

#CHAIR2020

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Master Class for Neuroscience Professional Development

February 27-29, 2020 | The LINQ | Las Vegas, Nevada

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Updates on the Management of Insomnia: Expert Guidance Through the Latest Clinical Trials on Dual Orexin Receptor Antagonists

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Learning Objective 1

Query your patients about insomnia to facilitate diagnosis and treatment to reduce the personal, clinical, and societal burden it imposes.



Learning Objective 2

Examine the role of orexin in sleep/wake regulation to facilitate treatment selection, particularly in the elderly and those with comorbid conditions.



Learning Objective 3

Incorporate clinical trial updates on dual orexin reuptake inhibitors to identify effective strategies to safely manage insomnia, particularly in older adults with high medical burden and polypharmacy.



What is “Insomnia Disorder”?



- Insomnia symptoms:
 - Trouble falling asleep, staying asleep, or waking too early (note there is no time dimension to the sleep complaints)
- Insomnia Disorder (per DSM-5):
 - Insomnia symptoms, associated with distress or impairment (i.e., irritability, fatigue, concentration problems, etc.)
 - At least 3 nights per week, for at least 3 months
- Note there is no lab testing required!

DSM = The Diagnostic and Statistical Manual of Mental Disorders.
American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013.

Epidemiology of Insomnia



- About 50% of American adults will have occasional insomnia lasting a few nights
- About 10% of adult Americans have persistent insomnia - “insomnia disorder”
- Adolescents and young adults more likely to have trouble falling asleep but not staying asleep
- Older adults more likely to start complaining of difficulty sleeping through the night

Insomnia and Depression



- Diagnostic criterion for MDD
- Included in many scales of depression (e.g., PHQ-9, HAM-D, MADRS)
- Prevalent in 90% of clinical depression
- 60% - 70% positive predictive value in MDD
- Marker for increased risk of suicidal thinking
- Risk factor for relapse

HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; PHQ-9 = Patient Health Questionnaire.

Khurshid KA. *Innov Clin Neurosci*. 2018;15(3-4):28-32.

