Dual Orexin Receptor Antagonists (DORAs) for Insomnia Systematic Review

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Abbreviations

- CBT cognitive behavioral therapy
- DORAs dual orexin receptor antagonists
- LPS latency to persistent sleep
- MCID minimal clinically important difference
- TST total sleep time
- WASO wake after sleep onset

Overview

- Background
- PICOS
- Key Questions
- Methods
- Findings
- Discussion
- State Considerations

Background, PICOS, and Key Questions

Background *(1 of 2)*

- Insomnia is common
- Characteristics
  - Difficulty falling asleep
  - Difficulty staying asleep
  - Difficulty getting quality sleep
  - Tiredness upon waking
  - Low energy
  - Mood changes
- May be acute or chronic
- May be primary or secondary

Background *(2 of 2)*

- Cause unknown
  - May be multifaceted
- Risks of sleep deprivation
  - Operating vehicles or machinery
  - Performing tasks requiring alertness
  - Depression
  - Anxiety
  - High blood pressure
  - Heart attack
  - Stroke
  - Obstructive sleep apnea
  - Type 2 diabetes
  - Other conditions

Insomnia Drugs

- Classes of drugs
  - Benzodiazepines
  - Nonbenzodiazepine hypnotics (Z drugs)
  - Melatonin agonists
  - Atypical antidepressants
  - Orexin modulators
- Focus on dual orexin receptor antagonists (DORAs)
  - Suvorexant
  - Lemborexant
  - Daridorexant

PICOS *(1 of 2)*

- Populations:
  - Adults aged 18 years and older with insomnia
- Interventions:
  - DORAs
    - Daridorexant (Quviviq)
    - Lemborexant (Dayvigo)
    - Suvorexant (Belsomra)
- Comparators:
  - Another listed intervention
  - Another pharmacological treatment for insomnia (e.g., benzodiazepines, Z-drugs)

PICOS *(2 of 2)*

- Outcomes:
  - Wake time after sleep onset (WASO)
  - Latency to persistent sleep (LPS)
  - Total sleep time (TST)
  - Sleep quality
  - Fatigue
  - Alertness after waking
  - Adverse events (AEs), including the potential for misuse
  - Serious adverse events (SAEs; e.g., hospitalization, life-threatening event, disability, mortality)
- Study Designs:
  - Randomized controlled trials (RCTs)
  - Studies from countries that are *very high* on the United Nations Human Development Index

Key Questions

1. Effectiveness of DORAs for insomnia
    a. Variation by patient characteristics
2. Potential harms of DORAs for insomnia
    a. Variation by patient characteristics
3. Characteristics of ongoing studies
4. Characteristics of pipeline therapies

Methods

Methods

- Searched relevant DERP evidence (e.g., Ovid MEDLINE, Cochrane Central)
- Examined reference lists of systematic reviews
- Assessed the risk of bias of published literature
- Assessed the certainty of evidence of published literature (GRADE)
- Searched for ongoing studies (e.g., ClinicalTrials.gov, Scan Medicine)
- Searched for pipeline drugs with upcoming PDUFA dates (IPD Analytics)

Risk of Bias Assessment

- **Low**

  Clear reporting of methods and mitigation of potential biases and conflicts of interest

- **Moderate**

  Incomplete information about methods that might mask important limitations or a meaningful conflict of interest

- **High**

  Clear flaws that might introduce serious bias

GRADE Certainty of Evidence

Outcomes Rated: *WASO, LPS, TST, and safety*

- **High** *(RCTs start here)*
  Very confident that the estimate of effect of intervention on outcome lies close to the true effect
- **Moderate**
  Moderately confident in estimate of effect of intervention on outcome; true effect is likely close to estimate, but possibly different
- **Low** *(Nonrandomized studies start here)*
  Little confidence in estimate of effect of intervention on outcome; true effect may be substantially different from estimate
- **Very Low**
  No confidence in estimate of effect of intervention on outcome; true effect is likely substantially different from estimate

Abbreviations. LPS: latency to persistent sleep; TST: total sleep time; WASO: wake after sleep onset;

