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Drug Class Update: Sedatives

Date of Review: February 2026

Date of Last Review: April 2023 (circadian rhythm disorders)
August 2022 (insomnia)
Dates of Literature Search: 09/01/2022 - 11/21/2025

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this update is to review recent evidence for the use of sedatives in the treatment of chronic insomnia disorder.

Plain Language Summary:

- Is there any new evidence that would change the current policy for medicines to treat a person's ability to fall asleep and/or stay asleep?
- Insomnia is the inability to fall asleep, stay asleep, or achieve quality sleep.
- CBT-I is a sleep management method that involves a combination of thinking and behavior techniques such as control of surroundings, limiting sleep to only certain times, relaxation methods, and good sleep practices.
- A 2025 evidence review concluded that it is uncertain whether a specific type of medicines called dual orexin receptor antagonists (DORAs) are equal or better than other medicines for insomnia.
- The Veterans Administration/Department of Defense (VA/DoD) strongly recommends cognitive behavioral therapy for insomnia (CBT-I) for chronic insomnia. CBT-I is a non-medical program that helps people change habits and thoughts that make it hard to sleep.
- In 2024, the Oregon Mental Health Clinical Advisory Group (MHCAG) recommended cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for all patients with sleep disorders before using medicine. When medicine is necessary, patients should not take it for more than 4 weeks whenever possible. MHCAG recommends providers prescribe a type of medicine called benzodiazepines only as needed for 7-10 days, and prescribers should have a plan for tapering (or gradually stopping the medicine).
- Certain types of medicines may be helpful for specific sleep symptoms including:
    - non-benzodiazepine hypnotics [zolpidem, eszopiclone] for getting to sleep and/or staying asleep,
    - dual orexin receptor antagonists (DORAs) [suvorexant, lemborexant] or antidepressants [doxepin, trazodone] for staying asleep, and
    - benzodiazepines [temazepam, triazolam] for severe sleep problems linked to anxiety.
- Providers must explain to the Oregon Health Authority why someone needs a sedative before Medicaid will pay for it. This process is called prior authorization.

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- Providers must document that the patient has tried CBT-I. Use of a sedative beyond 30 days requires documented improvement in sleep, function or quality of life, and evaluation of long-term side effects.

Research Questions:

1. What is the comparative evidence of efficacy or harms between sedatives when used for treatment of sleep disorders?
2. Are sedatives more effective or associated with more harms than no treatment when used to treat sleep disorders?
3. Are there subgroups of patients based on specific demographics, co-morbidities or other factors (e.g., age, co-morbid behavioral or mental disorders, concomitant medications, etc.) in which one sedative is more effective or associated with fewer adverse events than another sedative?

Conclusions:

- Based on evidence reviewed in a 2025 DERP report, there is uncertainty if dual orexin receptor antagonists (DORAs) are equally effective or more effective than other medications for insomnia.[1] Four studies evaluated daridorexant (n=1), lemborexant (n=2), and suvorexant (n=1) compared to alternative therapy.[1]
    - It is unclear whether daridorexant is more or less effective than zolpidem (moderate quality of evidence; 1 randomized controlled trial [RCT]).[1]
    - There is insufficient evidence on the effectiveness of either lemborexant compared with flurazepam or suvorexant compared with zolpidem for insomnia.[1]
    - Lemborexant may be associated with greater improvements in sleep compared with zolpidem; however, the differences are small and may not be clinically meaningful (low quality of evidence; 1 RCT). [1]
    - DORAs have overall similar or lower rates of adverse events compared to flurazepam, zolpidem, and eszopiclone.[1]
- In individuals with Alzheimer's disease (AD), sedative-hypnotics reduced wakefulness after sleep onset compared to placebo but were also associated with safety concerns such as potential for mental confusion, hallucinations, and agitation.[2] Sleep efficiency and total sleep time were improved with eszopiclone and DORA treatment.[2] Although sleep latency slightly improved with eszopiclone compared to placebo, REM latency also increased. Melatonin showed no significant benefit over placebo for sleep efficiency or total sleep time.[2]
- In 2025, the VA/DoD issued the following recommendations for adult patients with chronic insomnia:[3]
    - Behavioral Therapy Recommendations (e.g., CBT-I and Brief behavioral treatment for insomnia [BBT-I])
        - FOR CBT-I treatment (Strong recommendation; moderate-quality evidence)
        - FOR BBT-I treatment (Weak recommendation; moderate-quality evidence)
        - AGAINST sleep hygiene education as a stand-alone treatment (Weak recommendation; low-quality evidence)
    - Pharmacotherapy Recommendations (if offered by provider)
        - FOR CBT-I over pharmacotherapy as first-line treatment for chronic insomnia (Weak recommendation; low-quality evidence)
        - FOR use of daridorexant, lemborexant, suvorexant, doxepin, eszopiclone, zaleplon, or zolpidem (Weak recommendation; low-quality evidence)
        - AGAINST use of antipsychotic drugs, benzodiazepines, diphenhydramine, or trazodone (Weak recommendation; very low-quality evidence)
        - NEITHER FOR NOR AGAINST use of ramelteon (No recommendation; very low-quality evidence)
- In 2024, the MHCAG updated recommendations for management of chronic insomnia.[4]
    - Use an evidence-based approach.
    - Offer CBT-I to all patients as the initial treatment for chronic insomnia.

    - CBT-I provides clinically meaningful long-term improvement in critical outcomes of remission, response, sleep onset latency (SOL), wake after sleep onset (WASO), and sleep quality (moderate-quality evidence).
    - CBT-I treatment is usually 6 sessions, which can be provided in-person or via telemedicine. A minimum of 4 sessions is needed for treatment response.
- Use shared decision-making when adding pharmacologic therapies: Discuss benefits, risks, costs, and patient preferences before prescribing medications.
    - Reserve short-term pharmacotherapy for patients who cannot access CBT-I, who have persistent symptoms despite CBT-I, or who need temporary relief.
- Use medications if necessary for limited duration (<4 weeks)
    - Non-benzodiazepine hypnotics (zolpidem, eszopiclone) for sleep onset and/or sleep maintenance.
    - Consider orexin receptor antagonists (suvorexant, lemborexant) or antidepressants (doxepin, trazodone) for sleep maintenance.
    - Benzodiazepines (temazepam, triazolam) may be considered for severe insomnia with anxiety; use as needed for 7-10 days and plan for tapering; discouraged for long-term use.
- Reassess medication efficacy and adverse effects within 2-4 weeks of initiation.
    - Avoid use of medications in patients with significant respiratory, hepatic, or renal impairment, or those with increased fall risk.
    - Taper medications to minimize rebound insomnia and withdrawal.
- Special Populations
    - Older adults: prioritize non-pharmacologic strategies; use lower doses and shorter durations if medications are needed.
    - Comorbid psychiatric or medical conditions: tailor therapy to address both insomnia and the underlying disorder.