Insomnia and Other Psychiatric Disorders

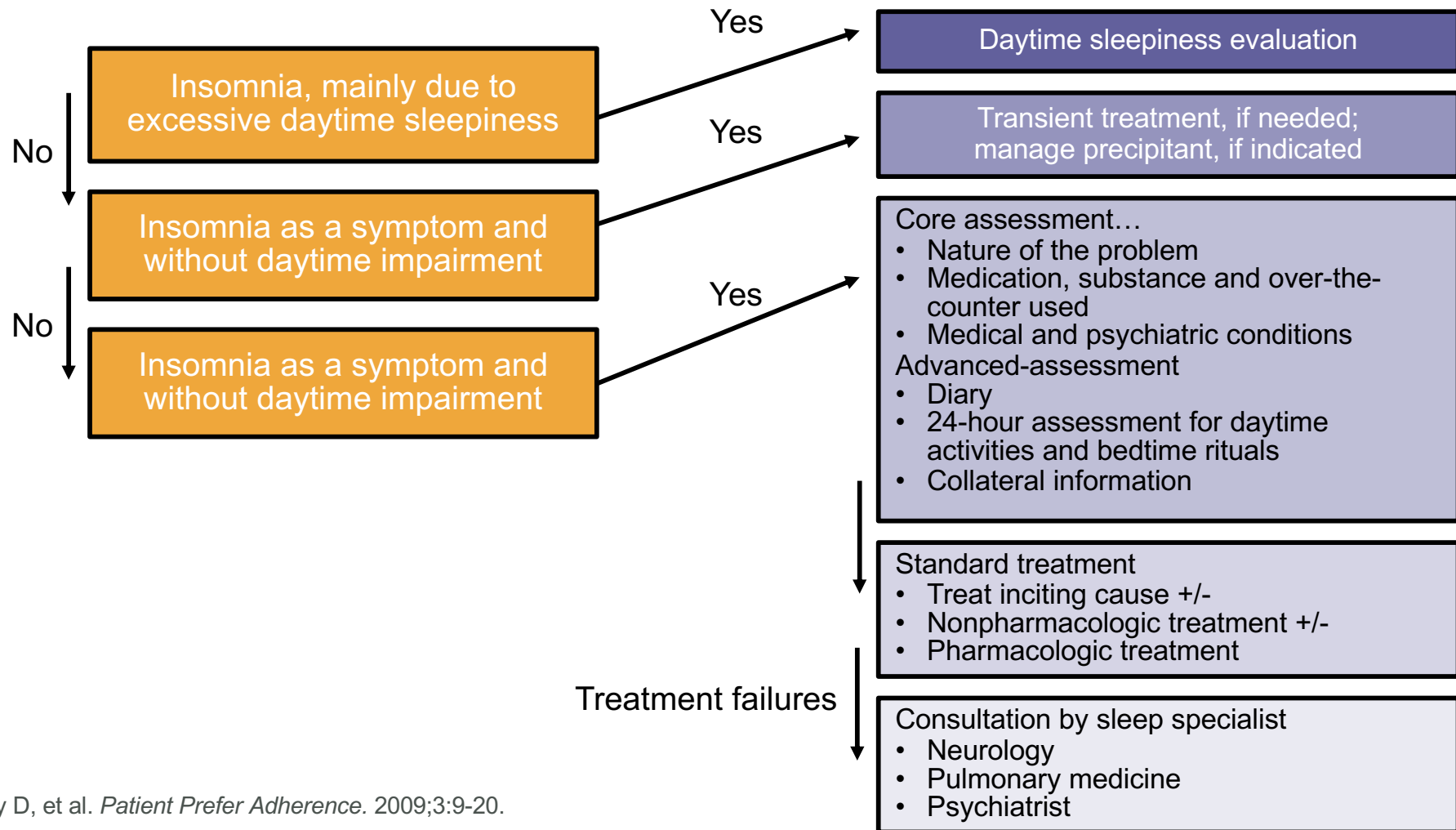
● Psychotic Disorders

- Severe insomnia is a hallmark of prodromal phase of psychosis
- Risk factor for relapse
- Correlated with cognitive dysfunction in schizophrenia

● Anxiety Disorders

- Most common sleep disturbance in anxiety disorders
- Individuals with panic disorders have higher prevalence of insomnia than healthy controls
- Sleep disturbance is one of the DSM-5 diagnostic criterion for generalized anxiety disorder and separation anxiety

Insomnia Evaluation and Treatment Algorithm



Methods to Assess Insomnia



- Sleep diary
- Direct inquiry
- Polysomnography
- Inventories:
 - Insomnia Severity Index (ISI)
 - 7-item, self-administered scale
 - Epworth Sleepiness Scale (ESS)
 - 8-item, self-administered scale
 - Reduced Morningness-Eveningness Questionnaire (rMEQ)
 - 5-item, self-administered scale
 - Disturbing Dreams and Nightmare Severity Index (DDNSI)
 - 5-item, self-administered scale

***Refer to the Resources tab on your iPad to access the full inventories.**

ACP Recommendations for Insomnia

- **Recommendation 1:** ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. (Grade: strong recommendation, moderate-quality evidence)
- **Recommendation 2:** ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful. (Grade: weak recommendation, low-quality evidence)

Short- and Long-term Treatment Effects of Behavioral Therapy vs Pharmacotherapy for Insomnia

| Comparison | Outcome period (quantitative sleep measures) | Conclusion | Quantity and type of evidence | Starting level of evidence strength | Final level of evidence strength |
|-------------------------------|--|--------------------------|-------------------------------|-------------------------------------|----------------------------------|
| CBT-I vs. benzodiazepines | Short term | Improved less with CBT-I | 3 RCT | High | Very low |
| | Long term | Improved more with CBT-I | 3 RCT | High | Moderate |
| CBT-I vs. non-benzodiazepines | Short term | Improved more with CBT-I | 2 RCT | High | Moderate |
| | Long term | Improved more with CBT-I | 1 RCT | High | Low |

RCT = randomized controlled trial.

Mitchell MD, et al. *BMC Fam Pract.* 2012;13:40.

FDA-Approved Drugs for Insomnia



| Drug name | Approved Indication | Available Doses (mg) | Elimination Half-life (hr) |
|--|---|----------------------|--------------------------------|
| <i>BENZODIAZEPINE RECEPTOR AGONISTS</i> | | | |
| <i>Benzodiazepine Immediate Release</i> | | | |
| Estazolam | Sleep onset, sleep maintenance, early awakening | 1, 2 | 10 - 24 |
| Flurazepam | Sleep onset, sleep maintenance, early awakening | 15, 30 | 2.3/48 – 160 active metabolite |
| Quazepam | Sleep onset, sleep maintenance, early awakening | 7.5, 15 | 39/73 active metabolite |
| Temazepam | Unspecified insomnia | 7.5, 15, 22.5, 30 | 3.5 – 18.4 |
| Triazolam | Unspecified insomnia | 0.125, 0.25 | 1.5 – 5.5 |

FDA-Approved Drugs for Insomnia (cont.)

