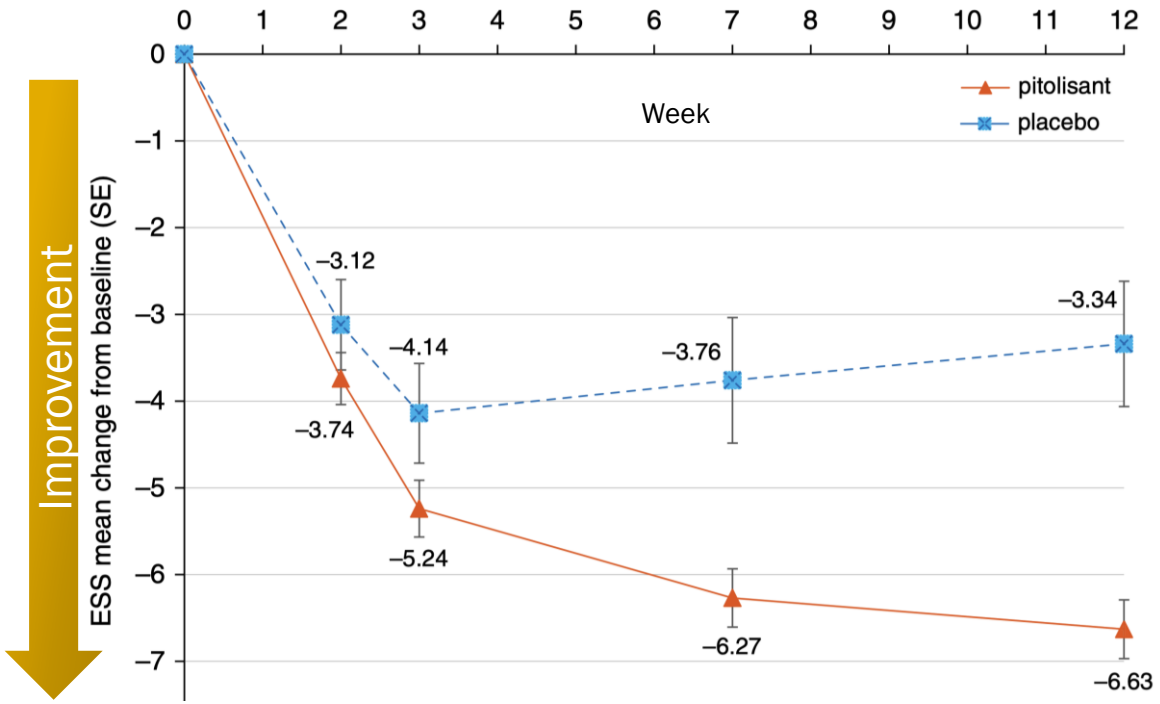
Currently approved for adults with narcolepsy;
Not a scheduled medication

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

Weak CYP3A4 inducer; Increases QT ~4 msec
Centrally acting antihistamines reduce effectiveness