Key Outcomes of Interest and MCIDs

Outcome	Assessment	Interpretation	MCID
Total sleep time	Subjective or objective measures of total time asleep	Higher numbers better	55 min
Wake after sleep onset	Subjective or objective measures of total time awake after initially falling asleep	Lower numbers better	20 min
Latency to persistent sleep	Subjective or objective measures of length of time to fall asleep	Lower numbers better	15 min
Insomnia severity index	Subjective measure of insomnia severity and impact on daytime functioning	Lower numbers better	6 points

Abbreviations. MCID: minimal clinically important difference

Findings

Bottom Line

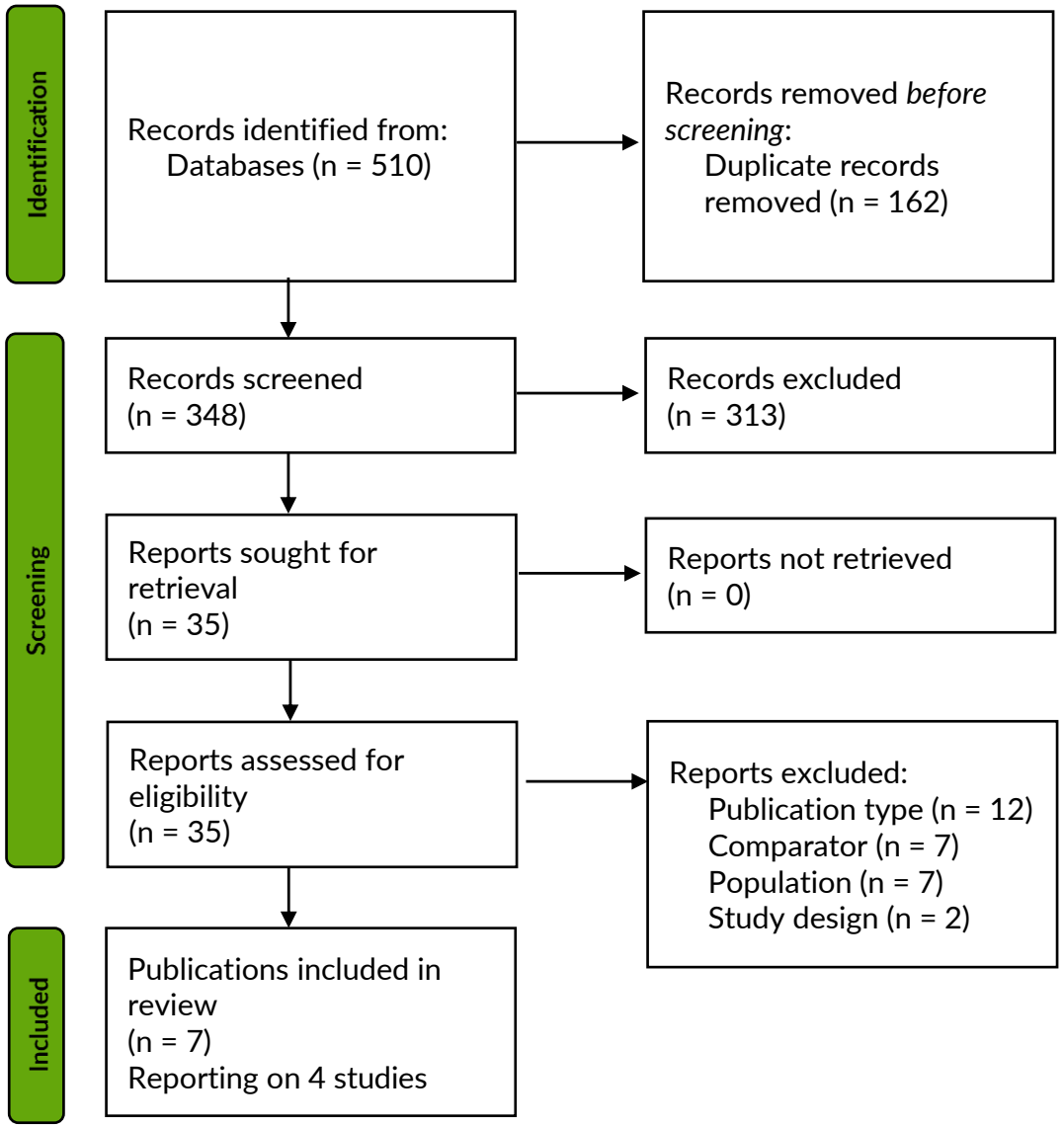
Key Findings

- Based on the evidence reviewed in this report, it is not certain if DORAs are equally effective or more effective than other medications for insomnia.
  - Overall, evidence was limited
    - 4 studies (1 each for daridorexant and suvorexant, and 2 for lemborexant)
    - Very low to moderate certainty of evidence
  - Lemborexant may be associated with greater improvements in sleep compared with zolpidem
    - Differences are small and may not be clinically meaningful
  - Overall, DORAs have similar or lower rates of adverse events compared to other medications for insomnia (flurazepam, zolpidem, and eszopiclone)