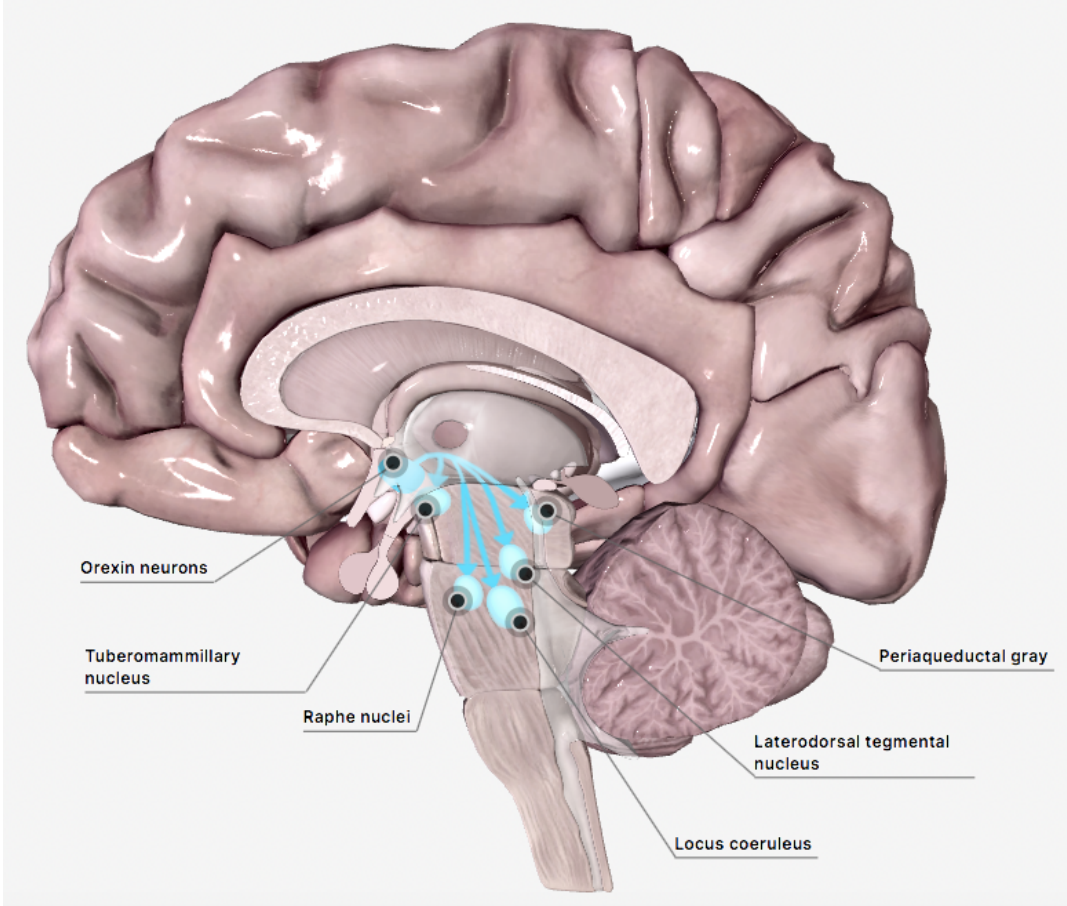
| Drug name | Approved Indication | Available Doses (mg) | Elimination Half-life (hr) |
|--|--------------------------------|----------------------|----------------------------|
| <i>Nonbenzodiazepine Immediate Release</i> | | | |
| Eszopiclone | Sleep onset, sleep maintenance | 1, 2, 3 | 6/ 9 in elderly |
| Zaleplon | Sleep onset | 5, 10 | 1 |
| Zolpidem | Sleep onset | 5, 10 | 2.8 in males |
| <i>Nonbenzodiazepine Extended Release</i> | | | |
| Zolpidem ER | Sleep onset, sleep maintenance | 6.25, 12.5 | 1.6 – 4.5 |
| <i>Nonbenzodiazepine Alternate Delivery</i> | | | |
| Zolpidem oral spray | Sleep onset | 5, 10 | 2.7 – 3.0 |
| Zolpidem sublingual | Sleep onset | 5, 10 | ~2.5 |
| Zolpidem sublingual (middle of the night) | Sleep maintenance | 1.75, 3.5 | ~2.5 |

FDA-Approved Drugs for Insomnia (cont.)