Positive phase 2 study in EDS in OSA;
ex-US phase 3 study in progress

Pitolisant in EDS in OSA

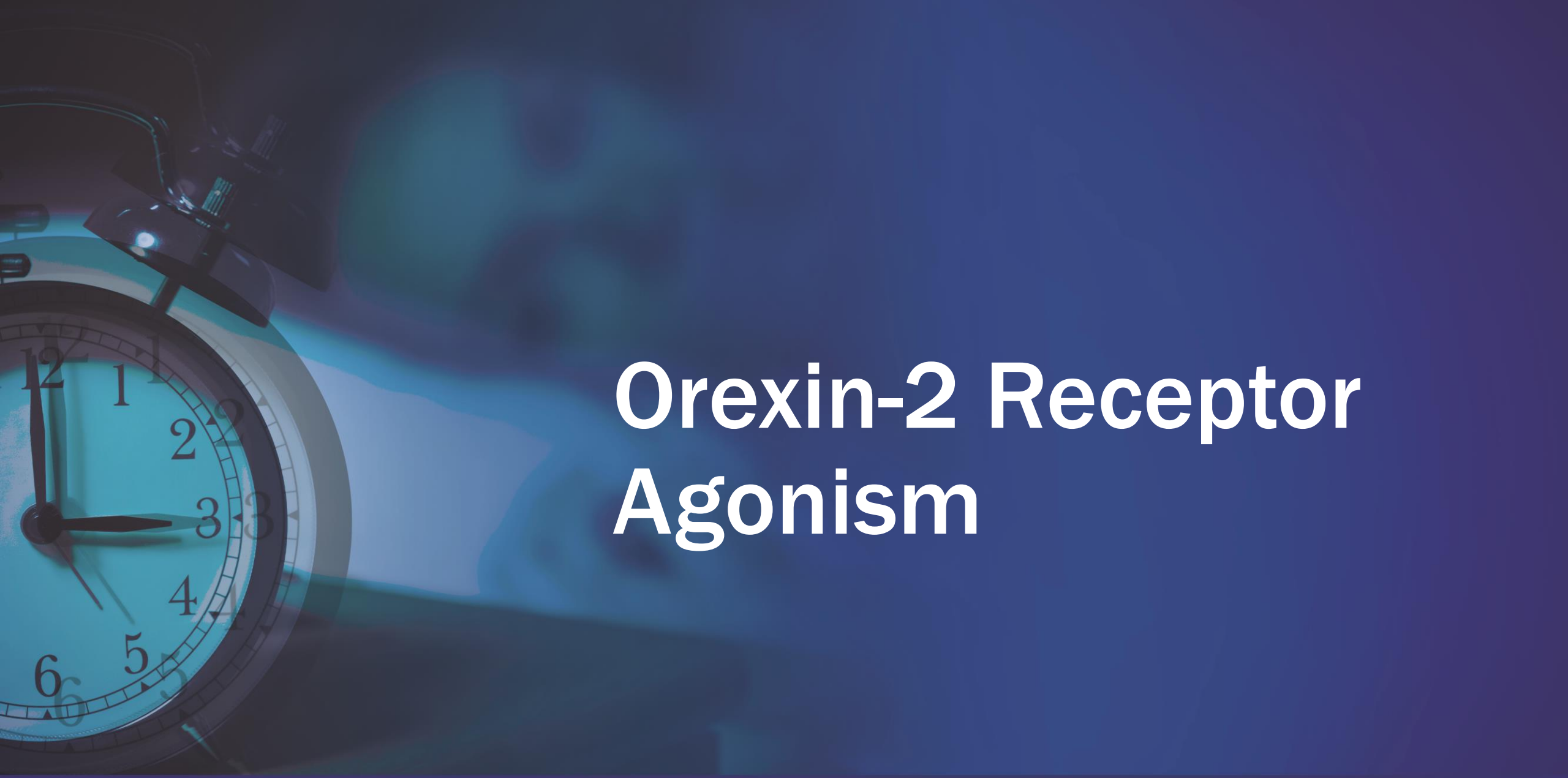


Pipeline Preview!

Samelisant (SUVN-G3031)

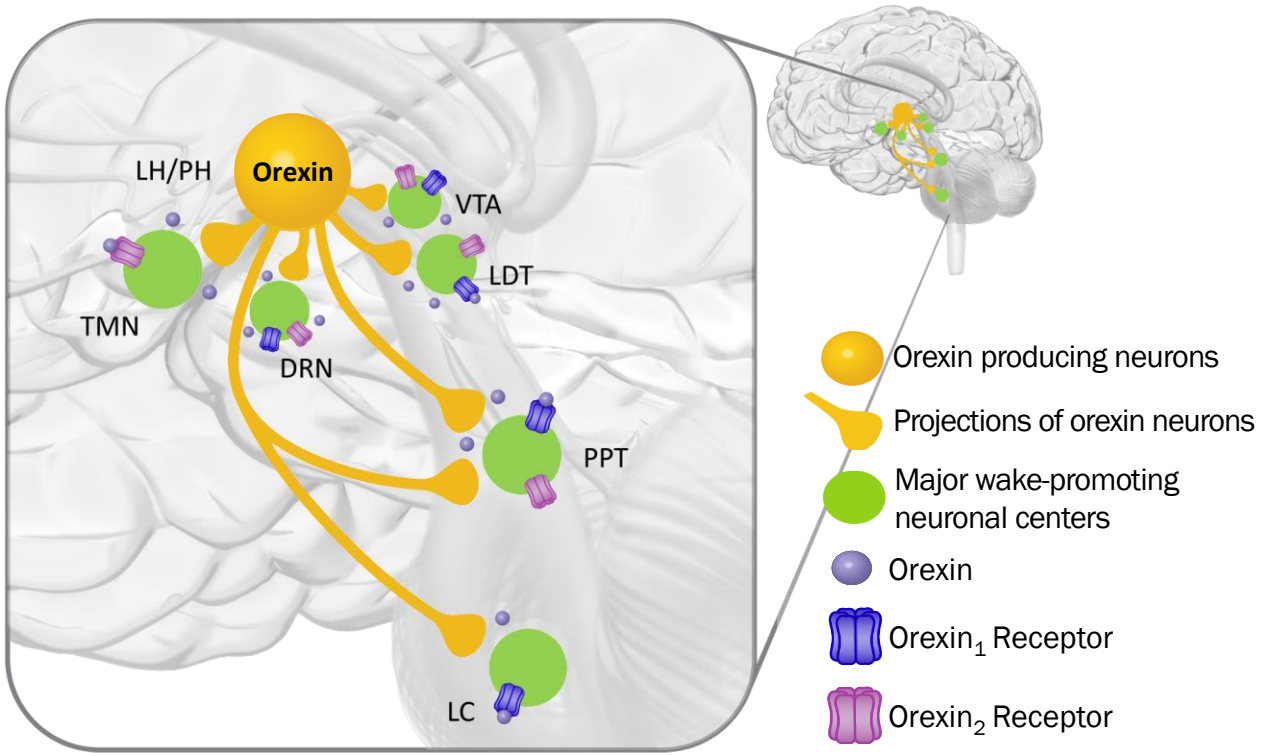
- Currently in phase 2 for narcolepsy
- Phase 2 studies for cognitive disorders planned