Recommendations:

- Remove PA for preferred products when there is no history of an opioid or sedative agent for short term use (4 weeks).
- Designate one sedative agent that is not from the benzodiazepine or GABA-A receptor agonist class as preferred on the preferred drug list (PDL).
- After evaluation of comparative costs in executive session, make suvorexant (BELSOMRA) preferred.

Summary of Prior Reviews and Current Policy

Insomnia

- CBT-I is highly recommended as first-line therapy for chronic insomnia by both the American Academy of Sleep Medicine and the European Sleep Research Society based on high-quality evidence. A sedative can be offered if CBT is not effective or not available.[5] Long-term treatment of chronic insomnia with a sedative is not recommended because of lack of evidence and possible adverse effects (e.g., fractures, dementia) based on low-quality evidence.[5]
- FDA labeling for non-benzodiazepine sedatives includes warnings for risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, parasomnias (such as sleep paralysis), complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions.[5]
- There is insufficient evidence to compare efficacy of tapering regimens to improve rates of sedative discontinuation. Interventions to improve patient education and increase psychosocial support have improved rates of benzodiazepines discontinuation when used in combination with tapering strategies.[5] Resources describing best practices for benzodiazepine tapers have been published by the MHCAG.

- In elderly patients over 65 years of age, there is evidence supporting use of eszopiclone to improve total sleep time and wake time after sleep onset, use of zolpidem and ramelteon to improve sleep onset latency, and doxepin to improve insomnia symptoms.[5]
- In patients with sleep disturbances and dementia, there is low quality evidence that short-term (2 weeks) treatment with trazodone may improve sleep efficiency and total sleep time.[6]
- Melatonin did not demonstrate any change in sleep outcomes in adults based on low quality evidence.[6]

Circadian Rhythm Sleep-Wake Disorders

- There is insufficient direct evidence to evaluate comparative efficacy or safety of stimulants or sedatives for circadian rhythm sleep-wake disorders.
- Melatonin or a melatonin agonist may be an option for adults, adolescents, and children with delayed sleep-wake phase disorder (low to moderate quality evidence), and in children and adolescents with neurologic disorders and irregular sleep-wake rhythm disorder (moderate quality evidence).[7]

Current Policy

- Prior authorization is currently required for all sedative medications except for melatonin in patients less than or equal to 18 years of age.
- Insomnia is funded when paired with CBT. Short term (up to 1 month per year) treatment with sedative-hypnotic medications is funded if the patient is currently in CBT or has failed to respond to recent CBT (in the past year). Long-term (more than 1 month) treatment of insomnia with sedative-hypnotic medications is not currently funded.
- All drugs currently require prior authorization (PA) for this class except melatonin in children.[5-7]

Background:

Insomnia is the most common of type sleep disorder identified by the American Academy of Sleep Medicine's (AASM) International Classification of Sleep Disorders, Third Edition (ICSD-3).[8] Other frequently observed conditions that affect sleep include central disorders of hypersomnolence, sleep-related breathing disorders, circadian rhythm sleep-wake disorders, parasomnias, and sleep-related movement disorders.[8,9] The current review will emphasize medications listed in the Sedative PDL class (see **Appendix 1**) for treatment of insomnia. Drugs that are sometimes used for sleep but not covered in this review include lorazepam, sodium oxybate, barbiturates, sedating antidepressants, and atypical antipsychotics. Many of these medications are covered in other class reviews and are addressed through different PA criteria. For example, lorazepam is included in PA criteria for the benzodiazepine class, and current PA criteria restrict use of low-dose quetiapine when prescribed specifically for insomnia.

Insomnia is the inability to fall asleep, stay asleep, or achieve quality sleep.[10,11] Insomnia may be classified by duration (e.g., short-term or chronic) and by type of sleep disturbance. People with insomnia may have trouble with sleep initiation, maintenance of sleep, or with premature awakening which can cause concentration or memory issues, reduced productivity, cause mood fluctuations, and contribute to fatigue during hours of wakefulness.[12] Up to 20% of people are affected by intermittent short-term insomnia (typically < 3 months), and roughly 10% experience chronic insomnia (symptoms for $\geq$ 3 months that occur $\geq$ 3 times weekly) with symptoms severe enough to affect daily function.[11,13,14] Older individuals tend to experience insomnia at higher rates than the general population, and insomnia is more common in women than men.[15,16] Other risk factors that may predispose an individual to develop insomnia include shift work, lower socioeconomic status, family history of insomnia, and genetic factors.[17] Insomnia may occur either independently or as a result of other medical and psychiatric conditions.[15] Chronic insomnia symptoms have been associated with metabolic complications, cognitive impairment, depression and psychiatric issues that can result in a reduced health-related quality of life (HRQoL) especially in patients over 65 years of age.[13,18] Insomnia can also worsen outcomes for patients with comorbid illness such as post-traumatic stress disorder and cardiovascular disease.[10,18-20] Therefore, prompt identification and treatment of contributing factors is important for the effective management of insomnia symptoms.