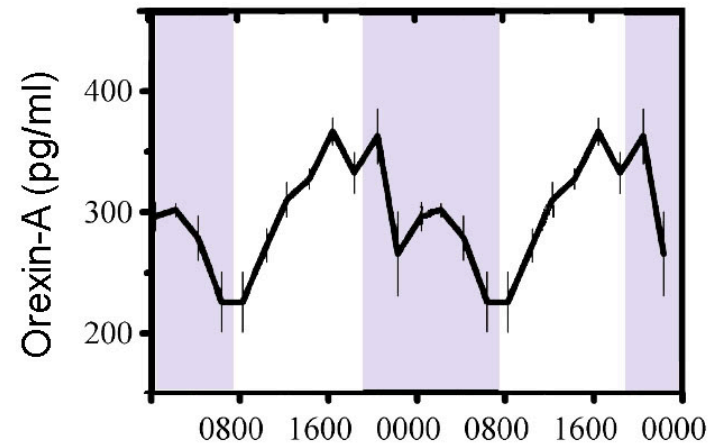
| Drug name | Approved Indication | Available Doses (mg) | Elimination Half-life (hr) |
|---|--------------------------------|----------------------|----------------------------|
| <i>SELECTIVE MELATONIN RECEPTOR AGONIST</i> | | | |
| Ramelteon | Sleep onset | 8 | 1 – 2.6 |
| <i>SELECTIVE HISTAMINE RECEPTOR ANTAGONIST</i> | | | |
| Doxepin (low dose) | Sleep maintenance | 3, 6 | 15.3 |
| <i>DUAL OREXIN RECEPTOR ANTAGONIST</i> | | | |
| Suvorexant | Sleep onset, sleep maintenance | 5, 10, 15, 20 | 12 |
| Lemborexant | Sleep onset, sleep maintenance | 5, 10 | 17, 19 |

Orexins Promote Wakefulness

Opioi... Use Dis... Eating
Multiple Sclerosis...
Pain...
Artifi...



Orexin levels are high during wake



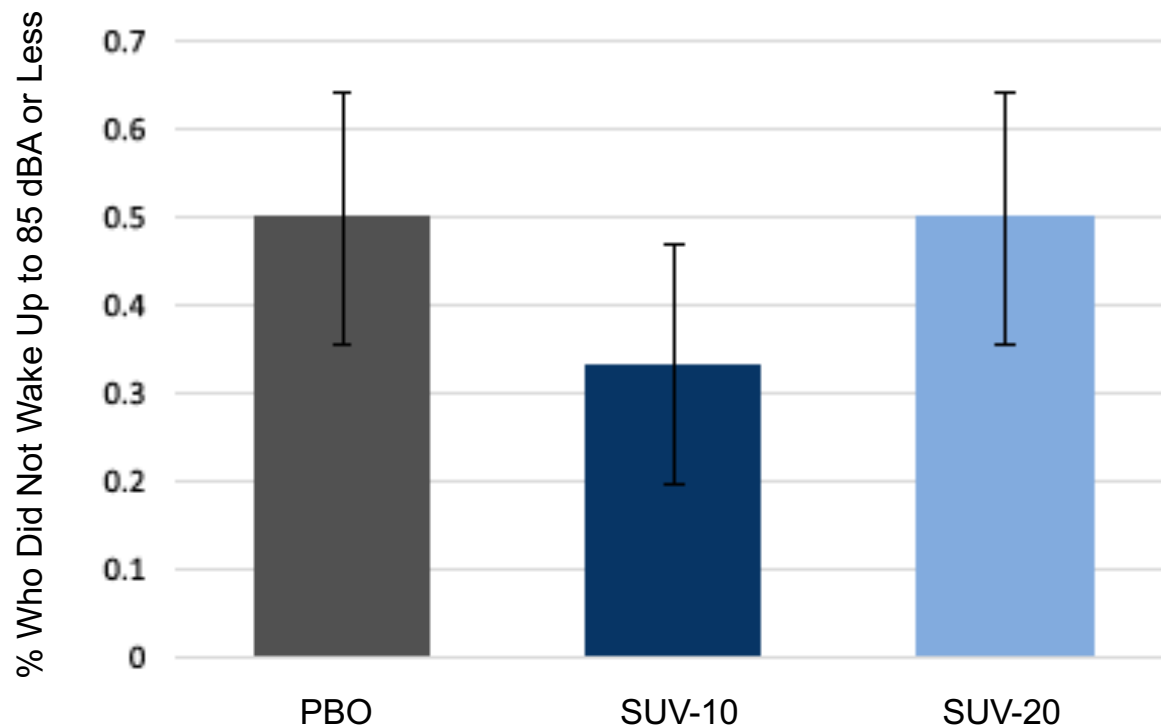
Zeitler JM, et al. *J Neurosci.* 2003;23(8):3555-3560.