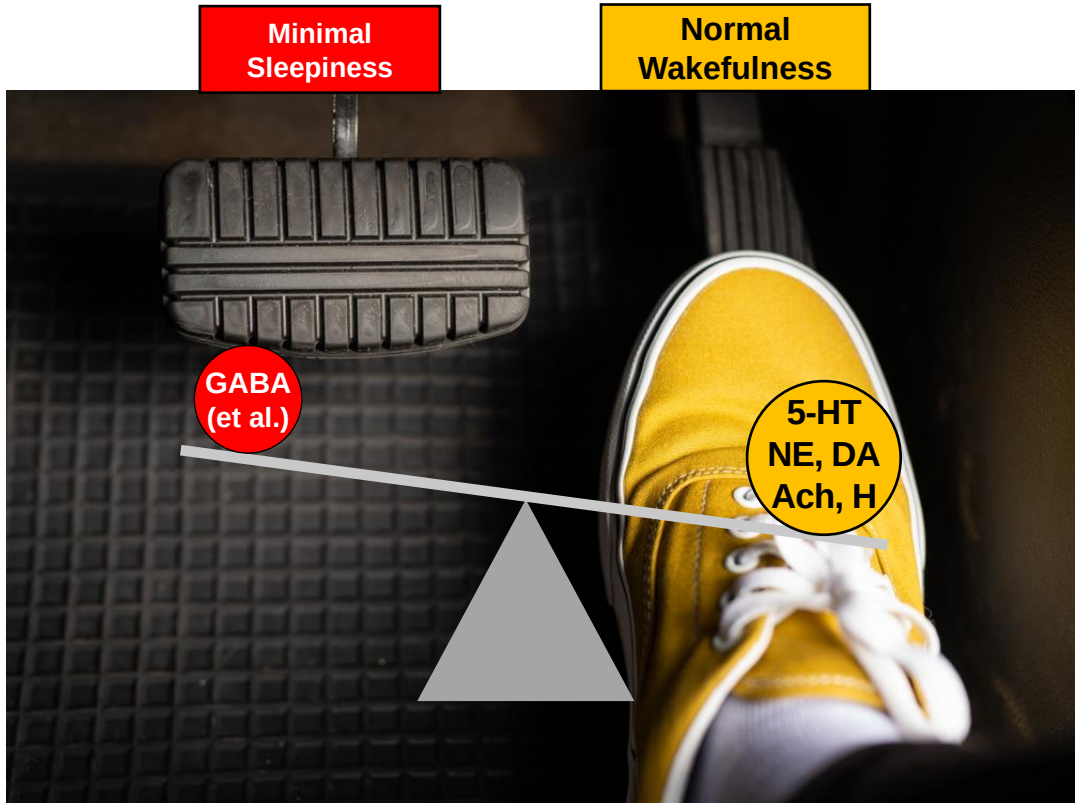
H_3R = Histamine-3 receptor; CYP = cytochrome P450; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnea; ESS = Epworth Sleepiness Scale. Pitolisant PI. Harmony Biosciences, 2021. Dauvilliers Y, et al. Am J Respir Crit Care Med. 2020;201(9):1135-1145. https://clinicaltrials.gov/show/NCT05223166. Accessed 5-14-22. Nirogi, R, et al. Journal of Psychopharmacology. 2021;35(6):713-729. https://clinicaltrials.gov/show/NCT04072380. Accessed 5-14-22.