Insomnia etiology and pathology is not fully understood but likely involves a complex interplay of genetic, psychophysiological, behavioral, and biochemical interactions.[15,21,22-28] Treatment goals for insomnia are to improve the quality and quantity of sleep and to reduce associated daytime impairments.[29] Once comorbidities and other contributing factors that interfere with sleep quality have been addressed, nonpharmacologic interventions such as CBT-I are recommended as standard first-line therapy for chronic insomnia.[12,13,30-33] CBT-I is a multi-faceted sleep management strategy that involves a combination of psychological and behavioral techniques such as stimulus control, sleep restriction, relaxation therapy, and sleep hygiene (**See Table 1**).[13,35] Both brief and longer CBT-I interventions are recommended by the AASM guidelines.[30] If CBT-I is not effective or not available, a sedative can be offered but combination therapy has not demonstrated additional benefits or harms compared to CBT-I alone.[11,31] CBT-I has internet-based offerings that have demonstrated outcomes equally efficacious as face-to-face CBT-I and may be a viable alternative for patients with provider access challenges.[35,36]

Table 1. Key Components of Cognitive Behavioral Therapy for Insomnia (modified)[34]

Method	Goals	How Accomplished
Stimulus Control	Strengthen association between bed/bedroom and sleep; produce a consistent sleep schedule	-Minimize napping -Go to bed only when sleepy -Get out of bed if unable to sleep -Use the bed/bedroom only for sleep and intimacy -Wake up at the same time each day
Sleep Restriction	Increase homeostatic drive for sleep to improve sleep quality	-Reduce time in bed to the actual sleep duration (based on sleep diaries) -Time in bed is then gradually increased until the individual achieves an optimal sleep duration
Relaxation Training	Reduce tension and intrusive thoughts which interfere with the ability to sleep	-Deep breathing exercises -Progressive muscle relaxation -Biofeedback -Guided imagery
Cognitive Restructuring	Reduce worry and change misconceptions associated with sleep and insomnia	-Use Socratic questioning to challenge inaccurate patterns of thinking regarding the effect of sleep on patient's life
Sleep Hygiene Education	Provides guidelines about factors that may help or interfere with sleep	-Do not eat a heavy meal or drink alcohol within two hours of bedtime -Limit caffeine intake after lunchtime -Exercising regularly but not within 2 hours of bedtime -Keep the bedroom quiet, dark and at a cool, comfortable temperature

Medications may be used for short-term (<4 weeks) treatment of insomnia due to their rapid onset, however, the safety and efficacy of long-term use is limited due to tolerance, the potential for dependence, and dangerous withdrawal symptoms upon discontinuation.[11,13] DORAs (e.g. suvorexant, lemborexant, daridorexant) are indicated for sleep maintenance or to improve sleep onset.[13] Certain benzodiazepines (such as triazolam and temazepam) have sleep indications, but are usually prescribed very short-term (<10 days) due to an extensive adverse effect profile.[11,13] The benzodiazepine receptor agonists (BzRAa) eszopiclone and zolpidem have indications to treat sleep onset and sleep maintenance while zaleplon is only indicated for the treatment of sleep onset insomnia.[11,13] Heterocyclic antidepressants such as the histamine receptor antagonist doxepin and the melatonin receptor agonist ramelteon also have indications to treat insomnia.[11,13] A summary of recommended therapies by the AASM may be found in **Table 2**. The newer DORAs, lemborexant and

daridorexant, were FDA approved after the AASM guidelines were published but clinical trials support their efficacy for sleep-onset and sleep-maintenance symptoms.[13]

Table 2. Sedative Therapies and Recommendations by the American Academy of Sleep Medicine (Modified) [12]

Sedative Class	Treatment	AASM Recommendation	Quality of Evidence	AASM Benefits vs. Harm Assessment
Benzodiazepine (GABA-A) receptor agonists	Eszopiclone (2–3 mg)	Option for sleep-onset & sleep-maintenance insomnia (versus no treatment)	Low	Benefits outweigh harm
	Zaleplon (10 mg)	Option for sleep-onset insomnia (versus no treatment)	Low	Benefits outweigh harm
	Zolpidem (10 mg)	Option for sleep-onset & sleep-maintenance insomnia (versus no treatment)	Very Low	Benefits outweigh harm
Orexin (hypocretin) receptor antagonist	Suvorexant (10–20 mg)	Option for sleep-maintenance insomnia (versus no treatment)	Low	Benefits outweigh harm
Benzodiazepines	Temazepam (15 mg)	Option for sleep-onset & sleep-maintenance insomnia (versus no treatment)	Moderate	Benefits outweigh harm
	Triazolam (0.25 mg)	Option for sleep-onset insomnia (versus no treatment)	High	Benefits ≈ harm
Melatonin agonist	Ramelteon (8 mg)	Option for sleep-onset insomnia (versus no treatment)	Very Low	Benefits outweigh harm
Heterocyclics	Doxepin (3–6 mg)	Option for sleep-maintenance insomnia (versus no treatment)	Low	Benefits outweigh harm
	Trazodone (50 mg)	Not suggested for sleep-onset or sleep-maintenance insomnia	Moderate	Harm outweighs benefits
Anticonvulsant	Tiagabine (4 mg)	Not suggested for sleep-onset or sleep-maintenance insomnia	Very Low	Harm outweighs benefits
Over-the-counter preparations	Diphenhydramine (50 mg)	Not suggested for sleep-onset or sleep-maintenance insomnia	Low	Benefits ≈ harm
	Valerian (varied doses)		Low	Benefits ≈ harm
	Melatonin (varied doses)		Low	Benefits ≈ harm
	L-tryptophan		Low	Harm outweighs benefits

Abbreviations: GABA-A = Gamma-aminobutyric acid-A

Long-term treatment of chronic insomnia with a sedative (≥12 weeks) is not recommended because of lack of evidence and increased risk of adverse effects based on low-quality evidence.[11] Most sedative drugs indicated for insomnia contain FDA labeling recommendations to re-evaluate comorbid diagnoses which could be contributing to symptoms if insomnia persists for more than 7-10 days of treatment.[13] In general sedating antidepressants (e.g., trazodone) and antihistamines (e.g. diphenhydramine) are not generally recommended due to lack of efficacy and increased risk of adverse effects.[11] Melatonin is not recommended as a treatment to improve sleep onset or sleep maintenance due to insufficient evidence of benefit.[11]

Sedative medications may cause dizziness, daytime drowsiness, respiratory depression, and somnolence.[37-45] Long-term sedative use may be associated with increased risk of fractures and dementia based on evidence from observational studies.[3,46,47] The fracture risk appeared to correlate with the length of use, with new users of these drugs at greatest risk of hip fracture.[3,46,47] Non-benzodiazepine sedatives include FDA warnings for risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, parasomnias (such as sleep paralysis), complex behaviors