Efficacy of Suvorexant vs. Placebo in Insomnia

| Endpoint | Week 1 | | Week 2 | | Week 3 | |
|----------------------------------|----------------|-------------------|----------------|-------------------|----------------|-------------------|
| | N/N (%) | OR (95% CI) | N/N (%) | OR (95% CI) | N/N (%) | OR (95% CI) |
| ISI ≥ 6 point improvement | | | | | | |
| Placebo | – | | 157/685 (22.9) | | 269/638 (42.2) | |
| Suvorexant 20/15mg | – | | 149/440 (33.9) | 1.8 (1.4, 2.4)*** | 228/411 (55.5) | 1.8 (1.4, 2.3)*** |
| sTST ≥ 15% improvement | | | | | | |
| Placebo | 145/740 (19.6) | | 270/715 (29.4) | | 278/664 (41.9) | 1.5 (1.2, 2.0)** |
| Suvorexant 20/15mg | 150/479 (31.3) | 2.1 (1.6, 2.8)*** | 197/463 (42.5) | 2.0 (1.5, 2.5)*** | 213/425 (50.1) | |
| sTSO ≥ 15% improvement | | | | | | |
| Placebo | 316/740 (42.7) | 1.7 (1.4, 2.2)*** | 384/715 (53.7) | | 438/664 (66.0) | 1.2 (0.9, 1.5) |
| Suvorexant 20/15mg | 267/479 (55.7) | | 289/463 (62.4) | 1.5 (1.1, 1.9)** | 297/425 (69.9) | |

ISI = insomnia severity index; sTST = total sleep time; sTSO = time to sleep onset
Herring WJ, et al. *J Clin Sleep Med.* 2016;12(9):1215–1225.

Impact of Suvorexant on Nocturnal Sensitivity in Patients with Insomnia

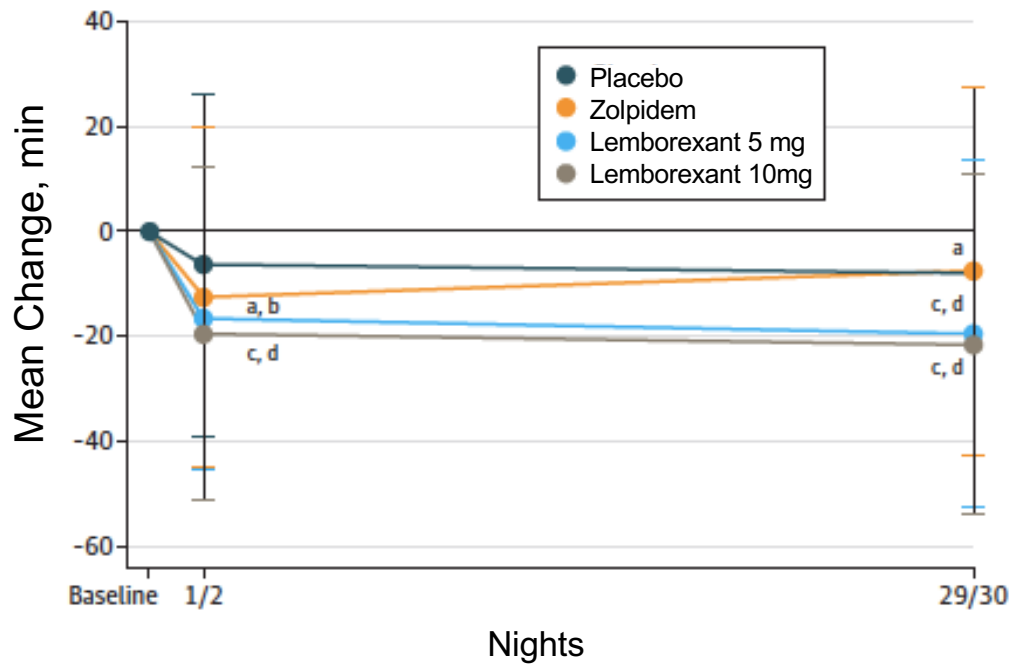


- 50% of individuals in the PBO and SUV-20 groups awakened to 85 dB or less
- 33% in SUV-10 group awakened to 85 dB or less