Orexin-2 Receptor Agonism

The Normal Orexin System





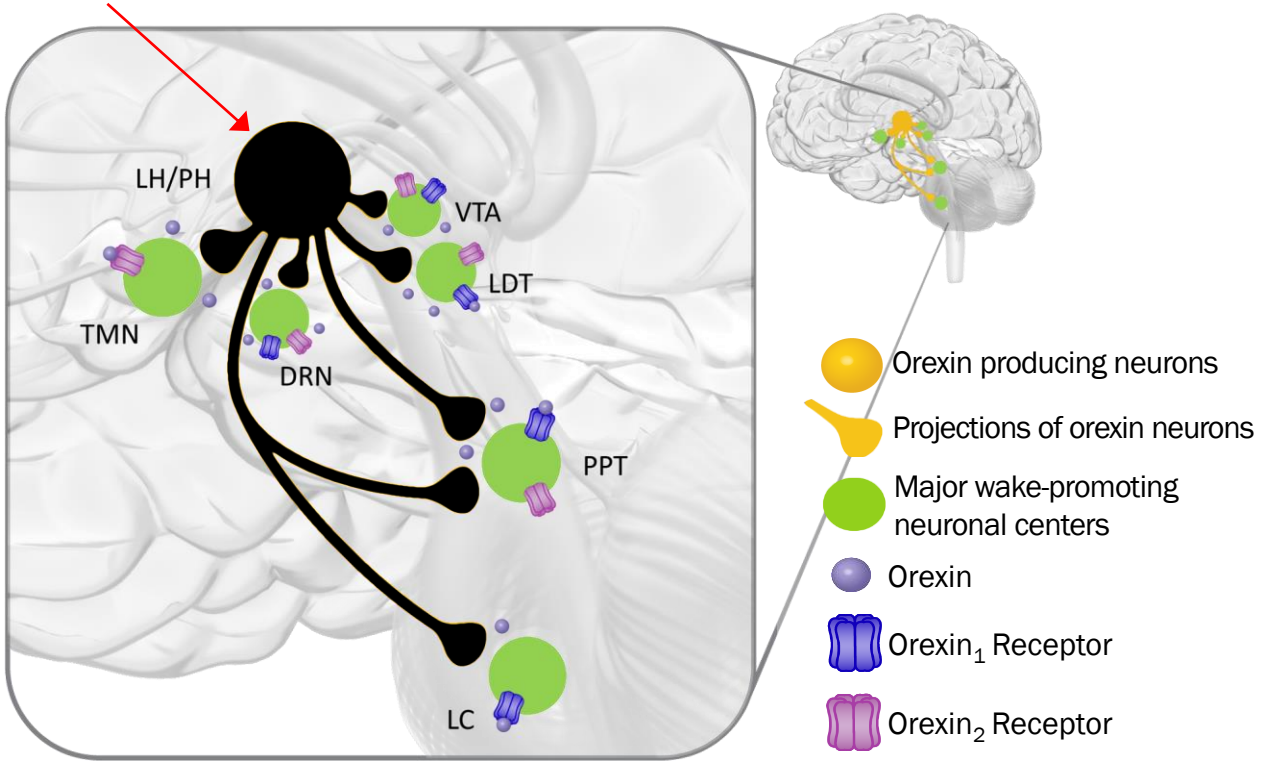
Orexin stabilizes the wake-promoting neurotransmitter centers of the brain to produce wakefulness