Findings

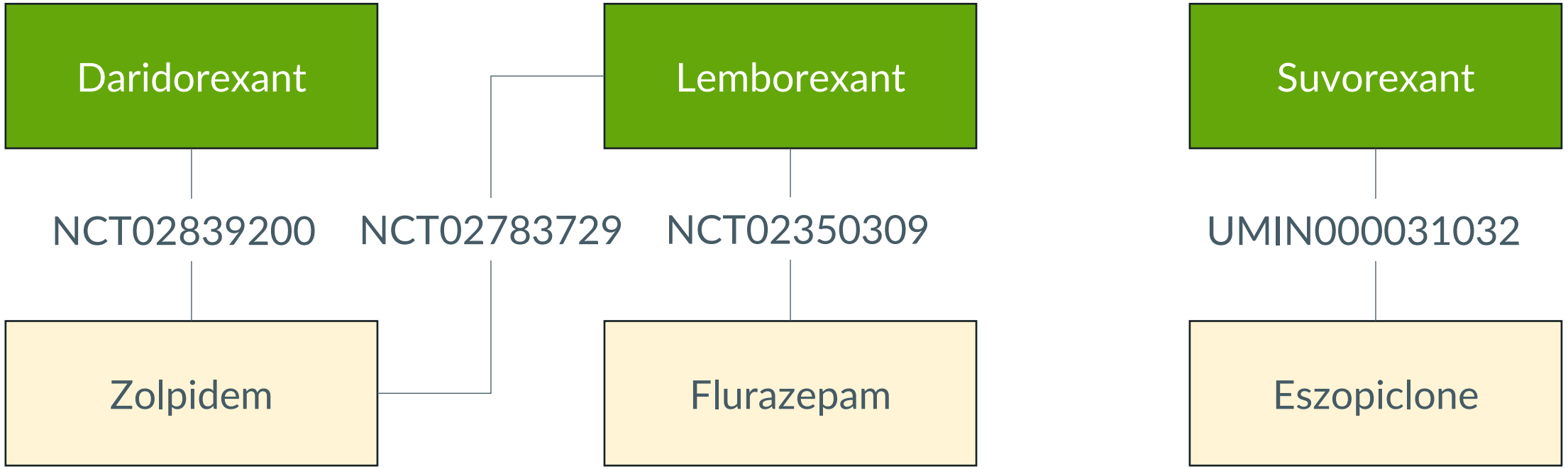
Effectiveness and Harms

Study Flow Diagram



Findings Overview

- We identified 4 eligible RCTs with active comparators



Findings: Study Characteristics *(1 of 2)*

Author, Year Study ID	Risk of Bias	Treatment Groups	Length of Treatment
Daridorexant vs. zolpidem			
Dauvilliers et al., 2020 NCT02839200	Moderate	6-arm parallel study • Daridorexant (5 mg, 10 mg, 25 mg, and 50 mg) • Zolpidem 10 mg • Placebo	30 days plus 30-day safety follow-up
Lemborexant vs. flurazepam			
Mayleben et al., 2021 NCT02350309 Study 107	High	4-phase crossover study • Lemborexant (5 mg and 10 mg) • Flurazepam 30 mg • Placebo	1 day of treatment followed by 14-day washout period for each phase
Lemborexant vs. zolpidem			
Rosenberg et al., 2019 NCT02783729 SUNRISE 1	Moderate	4-arm parallel study • Lemborexant (5 mg and 10 mg) • Zolpidem ER 6.25 mg • Placebo	30 days plus 14-day safety follow-up
Suvorexant vs. eszopiclone			
Shigetsura et al., 2022 UMIN000031032	High	2-arm parallel study • Suvorexant (15 mg or 20 mg, depending on age) • Eszopiclone (2 mg or 3 mg, depending on age)	2-week run-in period followed by 4 weeks of treatment