(such as sleep driving), depression, and suicidal thoughts and actions.[39-45] Women or elderly who metabolize and eliminate sedative medications more slowly from the body may be at higher risk for daytime impairment.[39,40] The FDA warns that a sedative can result in next-day impaired function even if patients feel fully awake.[39,40] Benzodiazepine sedatives are also associated with physical dependence; therefore, taper plans are used to minimize withdrawal symptoms and facilitate safe discontinuation after routine, extended use.[3] Although non-benzodiazepine sedatives do not carry a boxed warning for dependence, abrupt discontinuation may still produce troublesome adverse effects such as nausea, sweating, tremors, and seizures.[39-45,48,49] Provider resources and best practices for benzodiazepine tapers were recently published by the Oregon Health Authority MHCAG.[50] Taper schedules should be individualized based on patient circumstances, diagnoses, dose, and length of benzodiazepine use.[49] Many patients may benefit in switching, or cross-tapering, to a longer-acting benzodiazepine like diazepam before reducing their total benzodiazepine dose.[50] For the majority of sedative agents, such as benzodiazepines, BzRAs, and sedating antidepressants, a gradual reduction of 5-10% of the current daily dose every 1 to 2 weeks has been recommended by multiple major guidelines as safe and reasonable initial taper strategy.[30,48] Due to the potential for withdrawal, patients on low-dose use of benzodiazepines may find benefit from a 20% weekly reduction.[49] Patients on higher doses of benzodiazepines will likely require a longer taper period such as 2 to 6 months (or longer in unique cases).[49] A common taper strategy for patients on high doses of benzodiazepines is a weekly dose reduction of 25% over 2 weeks until 50% of the dose remains then further reduce the dose by 1/8 (~12%) every week.[49] Due to the potential for withdrawal symptoms with rapid dose reduction, periodic monitoring is recommended with adjustments to slow down the taper plan if needed.[49] Tapering of DORAs and melatonin/melatonin receptor agonists are generally not recommended.[51-54] The Oregon Health Plan typically requires PA and engagement in a CBT-I program before a prescription claim for a sedative is approved. Use of a sedative beyond 30 days requires documentation of improvement in symptoms, function or quality of life, and a provider discussion with the patient about the long-term effects of ongoing medication use.[4]

Although polysomnography is the gold standard for objective sleep assessment, it is not required for diagnosis of chronic insomnia due to an inconsistent correlation with clinical symptoms.[12] Therefore, patient surveys, sleep logs, or actigraphy are often used to assess symptoms, functioning, and health-related quality of life (HRQoL).[55-58] However, efficacy differences among sedatives are often difficult to evaluate due to a strong placebo response which is apparent with both subjective and objective measures of efficacy.[59] Some studies of sedatives for primary insomnia have reported that almost two-thirds of the drug response could be also be observed in the placebo group.[59] Common outcomes for sleep interventions in clinical trials include subjective change in sleep latency, total sleep time, wake time after sleep onset, sleep efficiency, and sleep quality. Clinically meaningful improvement has been proposed by the AASM (**Table 3**).[11] Other assessment scales include the Insomnia Severity Index (ISI) or the Pittsburgh Sleep Quality Index (PSQI) which document overall symptom severity.[60]

Table 3. Clinically Meaningful Outcomes for Chronic Insomnia (Adapted from the American Academy of Sleep Medicine).[11]

Outcome (units)	Description	Minimum Clinically Important Difference Versus Placebo**		
		Polysomnography (PSG)	Actigraphy	Subjective
Sleep Onset Latency (min)	Time elapsed from getting into bed to falling asleep	10	10	20
Total Sleep Time (min)	Represents the total sleep duration during a 24-hour period.	20	20	30
Wake After Sleep Onset (min)	Duration of time spent awake after the onset of sleep.	20	20	30
Sleep Efficiency (%)	Percentage representing the proportion of time spent asleep while in bed.	5	5	10
Number of Awakenings (n)	Expressed as the total count of awakenings during nighttime sleep.	2	2	0.5
Quality of Sleep (varies***)	Satisfaction of sleep experience	Varies	Varies	Varies

**Clinical significance was judged to be present when a specific agent led to a mean change in the outcome of this magnitude, compared to placebo.

***For standardized mean difference (SMD), an effect size of 0.5 is considered clinically significant.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
After review, 33 systematic reviews were excluded due to poor quality (e.g, indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Drug Effectiveness Review Project (DERP): Dual Orexin Receptor Antagonists (DORAs) for Insomnia[1]
A 2025 DERP systematic review evaluated DORAs for the treatment of insomnia.[1] The review included RCTs published through February 24, 2025. Clinical outcomes of interest included WASO, latency to persistent sleep (LPS), total sleep time (TST), sleep quality, fatigue, alertness, and safety/adverse events (AEs).[1] The review identified 4 studies comparing daridorexant (n=1), lemborexant (n=2), and suvorexant (n=1) to an alternative thearpy.[1] Evidence was graded as moderate (1 study), low (2 studies), or very low (1 study) quality reflecting substantial uncertainty in the estimate of treatment effects.[1] The evidence summary for each of the trials is presented in **Table 4**.

Table 4. DERP Evidence Summary Dual Orexin Receptor Antagonists (DORAs) for Insomnia[1]

Comparisons	Number of Studies; Participants	Outcomes Assessed	Quality of Evidence	Rationale
Daridorexant vs. Zolpidem	1 RCT (N = 299)	TST, WASO, LPS, Safety	Moderate	Downgraded 1 level for imprecision (i.e., not assessable)
Lemborexant vs. Flurazepam	1 RCT (N = 69)	Safety	Low	Downgraded 1 level for imprecision and 1 level for indirectness (i.e., only single dose administered)
Lemborexant vs. Zolpidem	1 RCT (N=798)	WASO, LPS, Safety	Low	Downgraded 1 level for risk of bias and 1 level for indirectness (i.e., only people aged 55 and older were included)
Suvorexant vs. Eszopiclone	1 RCT (N – 18)	Safety	Very low	Downgraded 1 level for risk of bias, 1 level for indirectness (i.e., specific population) and 2 levels for imprecision (i.e., very small sample size)

Abbreviations: DERP = drug effectiveness review project; LPS = latency to persistent sleep; RCT = randomized controlled trial; TST = total sleep time; WASO = wake after sleep onset.