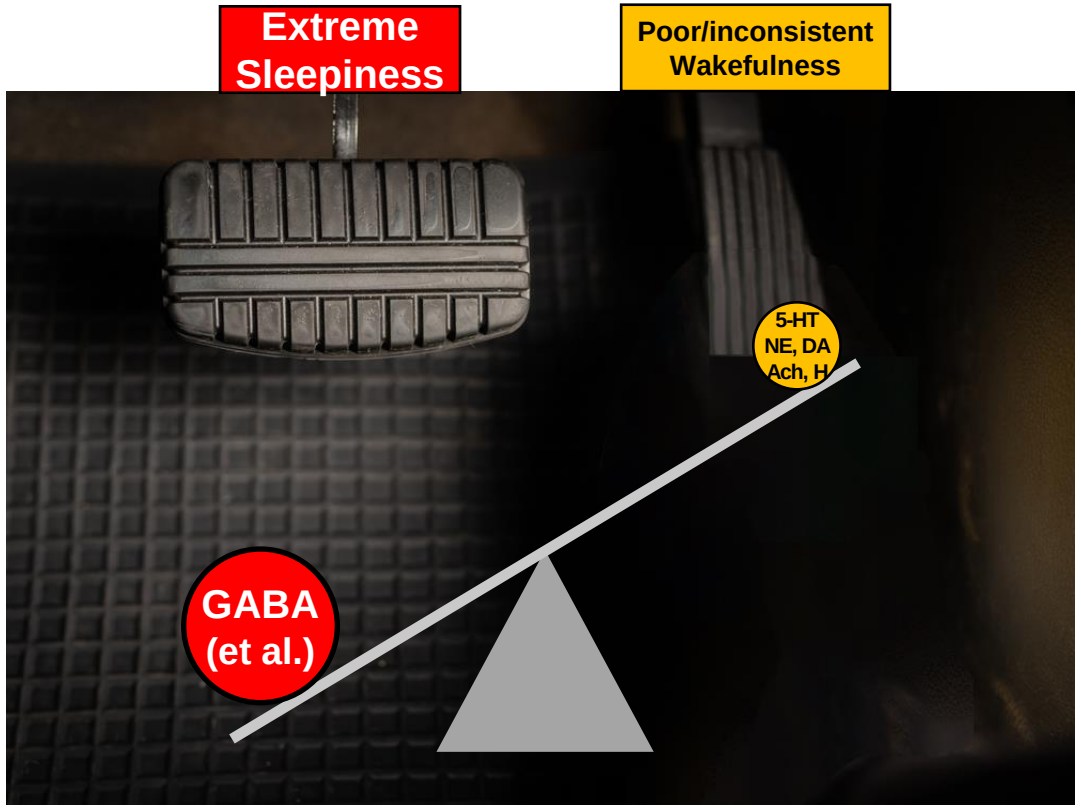
DRN = dorsal raphe nucleus; LC = locus coeruleus; PPT = pedunculopontine tegmental nucleus; LDT = laterodorsal tegmental nucleus; LH/PH = lateral/posterior hypothalamus; TMN = tuberomammillary nucleus; VTA = ventral tegmental area.

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.

Narcolepsy Type 1

Deficiency of Orexin Neurons





Deficiency of orexin neurons produces unrelenting sleepiness and intermittent cateplexy