Findings: Study Characteristics *(2 of 2)*

Author, Year Study ID	Primary Outcomes Included and Assessed with GRADE				Secondary Outcomes Included	
	WASO	LPS	TST	Safety	ISI	Other
Daridorexant vs. zolpidem						
Dauvilliers et al., 2020[20] NCT02839200	✓	✓	✓	✓	✓	• Sleep Quality • Morning Sleepiness • Daytime Alertness
Lemborexant vs. flurazepam						
Mayleben et al., 2021[21] NCT02350309 Study 107	⊘	⊘	⊘	✓	⊘	Sleep Onset Latency
Lemborexant vs. zolpidem						
Rosenberg et al., 2019[22] NCT02783729 SUNRISE 1	✓	✓	✓	✓	✓	⊘
Suvorexant vs. eszopiclone						
Shigetsura et al., 2022[23,a] UMIN000031032	⊘	⊘	⊘	✓	✓	⊘

Abbreviations. ISI: insomnia severity index; LPS: latency to persistent sleep; TST: total sleep time; WASO: wake after sleep onset

Findings: Participant Baseline Characteristics *(1 of 2)*

Author, Year Study ID	Number of Participants Randomized	Mean Age (SD)	Female	Ethnicity			Mean ISI (SD)	Mean BMI (SD)
				White	Black or African American	Other		
Daridorexant vs. zolpidem								
Dauvilliers et al., 2020[20] NCT02839200	359	44.7 (11.3)	230 (64%)	321 (89%)	35 (10%)	3 (1%)	21.2 (2.8)	25.2 (3.3)
Lemborexant vs. flurazepam								
Mayleben et al., 2021[21] NCT02350309 Study 107	69	50.2 (12.9)	51 (74%)	35 (51%)	33 (48%)	1 (1%)	21.4 (3.4)	27.3 (4.4)

Notes. Blank cells indicate baseline data that were not reported. [a] Ethnicity of participants not reported, but study was conducted in Japan.
Abbreviations. BMI: body mass index; ISI: insomnia severity index; SD: standard deviation

Findings: Participant Baseline Characteristics *(2 of 2)*

Author, Year Study ID	Number of Participants Randomized	Mean Age (SD)	Female	Ethnicity			Mean ISI (SD)	Mean BMI (SD)
				White	Black or African American	Other		
Lemborexant vs. zolpidem								
Rosenberg et al., 2019[22] NCT02783729 SUNRISE 1	1,006	63.9 (6.8)	869 (86%)	727 (72%)	256 (25%)	23 (2%)	19.1 (3.5)	--
Suvorexant vs. eszopiclone								
Shigetsura et al., 2022[23,a] UMIN000031032	18	58.7	11 (61%)	--	--	--	14.7	--

Notes. Blank cells (--) indicate baseline data that were not reported. [a] *Ethnicity of participants not reported, but study was conducted in Japan.*
Abbreviations. BMI: body mass index; ISI: insomnia severity index; SD: standard deviation

Findings: Daridorexant vs. Zolpidem *(1 of 2)*

No. of Studies Sample Size	CoE	Relationship With Outcome	Rationale for CoE Rating
Wake after sleep onset (WASO)			
1 RCT N = 299	●●●○ Moderate	Unknown • Reduced across all groups; no formal statistical comparison; unclear if any significant differences between groups	Downgraded • 1 level for imprecision (i.e., not assessable)[a]
Latency to persistent sleep (LPS)			
1 RCT N = 299	●●●○ Moderate	Unknown • Reduced across most groups; no formal statistical comparison; unclear if are any significant differences between groups	Downgraded • 1 level for imprecision (i.e., not assessable)[a]
Total sleep time (TST)			
1 RCT N = 299	●●●○ Moderate	Unknown • Increased across all groups; no formal statistical comparison; unclear if are any significant differences between groups	Downgraded • 1 level for imprecision (i.e., not assessable)[a]

Notes. [a] We could not assess inconsistency due to the inclusion of only 1 eligible RCT.

Abbreviations. AE: adverse event; CoE: certainty of evidence; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; No: number.