The findings for each outcome of interest may be summarized as follows:

- Total sleep time (TST):
  - In the trial evaluating daridorexant versus zolpidem, TST was increased in both groups; only higher daridorexant doses (10 mg, 25 mg, 50 mg) achieved the TST MCID of 55 minutes; it was unclear if there are any significant differences between both agents.[1]
- Wake after sleep onset (WASO):
  - In the trial of daridorexant versus zolpidem, WASO was reduced from baseline in a dose-dependent fashion for both groups at weeks 2 and 4; it was unclear if there are any significant differences between both agents.[1]
  - In the trial of lemborexant versus zolpidem, lemborexant had statistically significant improvements in WASO compared with zolpidem, but differences between groups were less than the MCID threshold of 20 minutes and, therefore, may not be clinically meaningful.[1]
- Latency to persistent sleep (LPS):
  - In the trial of daridorexant versus zolpidem, LPS was reduced in both groups, but it was unclear if there are any significant differences between both agents.[1]
  - In the trial of lemborexant versus zolpidem, lemborexant demonstrated statistically significant reductions in LPS, but differences between groups were less than the MCID threshold of 15 minutes and, therefore, may not be clinically meaningful.[1]
- Insomnia severity index (ISI):
  - In the trial of daridorexant versus zolpidem, improvements in the insomnia severity index (ISI) were observed across both groups compared to baseline; the MCID of 6 points was met for both groups at day 30.[1]
- Adverse events (AEs):
  - In the trial of daridorexant versus zolpidem, roughly one-third of people experienced an AE but serious AEs were rare; the most common AEs in both groups were headache (around 8% to 10%) and somnolence (around 5% to 7%); upper abdominal pain, dizziness, fatigue, nasopharyngitis, and nausea were also reported in the zolpidem group (around 7% to 8%).[1]
  - In the trial of lemborexant versus flurazepam, both groups experienced treatment-emergent AE, but no serious AEs were observed; the most common AEs in both groups was somnolence (1.4% in the lemborexant 5 mg group, 4.4% in the lemborexant 10 mg group, and 2.9% in the flurazepam group).[1]
  - In the trial of lemborexant versus zolpidem, both groups experienced treatment-emergent AEs (lemborexant: 28% to 31%; zolpidem: 36%); the most common AEs in both groups was headache (lemborexant: 5% to 7%; zolpidem: 5%).[1] Serious AEs and severe AEs were around 1% or less for both groups.[1]
  - In the trial of suvorexant versus eszopiclone, both groups experienced treatment-emergent AEs. The most common AE in the suvorexant group was fatigue (89%) and in the eszopiclone group was somnolence (67%); no serious AEs were observed in either group.[1]

Pharmacological Interventions to Improve Sleep In People With Alzheimer's Disease: A Meta-Analysis Of Randomized Controlled Trials [2]

A 2024 systematic review and meta-analysis evaluated the efficacy and safety of pharmacological interventions for improving sleep in individuals with Alzheimer's disease (AD).[2] Literature was searched from January 2000 to July 2023.[2] The evidence for pharmacological treatments included 14 studies with trial sizes that ranged from 20 to 285 participants.[2] Placebo-controlled interventions included the following agents from the sedatives class: zopiclone (not available in United States - 1 study), zolpidem (1 study), eszopiclone (1 study), lemborexant (1 study), suvorexant (1 study), trazodone (2 studies), and melatonin (6

studies).[2] Twenty-nine sleep outcomes were analyzed via meta-analysis with sleep efficiency and daytime total sleep time as the most frequently assessed sleep outcomes. [2] Six of the 14 studies were graded as having low risk of bias while the remaining 8 studies had unclear risk of bias.[2] The review found that overall, sedative-hypnotics reduced wakefulness after sleep onset but also carry safety concerns such as potential for mental confusion, hallucinations, and agitation.[2] Sleep efficiency and total sleep time improved significantly with eszopiclone and DORAs.[2] Although sleep latency slightly improved with eszopiclone, undesirable rapid eye movement (REM) latency also increased.[2] Melatonin showed no significant benefit over placebo.[2] Outcomes of key sleep measures are summarized in **Table 5**.

Table 5. Pharmacological interventions to improve sleep in people with Alzheimer's disease.[2]

Outcome	Drug Therapy vs. Placebo Weighted Mean Difference (WMD)	Effects by Drug Class or Drug vs. Placebo
Sleep Efficiency (%)	WMD = 0.32 (95% CI 0.02 to 0.62)	• Eszopiclone: WMD 0.94 (95% CI 0.52 to 1.36); • Orexin antagonists: WMD 0.33 (95% CI 0.13 to 0.53)
Total Sleep Time (TST) - mins	WMD = 15.77 min (95% CI 2.88 to 28.65)	• Orexin antagonists: WMD +28 min (95% CI: 9.70, 46.30); • Eszopiclone: WMD +10 min (95% CI −3.65 to 23.65)
Wakefulness After Sleep Onset (WASO) - mins	WMD = −7.06 min (95% CI −21.21 to 7.09) (Not statistically significant)	• Sedative-hypnotics: WMD −23.89 min (95% CI −44.46 to −3.32)
REM Latency [higher values worse]	WMD = +12.82 min (95% CI 8.11, 17.53)	• Eszopiclone: WMD +13.73 min (95% CI 8.85 to 18.61)
Sleep Latency	WMD = −4.44 min (95% CI −8.93 to 0.05) (Not statistically significant)	• Eszopiclone: WMD −4.29 min (95% CI −6.85 to −1.73)

New Guidelines:

High Quality Guidelines:

Department of Veterans Affairs and Department of Defense: Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea[3]

In 2025, the VA/DoD updated guidance for the management of chronic insomnia and OSA.[3] Literature was reviewed through March 31, 2024 to support the revised recommendations.[3] Drug therapy included daridorexant, doxepin, eszopiclone, lemborexant, suvorexant, zaleplon, zolpidem, ramelteon, antipsychotics, benzodiazepines, diphenhydramine, and trazodone.[3] In adult patients with insomnia disorder, the guidelines evaluated 5 systematic reviews for the effectiveness of pharmacotherapy and included 2 systematic reviews and 2 RCTs for the effectiveness of behavioral treatment modalities on sleep outcomes.[3] The behavioral treatment modalities included individual therapy, group therapy, guided self-help, digital CBT-I, telephone CBT-I, and unguided self-help.[3] A sleep algorithm for the management of insomnia was developed that included the following best practices:[3]

- Use a patient-centered care approach and shared decision-making.