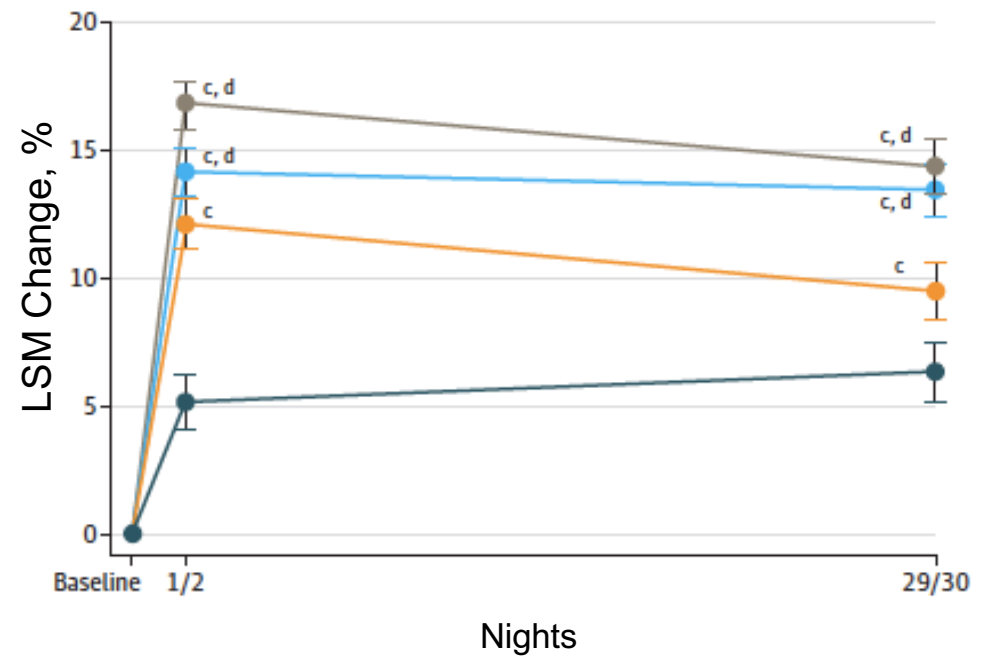
dBA = decibal; PBO = placebo; SUV-10 = suvorexant 10 mg; SUV = suvorexant.
Drake CL, et al. *J Clin Sleep Med*. 2019;15(9):1285–1291.