Findings: Daridorexant vs. Zolpidem *(2 of 2)*

No. of Studies Sample Size	CoE	Relationship With Outcome	Rationale for CoE Rating
Safety			
1 RCT N = 299	●●●○ Moderate	Around one-third of people experienced an AE • 35%, 38%, 38%, and 34% with daridorexant 5 mg, 10 mg, 25 mg, and 50 mg, respectively • 40% with zolpidem	Downgraded • 1 level for imprecision (i.e., not assessable)[a]

Notes. [a] *We could not assess inconsistency due to the inclusion of only 1 eligible RCT.*
Abbreviations. AE: adverse event; CoE: certainty of evidence; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; No: number.

Detailed Findings: Daridorexant vs. Zolpidem *(1 of 4)*

- No formal statistical comparison between groups
- WASO (time awake after having first fallen asleep) decreased across all active treatment groups
  - People had more sleep with daridorexant
    - Around 28 to 47 minutes more at days 1 and 2, depending on dose
    - Around 37 to 48 minutes more at days 28 and 29, depending on dose
  - People had more sleep with zolpidem
    - 30 minutes more at days 1 and 2
    - 36 minutes more at days 28 and 29
- Additional analysis found a dose-response effect for daridorexant

Detailed Findings: Daridorexant vs. Zolpidem *(2 of 4)*

- No formal statistical comparison between groups
- LPS (time to first 10 minutes of sleep) decreased across all groups
  - People fell asleep more quickly with daridorexant
    - 26 to 37 minutes quicker at days 1 and 2, depending on dose
    - 20 to 39 minutes quicker at days 28 and 29, depending on dose
  - People fell asleep more quickly with zolpidem
    - 44 minutes quicker at days 1 and 2
    - 45 minutes quicker at days 28 and 29
- Again, a dose-response effect for daridorexant

Detailed Findings: Daridorexant vs. Zolpidem *(3 of 4)*

- TST increased across all groups
  - Clinically meaningful except for the daridorexant 5 mg dose
  - Increases with zolpidem were somewhere between the lowest dose of daridorexant and the highest dose
- ISI decreased across all groups
  - Clinically meaningful
  - Higher in all doses of daridorexant relative to zolpidem except for the 5 mg daridorexant dose
- Sleep quality, morning sleepiness, and daytime alertness improved across all groups

Detailed Findings: Daridorexant vs. Zolpidem *(4 of 4)*

- Adverse events occurred in about one-third of participants
  - Slightly higher with zolpidem than with daridorexant
    - 34% to 38% with daridorexant, depending on dose
    - 40% with zolpidem
- Common AEs with either drug
  - Headache: 8% to 10%
  - Somnolence: 5% to 7%
- Serious AEs
  - 2% to 3% with daridorexant, depending on dose
  - None with zolpidem
- AEs leading to discontinuation
  - 2% to 3% with daridorexant, depending on dose
  - 2% with zolpidem

Findings: Lemborexant vs. Flurazepam *(1 of 2)*

Number of Studies Sample Size	CoE	Relationship With Outcome	Rationale for CoE Rating
Wake after sleep onset			
No eligible studies reported this outcome			
Latency to persistent sleep			
No eligible studies reported this outcome			
Total sleep time			
No eligible studies reported this outcome			

Abbreviations. CoE: certainty of evidence.

Findings: Lemborexant vs. Flurazepam *(2 of 2)*

Number of Studies Sample Size	CoE	Relationship With Outcome	Rationale for CoE Rating
Safety			
1 RCT N = 69	●●○○ Low	AEs • Around 7% to 11% of people experienced an AE • Most common AE was somnolence • No serious AEs	Downgraded • 1 level for imprecision (i.e., not assessable)[a] • 1 level for indirectness (i.e., only single dose administered)

Abbreviations. AE: adverse event; CoE: certainty of evidence; RCT: randomized controlled trial.

Detailed Findings: Lemborexant vs. Flurazepam *(1 of 2)*

- Sleep onset latency (i.e., how long it takes to fall asleep) decreased across all groups
  - People fell asleep more quickly with lemborexant
    - From 18 minutes at baseline to 11 or 13 minutes, depending on dose
  - People fell asleep more quickly with flurazepam
    - From 18 minutes at baseline to 9 minutes
- Sleep propensity (i.e., likelihood of falling or staying asleep) increased across all groups
- Next morning sleepiness showed a dose-response in the lemborexant groups