- Encourage non-pharmacologic approaches (e.g., CBT-I or BBT-I) before pharmacotherapy and consider sleep specialist referral in patients who do not respond to short-term pharmacotherapy.
- Before starting short-term pharmacotherapy, review patient sleep history, reproductive status, and evaluate contraindications for pharmacotherapy.
- Prior to starting pharmacotherapy, a deprescribing plan should be discussed and all patients offered a non-benzodiazepine benzodiazepine receptor agonist should be specifically counseled regarding the risk of complex sleep-related behaviors.

The Work Group used the GRADE approach for each recommendation and its strength using various domains including confidence in the recommendation quality, balance of desirable and undesirable outcomes, and patient values/preferences.[3] Recommendations include:[3]

Behavioral and Psychological Treatments for Chronic Insomnia Disorder

- CBT-I treatment (FOR - Strong recommendation; moderate quality evidence)
  - The benefits of CBT-I, including reducing insomnia severity and improved sleep efficiency, significantly outweighed the potential harms.[3]
- BBT-I treatment (FOR - Weak recommendation; moderate quality evidence)
  - The benefits of BBT-I, including reducing insomnia severity and improved sleep efficiency, significantly outweighed the potential harms. However, there was a much smaller literature base for BBT-I, and the evidence on BBT-I evaluates its effect on older adults only.[3]
- Sleep hygiene education as a stand-alone treatment (AGAINST - Weak recommendation; low-quality evidence)[3]
  - Since CBT-I and BBT-I require trained professionals who may not always be readily available, or due to potential burdens of multiple appointments, it is suggested that providers seek out CBT-I resources or alternative strategies such as BBT-I or self-help or internet-based CBT-I programs.[3]
  - Providers should use a patient-centered, motivational interviewing approach to encourage reluctant patients to engage in CBT-I or BBT-I.[3]

Insomnia Pharmacotherapy if Offered by Provider

- CBT-I over pharmacotherapy as first-line treatment (FOR – Weak recommendation; low-quality evidence)[3]
  - There are overall less concerns for harm associated with CBT-I compared to hypnotic medications which may cause complex behaviors such as "sleep-driving" and worsening of depression, including suicidal thoughts and actions.[3]
- Use of either daridorexant, lemborexant, suvorexant, doxepin, eszopiclone, zaleplon, or zolpidem (FOR – Weak recommendation; low-quality evidence)
  - The benefits of pharmacotherapy for chronic insomnia (e.g., sleep efficiency, wake after sleep onset, and daytime functioning) slightly outweighed the potential harm of adverse events.[3]
- Use of antipsychotics, benzodiazepines, diphenhydramine, or trazodone (AGAINST – Weak recommendation; very low-quality evidence)
  - The benefits of antipsychotics, diphenhydramine, benzodiazepines, and trazodone were lacking. The potential harm of adverse events outweighed the benefits.[3]
- Use of ramelteon (NEITHER FOR NOR AGAINST No recommendation – very low-quality evidence)[3]
  - The benefits of ramelteon were inconsistent but slightly outweighed the potential harm, which was small.[3]

Oregon Health Authority: Mental Health Clinical Advisory Group[4]

In 2024, the MHCAG updated recommendations for management of chronic insomnia.[4] The recommendations aim to improve patient sleep quality while minimizing medication-related harms. The clinical features of chronic insomnia disorder are outlined, and assessment tools are provided.[4] An algorithm was developed to guide treatment for insomnia with CBT-I or medications.[4] The guideline can be accessed here: https://www.oregon.gov/oha/HPA/DSI-

Pharmacy/MHCAGDocs/MHCAG_Treatment-of-Chronic-Insomnia-Disorder-in-Adults.pdf.[4] Several links to evidence-based online resources are provided within the document.[4]

MHCAG Recommendations for Treatment of Chronic Insomnia Disorder in Adults[4]

- Use stepwise evidence-based approach to manage insomnia.[4]
    - Emphasize sleep hygiene, stimulus control, sleep restriction, limitations on stimulating or sedating foods, drinks or substances, proper timing of sleep-disturbing medications, and use relaxation techniques.[4]
    - Offer CBT-I to all patients as the initial treatment.[4]
        - CBT-I provides clinically meaningful long-term improvement in critical outcomes of remission, response, SOL, WASO and sleep quality (moderate-quality evidence).[4]
        - CBT-I treatment is usually 6 sessions, which can be provided in-person or via telemedicine. A minimum of 4 sessions is needed for treatment response.[4]
        - Several free online evidence-based CBT-I programs and mobile apps exist (payment-based programs and paid mobile apps are also available).[4] See link above.
- Use shared decision-making when adding pharmacologic therapies.[4]
    - Discuss benefits, risks, costs, and patient preferences before prescribing medications.[4]
    - Reserve short-term pharmacotherapy for patients who cannot access CBT-I, who have persistent symptoms despite CBT-I, or who need temporary relief.[4]
- Use medications if necessary for limited duration (<4 weeks) such as:
    - Non-benzodiazepine hypnotics (zolpidem, eszopiclone) for sleep onset and/or sleep maintenance.[4]
    - Orexin receptor antagonists (lemborexant, suvorexant) or antidepressants (doxepin, trazodone) for sleep maintenance.[4]
    - Benzodiazepines (temazepam, triazolam) for severe insomnia with anxiety; use as needed for 7-10 days and plan for tapering; discouraged for long-term use.[4]
- Reassess medication efficacy and adverse effects within 2-4 weeks of initiation.
    - Avoid use of medications in patients with significant respiratory, hepatic, or renal impairment, or those with increased fall risk.[4]
    - Taper medications to minimize rebound insomnia and withdrawal.[4]
- Special Populations
    - Older adults: prioritize non-pharmacologic strategies; use lower doses and shorter durations if medications are needed.[4]
    - Comorbid psychiatric or medical conditions: tailor therapy to address both insomnia and the underlying disorder.[4]