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

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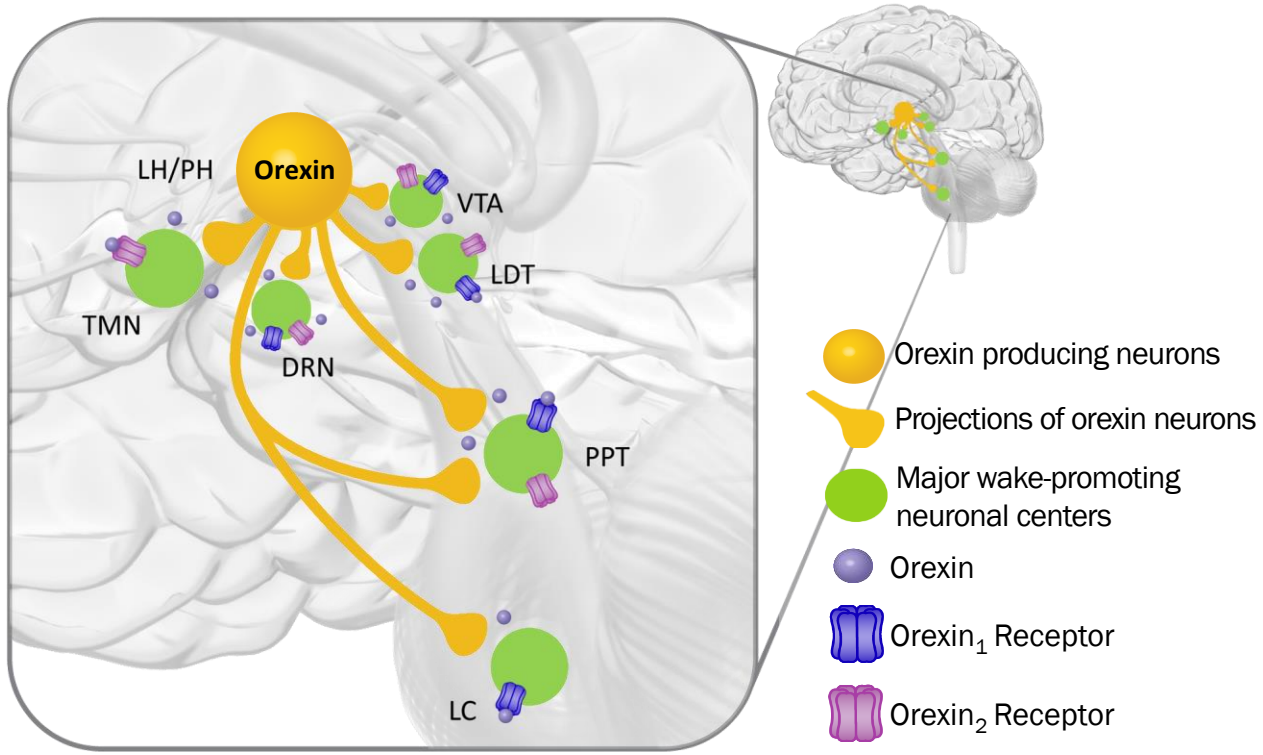
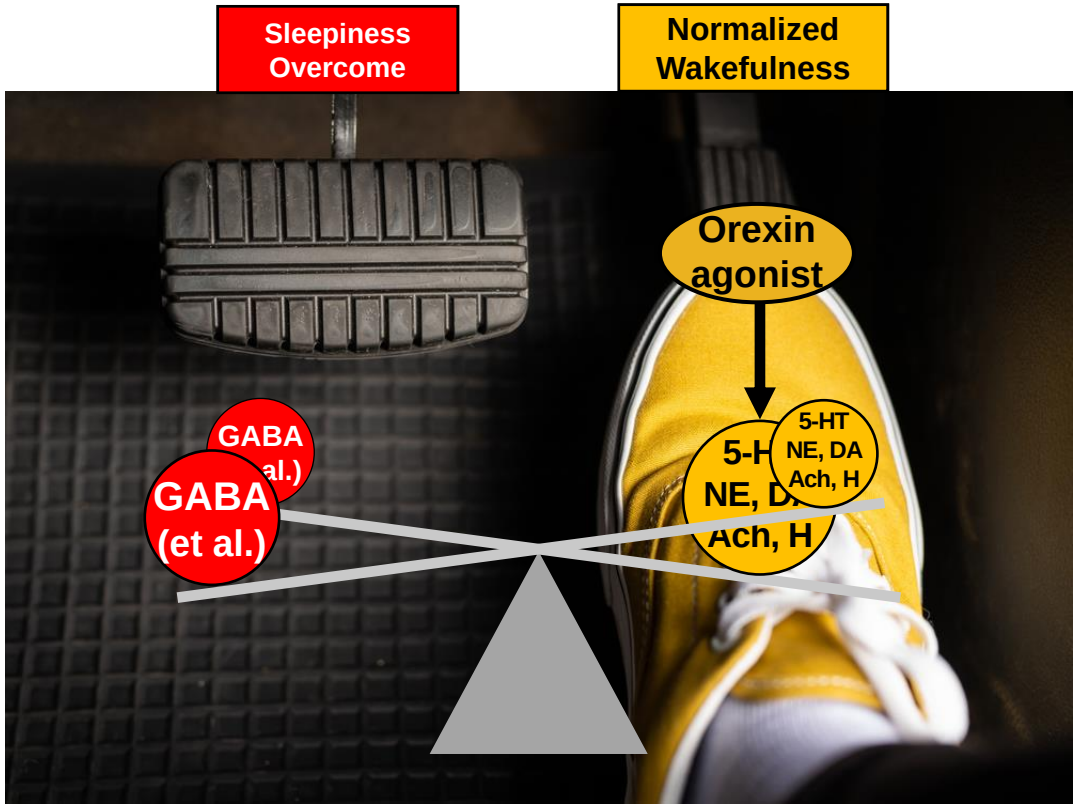
Orexin Agonists in OSA