Efficacy of Lemborexant vs. Zolpidem in Insomnia in Adults 55 Years and Older

Mean Change from Baseline in LPS



LSM Change from Baseline in Sleep Efficiency

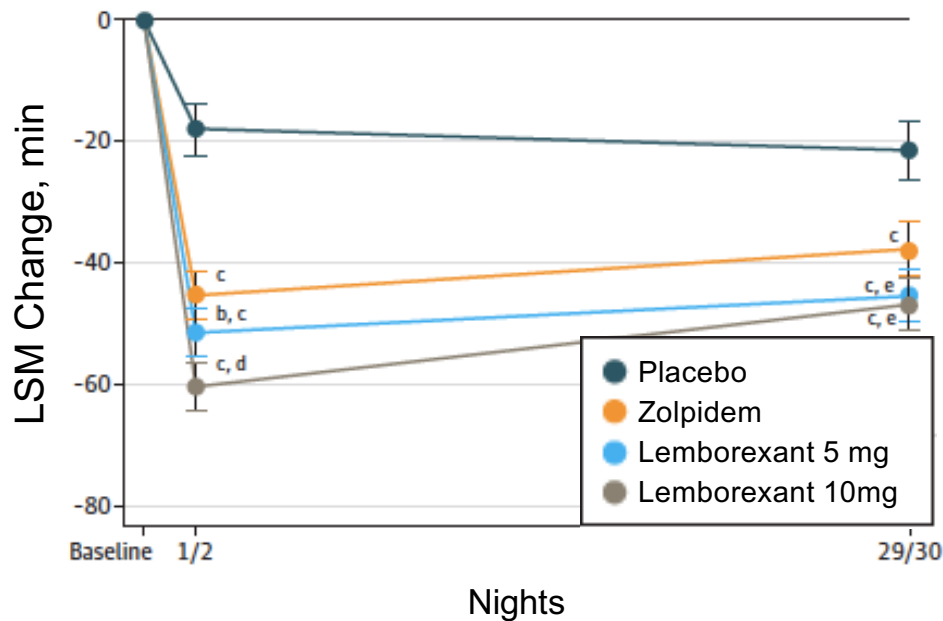


LPS = latency to persistent sleep
 Rosenberg R, et al. *JAMA Netw Open.* 2019;2(12):e1918254.

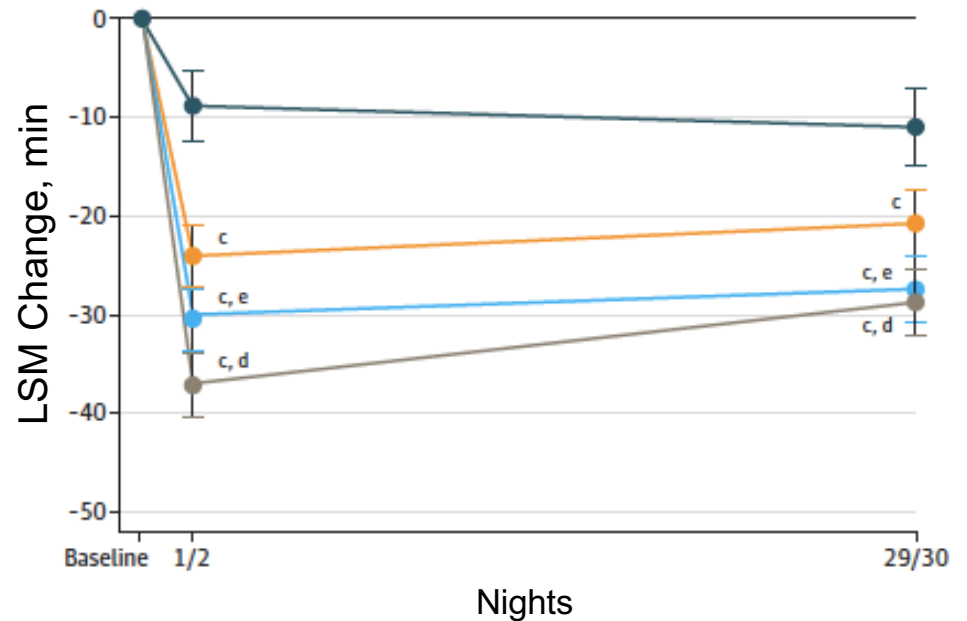
^a $p < .01$ vs. placebo; ^b $p < .05$ vs. zolpidem; ^c $p < .001$ vs. placebo;
^d $p \leq .001$ vs. zolpidem; ^e $p < .01$ vs. zolpidem.