Detailed Findings: Lemborexant vs. Flurazepam *(2 of 2)*

- Treatment emergent AEs
  - 7.2% with lemborexant 5 mg
  - 11.8% with lemborexant 10 mg
  - 7.4% with flurazepam
- Common AEs in both groups
  - Somnolence
    - 1.4% with lemborexant 5 mg
    - 4.4% with lemborexant 10 mg
    - 2.9% with flurazepam
- Serious AEs
  - None

Findings: Lemborexant vs. Zolpidem *(1 of 2)*

Number of Studies Sample Size	CoE	Relationship With Outcome	Rationale for CoE Rating
Wake after sleep onset (WASO)			
1 RCT N = 798	●●○○ Low	Lemborexant was associated with significant improvements in WASO compared with zolpidem; however, the difference may not be clinically meaningful	Downgraded • 1 level for risk of bias • 1 level for indirectness (i.e., only people aged 55 and older included)[a]
Latency to persistent sleep (LPS)			
1 RCT N = 798	●●○○ Low	Lemborexant was associated with significant improvements in LPS compared with zolpidem; however, the difference may not be clinically meaningful	Downgraded • 1 level for risk of bias • 1 level for indirectness (i.e., only people aged 55 and older included)[a]
Total sleep time			
No eligible studies reported this outcome			

Notes. [a] *We could not assess inconsistency due to the inclusion of only 1 eligible RCT.*
Abbreviations. CoE: certainty of evidence; RCT: randomized controlled trial.

Findings: Lemborexant vs. Zolpidem *(2 of 2)*

Number of Studies Sample Size	CoE	Relationship With Outcome	Rationale for CoE Rating
Safety			

1 RCT
N = 798
	●●○○
	Low
		AEs
		• Around 28% to 35% of people experienced an AE
		• Most common AE was headache
		• Serious AEs
		  • 0.8% with lemborexant 5 mg
		  • None with lemborexant 10 mg
		  • 1.5% with zolpidem
		• Severe AEs
		  • 0.4% with lemborexant 5 mg
		  • 0.7% with lemborexant 10 mg
		  • 3.0% with zolpidem
			Downgraded
			• 1 level for risk of bias
			• 1 level for indirectness (i.e., only people aged 55 and older were included)[a]

Notes. [a] *We could not assess inconsistency due to the inclusion of only 1 eligible RCT.*
Abbreviations. AE: adverse event; CoE: certainty of evidence; RCT: randomized controlled trial.

Detailed Findings: Lemborexant vs. Zolpidem *(1 of 3)*

- WASO (i.e., time awake after having first fallen asleep) decreased in all groups at days 1 and 2
  - People had more sleep with lemborexant
    - Around 50 to 60 minutes more at days 1 and 2, depending on dose
    - Around 44 to 46 minutes more at days 29 and 30, depending on dose
  - People had more sleep with zolpidem
    - Around 44 minutes more at days 1 and 2
    - Around 37 minutes more at days 29 and 30
  - Difference is statistically significant but probably not clinically meaningful
    - People had around 6 to 15 more minutes sleep with lemborexant than with zolpidem

Detailed Findings: Lemborexant vs. Zolpidem *(2 of 3)*

- LPS (i.e., time to first 10 minutes of sleep) decreased in all groups
  - All participants fell asleep more quickly after a single dose and over the 30-day study period
    - Around 17 to 22 minutes quicker with lemborexant
    - Around 7 to 13 minutes quicker with zolpidem
  - Difference is statistically significant, except 5mg dose on nights 1 and 2, but probably not clinically meaningful

Detailed Findings: Lemborexant vs. Zolpidem *(3 of 3)*

- Treatment emergent AEs
  - 27.8% with lemborexant 5 mg
  - 30.6% with lemborexant 10 mg
  - 35.4% with zolpidem
- Common AEs in both groups
  - Headache
    - 6.4% with lemborexant 5 mg
    - 4.9% with lemborexant 10 mg
    - 5.3% with zolpidem
- Serious AEs
  - 0.8% with lemborexant 5 mg
  - 0 with lemborexant 10 mg
  - 1.5% with zolpidem
- Severe AEs
  - 0.4% with lemborexant 5 mg
  - 0.7% with lemborexant 10 mg
  - 3.0% with zolpidem

Findings: Suvorexant vs. Eszopiclone *(1 of 2)*

Number of Studies Sample Size	CoE	Relationship With Outcome	Rationale for CoE Rating
Wake after sleep onset			
No eligible studies reported this outcome			
Latency to persistent sleep			
No eligible studies reported this outcome			
Total sleep time			
No eligible studies reported this outcome			

Abbreviations. CoE: certainty of evidence.