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

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

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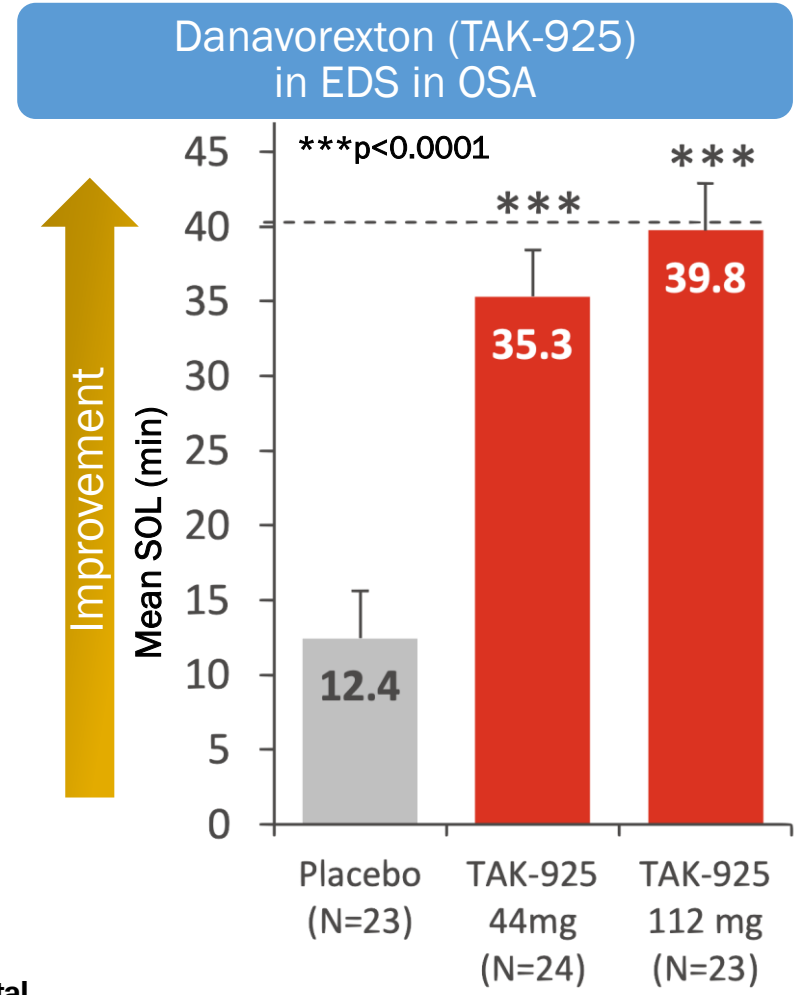
Orexin Agonists in Development

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

- Positive Phase Ib study in EDS in OSA
- Most common TEAEs were urinary system-related.
- No serious TEAEs or discontinuations due to TEAEs occurred
- Oral OX_2R agonist (TAK-861) in phase I in Japan



Pipeline Preview!

JZP 441: oral orexin-2 receptor agonist

- Currently in phase 1 trial for narcolepsy in Japan
- Potential to treat other sleep disorders, such as EDS in OSA

ALKS 2680: oral orexin-2 receptor agonist

- Currently in preclinical studies, narcolepsy trials planned

EDS = excessive daytime sleepiness; OSA = obstructive sleep apnea; SOL = Sleep Onset Latency.

Rubens R. Poster Presentation at 73rd Annual Meeting of the American Academy of Neurology, 2021. JPRN Search Portal. https://rctportal.niph.go.jp/en/detail?trial_id=jRCT2071210007. Accessed 5-19-22. Jazz Pharmaceuticals. https://investor.jazzpharma.com/news-releases/news-release-details/jazz-pharmaceuticals-and-sumitomo-pharma-announce-exclusive. Accessed 5-16-22. JPRN Search Portal. https://rctportal.niph.go.jp/en/detail?trial_ id=jRCT2071210103. Accessed 5-19-22. Alkermes, plc. https://investor.alkermes.com/static-files/d55375ad-a9bf-4a2f-8276-e657f8285d74. Accessed 5/19/2022.