Efficacy of Lemborexant vs. Zolpidem in Insomnia in Adults 55 Years and Older

LSM Change from Baseline in WASO



LSM Change from Baseline in WASO2H

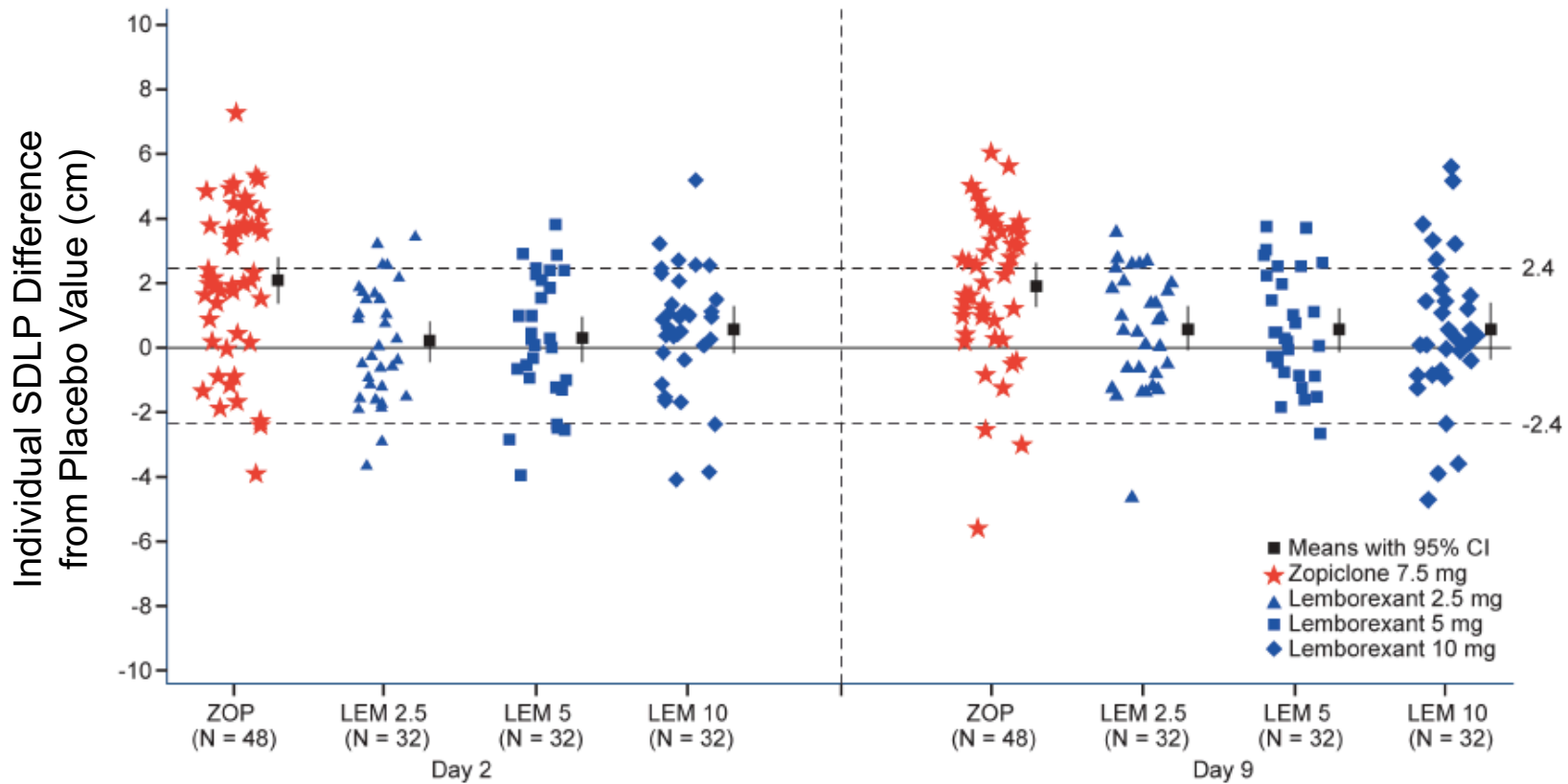


LSM = least square mean.
Rosenberg R, et al. *JAMA Netw Open.* 2019;2(12):e1918254.

^a $p < .01$ vs. placebo; ^b $p < .05$ vs. zolpidem; ^c $p < .001$ vs. placebo;
^d $p \leq .001$ vs. zolpidem; ^e $p < .01$ vs. zolpidem.

Effect of Single and Repeated Doses of Lemborexant vs. Zopiclone on Vehicle Driving Performance

Eating
Multiple Sclerosis
Pain
Artificial



LEM = Lemborexant; SDLP = standard deviation of lateral position; ZOP = Zopiclone.
Vermeeren A, et al. *Sleep*. 2019;42(4). pii: zsy260.

Conclusion



- Insomnia is often more than a mere symptom but an independent disorder that can significantly impact health and function.
- Pharmacotherapy for insomnia is usually initiated with benzodiazepines, non-benzodiazepines, and sedating antidepressants, but these therapies may be ineffective, unsuitable for long-term use, or pose serious adverse risks.
- Unlike traditional therapies that increase the activity of the sleep-promoting systems, orexin-targeted therapies such as lemborexant and suvorexant block wake-promoting systems.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely



- Assess insomnia in your patients with psychiatric disorders.
- Incorporate dual orexin reuptake inhibitors into treatment strategies for patients with insomnia, including older adults.

Questions & Answers

Don't forget to fill out your evaluations to collect your credit.