Findings: Suvorexant vs. Eszopiclone *(2 of 2)*

Number of Studies Sample Size	CoE	Relationship With Outcome	Rationale for CoE Rating
Safety			
1 RCT N = 18	●○○○ Very low	AEs occurred with suvorexant and eszopiclone • Most common AE with suvorexant was fatigue (88.9%) • Most common AE with eszopiclone was somnolence (66.7%)	Downgraded • 1 level for risk of bias • 1 level for indirectness (i.e., specific population) • 2 levels for imprecision (i.e., very small sample size)[a]

Notes. [a] *We could not assess inconsistency due to the inclusion of only 1 eligible RCT.*
Abbreviations. AE: adverse event; CoE: certainty of evidence; RCT: randomized controlled trial.

Detailed Findings: Suvorexant vs. Eszopiclone *(1 of 2)*

- ISI decreased in all groups
  - People had less severe insomnia with suvorexant
    - A reduction of 3.3 points at week 2 and 4.3 points at week 4
  - People had less severe insomnia with eszopiclone
    - A reduction of 4.5 points at week 2 and 4.1 points at week 4
  - No significant difference between groups

Detailed Findings: Suvorexant vs. Eszopiclone *(2 of 2)*

- Treatment emergent AEs in both groups
  - Fatigue
    - 88.9% with suvorexant
  - Somnolence
    - 66.7% with eszopiclone
- Serious AEs
  - None

Findings

Ongoing Studies

Findings: Ongoing Studies

- We didn’t identify any eligible ongoing studies

Findings

Pipeline Therapies

Findings: Pipeline Therapies

- We didn’t identify any pipeline therapies with upcoming PDUFA dates

Discussion and State Considerations

Discussion *(1 of 2)*

- Based on the evidence reviewed in this report, it is not certain if DORAs are equally effective or more effective than other medications for insomnia.
  - Overall, evidence was limited
    - 4 studies (1 each for daridorexant and suvorexant, and 2 for lemborexant)
    - Very low to moderate certainty of evidence
  - Lemborexant may be associated with greater improvements in sleep compared with zolpidem
    - Differences are small and may not be clinically meaningful
  - Overall, DORAs have similar or lower rates of adverse events compared to other medications for insomnia (flurazepam, zolpidem, and eszopiclone)

Discussion *(2 of 2)*

- Clinical guidelines echo this uncertainty
  - American Academy of Sleep Medicine (AASM; 2017) notes the evidence is weak
    - Recommends suvorexant
    - Guidelines completed before the approval of daridorexant and lemborexant
  - AASM and American College of Physicians (ACP; 2016) recommends that the decision to use insomnia medication should be made on an individual basis
  - AASM indicates there is strong evidence for CBT
    - Recommends CBT as primary intervention
    - Notes that not all patients have access to CBT
    - Pharmaceuticals (with or without CBT) are a beneficial secondary option

Discussion: Limitations *(1 of 2)*

- Studies have moderate or high risk of bias
- Studies funded by pharmaceutical companies
- Short studies
- No head-to-head studies among DORAs
- Few studies comparing DORAs to other classes of drugs

Discussion: Limitations *(2 of 2)*

- Looked for indirect evidence
  - No head-to-head studies among DORAs
- From 1 recent NMA:
  - DORAs were significantly better than placebo across a range of primarily subjective sleep parameters
    - However, differences were small
  - When compared with each other, most comparisons were not significantly different
    - When differences were statistically significant, they were generally very small with no clear pattern by individual drug

State Considerations

- State administrators may find it difficult to select preferred DORAs
  - Uncertain whether DORAs are equally effective or better than current treatments
  - Uncertain if any DORA is superior to the others
- Evidence for these drugs is limited
  - Risk of bias
  - Short-term evaluations
- DORAs as an alternative to other classes of sleep aids
  - Based on the individual patient
- DORAs are currently available as brand-name drugs
  - Cost may be a factor with upcoming changes to Medicaid funding
- Other options may be appropriate for insomnia
  - Especially if there are concerns about long-term safety with other drugs

Questions?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EVIDENCE-BASED POLICY