Summary

Historical treatments for EDS in OSA may be effective for many, but there are significant unmet needs

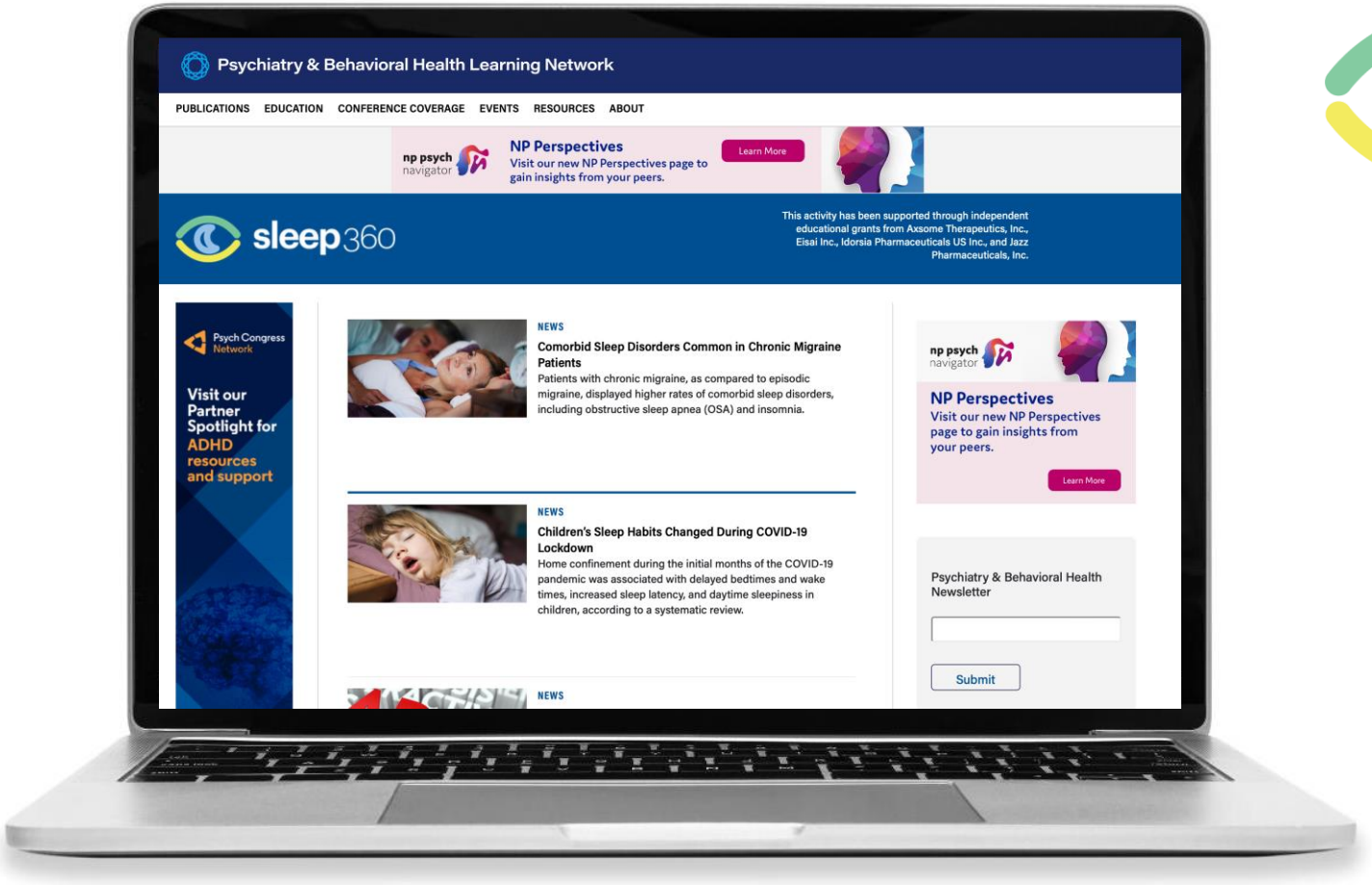
A novel nonstimulant DNRI has shown a favorable efficacy and tolerability profile and other pipeline agents may have potential

EDS in OSA is commonly missed in psychiatric practice, and can be debilitating and dangerous

This is within our scope and our responsibility to find and treat!

EDS = excessive daytime sleepiness; OSA = Obstructive Sleep Apnea; DNRI = dopamine-norepinephrine reuptake inhibitor

Visit the Resource Center



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Questions?