Guidelines for Clinical Context

European Insomnia Guideline – Treatment Recommendations for Chronic Insomnia in Adults (2023 Update) [31]

In 2023, the European Insomnia Guideline was developed by a team of researchers and clinicians consisting of the European Sleep Research Society (ESRS), and the European Insomnia Network (EIN).[31] Literature was reviewed from June 2016 through October 2022 (with another update added in May 2023) to support the revised recommendations.[31] Behavioral therapies such as CBT-I and pharmacologic agents for the treatment of insomnia disorder were included in the updated clinical practice guideline.[31] Drug therapy research included benzodiazepines, benzodiazepine receptor agonists, sedating antidepressants, antipsychotics, antihistamines, melatonin receptor agonists, and orexin receptor antagonists.[31] In the update, the results of meta-analyses were used as the basis for grading

recommendations.[31] Details regarding the quality of individual trials were not provided.[31] Evidence was graded as "A = Very strong recommendation (high-quality evidence) or B = Strong recommendation (moderate-quality evidence).[31] The treatment recommendations are summarized in **Table 6.**

Table 6. European Insomnia Guideline – Treatment Recommendations for Chronic Insomnia in Adults[31]

Treatment	Setting / Application	Recommended Duration	Evidence Grade
Cognitive Behavioral Therapy for Insomnia (CBT-I) – Face-to-face or guided digital (6-8 weekly sessions)	All adults (including comorbidities) as first line treatment	Typically, 4 to 8 weeks	A
Short-term pharmacotherapy (≤ 4 weeks): Benzodiazepines, BZRA, Daridorexant, low-dose sedating antidepressants	When CBT-I insufficient by itself	≤ 4 weeks	A (BZ/BZRA/Daridorexant) B (Antidepressants)
Longer-term pharmacotherapy (case-by-case): Orexin receptor antagonists, prolonged-release melatonin (≥ 55 years)	When benefits outweigh risks	Up to 3 months or more	A (Orexin antagonists) B (Melatonin)
Not recommended pharmacotherapies: Antihistamines, antipsychotics, fast-release melatonin, ramelteon, herbal remedies	All adults	n/a	A (against use)
Adjunctive non-pharmacological: Light therapy, Exercise	With CBT-I as augmentative support	20-30 minutes daily	B

Key: BZ = benzodiazepines; BZRA = benzodiazepine receptor agonists; CBT-I = Cognitive-Behavioral Therapy for Insomnia

After review, 6 guidelines were excluded due to poor quality.

New Formulations or Indications:
None identified.

New FDA Safety Alerts:

Table 7. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Suvorexant[51]	BELSOMRA	March 2025	Use in Special Populations	Suvorexant and its metabolite, hydroxy suvorexant, are present in low concentrations in breast milk. Developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for suvorexant and any potential adverse effects on the breastfed infant.
Daridorexant[52]	QUVIVIQ	Sept 2024	Warnings and Precautions	The effects of daridorexant on respiratory function should be considered if prescribed to patients with compromised respiratory function.
Lemborexant[53]	DAYVIGO	April 2023	Warnings and Precautions	The effects of lemborexant on respiratory function should be considered if prescribed to patients with compromised respiratory function.

Randomized Controlled Trials:
A total of 188 citations were manually reviewed from the initial literature search. After further review, most citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trials are summarized below (**Table 8**). The full abstracts are included in **Appendix 2**.

Table 8. Description of Randomized Comparative Clinical Trials and Safety Studies.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th><th>Notes/Limitations</th></tr>
<tr>
<td>Yu Z, et al.[61]</td>
<td>Doxepin (6 mg/day) vs. zolpidem (5-10 mg/day)</td>
<td>Adults with insomnia disorder</td>
<td>Sleep quality as measured by PSQI and PSG (WASO; TST; SOL; SE); Executive function as measured by the WSCT (64-card version); Safety measured by TESS</td>
<td>
<table>
<tr><th>Outcome</th><th>Doxepin (n=53)</th><th>Zolpidem (n=56)</th><th>P-value</th></tr>
<tr><td>WASO (min)</td><td>80.3</td><td>132.9</td><td><0.05</td></tr>
<tr><td>TST (min)</td><td>378.9</td><td>333.2</td><td><0.05</td></tr>
<tr><td>SOL (min)</td><td>28.2</td><td>20.3</td><td><0.05</td></tr>
<tr><td>SE (%)</td><td>77.8</td><td>68.6</td><td><0.05</td></tr>
<tr><td>PSQI</td><td>6.1</td><td>7.9</td><td><0.05</td></tr>
<tr><td>Adverse effects (%)</td><td>23</td><td>13</td><td><0.05</td></tr>
</table>
</td>
<td>Excluded patients with other sleep disorders (e.g. OSA); inclusion and exclusion criteria not reported</td>
</tr>
<tr>
<td>Cheng J, et al.[62]</td>
<td>Lemborexant 10 mg vs. placebo</td>
<td>Adult and older patients with and moderate-to-severe COPD</td>
<td>Difference in least-squares mean SpO_2 during TST test from day 1 to day 8</td>
<td>Day 1
1. lemborexant: 91.1 (SD 2.8)
2. Placebo: 91.5 (SD 2.2)
LSMD = -0.4 (95% CI -0.9 to 0.0); p=0.065
Not statistically significant

Day 8
1. lemborexant: 91.3 (SD 2.2)
2. Placebo: 90.8 (SD 2.6)
LSMD = 0.5 (95% CI 0.1 to 0.9); p=0.022</td>
<td>Not all patients had history of insomnia disorder (20% overall); Sample size was small; Low SpO_2 levels (below 88–92%) may be associated with unfavorable clinical outcomes in patients with COPD. Although therapy did not demonstrate negative impact on SpO2 at day 8, safety beyond 8 days in this population unclear. Effect on COPD exacerbations or clinical symptoms of fatigue may be a more clinically relevant endpoint</td>
</tr>
</table>

Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; min=minutes; LSMD = least squares mean difference; OSA=obstructive sleep apnea; PSG=polysomnography ; PSQI=Pittsburg Sleep Quality Index ; SD=standard deviation; SE=sleep efficiency ; SOL=sleep onset latency; SpO_2= peripheral oxygen concentration; TESS=treatment emergent symptom scale; TST=total sleep time ; WASO=wake after sleep onset ; WSCT=Wisconsin sorting card test

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
melatonin	MELATONIN	TABLET	Y
ramelteon	RAMELTEON	TABLET	Y
ramelteon	ROZEREM	TABLET	Y
zolpidem tartrate	AMBIEN	TABLET	Y
zolpidem tartrate	ZOLPIDEM TARTRATE	TABLET	Y
daridorexant HCl	QUVIVIQ	TABLET	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP-AID	CAPSULE	N
diphenhydramine HCl	EZZ NITE SLEEP AID	LIQUID	N
diphenhydramine HCl	SLEEP AID	LIQUID	N

diphenhydramine HCl	SLEEP TIME	LIQUID	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	TABLET	N
diphenhydramine HCl	REST SIMPLY	TABLET	N
diphenhydramine HCl	SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP TABS	TABLET	N
doxepin HCl	DOXEPIN HCL	TABLET	N
doxylamine succinate	NIGHTTIME SLEEP AID	TABLET	N
doxylamine succinate	SLEEP AID	TABLET	N
doxylamine succinate	SLEEP AID ULTRA	TABLET	N
estazolam	ESTAZOLAM	TABLET	N
eszopiclone	ESZOPICLONE	TABLET	N
flurazepam HCl	FLURAZEPAM HCL	CAPSULE	N
lemborexant	DAYVIGO	TABLET	N
melatonin	MELATONIN	TAB RAPDIS	N
midazolam HCl	MIDAZOLAM HCL	SYRUP	N
quazepam	DORAL	TABLET	N
quazepam	QUAZEPAM	TABLET	N
suvorexant	BELSOMRA	TABLET	N
tasimelteon	HETLIOZ	CAPSULE	N
tasimelteon	TASIMELTEON	CAPSULE	N
tasimelteon	HETLIOZ LQ	ORAL SUSP	N
temazepam	RESTORIL	CAPSULE	N
temazepam	TEMAZEPAM	CAPSULE	N
triazolam	HALCION	TABLET	N
triazolam	TRIAZOLAM	TABLET	N
zaleplon	ZALEPLON	CAPSULE	N
zolpidem tartrate	ZOLPIDEM TARTRATE	CAPSULE	N
zolpidem tartrate	AMBIEN CR	TAB MPHASE	N
zolpidem tartrate	ZOLPIDEM TARTRATE ER	TAB MPHASE	N
zolpidem tartrate	EDLUAR	TAB SUBL	N
zolpidem tartrate	ZOLPIDEM TARTRATE	TAB SUBL	N

Appendix 2: Abstracts of Comparative Clinical Trials

Yu, Z., Han, L., Yan, P. et al. Doxepin is more effective than zolpidem in improving executive function in patients with insomnia disorder. *Sleep Breath* 28, 929–934 (2024).

Background

Insomnia disorder is associated with an impairment in cognitive performance. Doxepin and zolpidem have been found to be effective in improving sleep. In this study, we aimed to compare the effects of doxepin and zolpidem on sleep structure and executive function in patients with insomnia disorder.

Methods
Patients with primary insomnia were randomly assigned to receive doxepin 6 mg/day orally or zolpidem 5–10 mg/day orally. Polysomnography (PSG) and the Pittsburgh Sleep Quality Index (PSQI) were used at baseline and after the 8-week treatment to compare clinical efficacy in the two groups. Safety was assessed using the Treatment Emergent Symptom Scale (TESS). Executive function was evaluated using the Wisconsin sorting card test (WSCT).
Results
Of 120 patients enrolled in the study, 60 participants were assigned to each group. A total of 109 participants (53 in the doxepin group and 56 in the zolpidem group) completed the study. After treatment, the wake after sleep onset (WASO) and total sleep time (TST) values in the doxepin group were 80.3 ± 21.4 min and 378.9 ± 21.9 min, respectively, which were significantly better than those in the zolpidem group (132.9 ± 26.5 min and 333.2 ± 24.2 min, respectively; ($P < 0.05$)). The sleep onset latency (SOL) value in the zolpidem group (20.3 ± 4.7 min) was significantly better than that in the doxepin group (28.2 ± 5.6 min; $P < 0.05$). The sleep efficiency (SE) in the doxepin group was 77.8 ± 4.2%, which was significantly better than that in the zolpidem group (68.6 ± 5.0%; $P < 0.05$). The PSQI score of the doxepin group was 6.1 ± 1.1, which was significantly lower than that in the zolpidem group (7.9 ± 1.9; $P < 0.05$). The treatment adverse events in the doxepin group was 23.3%, which was significantly higher than that in the zolpidem group (13.3%; $P < 0.05$). The WSCT showed a significant improvement in persistent errors (PE), random errors (RE), and categories in the two groups after 8-week treatment, and the improvement in RE and the categories was more obvious in the doxepin group ($P < 0.05$).
Conclusions
Both doxepin and zolpidem were found to be effective in improving sleep quality, but the effects exhibited different patterns. Doxepin improved executive function more effectively than zolpidem in patients with insomnia disorder.

Cheng JY, Lorch D, Hall N, Moline M. Respiratory safety of lemborexant in adult and elderly subjects with moderate-to-severe chronic obstructive pulmonary disease. J Sleep Res. 2025;34(2):e14334.
Background: Because some hypnotics worsen respiratory conditions, it was important to determine the respiratory safety of lemborexant, a competitive dual orexin-receptor antagonist approved to treat adults with insomnia, in subjects with moderate-to-severe chronic obstructive pulmonary disease.
E2006-A001-113 (Study 113; NCT04647383) was a multicentre, multiple-dose, randomised, double-blind, placebo-controlled, two-period crossover study in adult subjects with moderate or severe chronic obstructive pulmonary disease (per spirometry-based Global Initiative for Chronic Obstructive Lung Disease [GOLD] criteria).
Methods: Subjects (N = 30) were randomised to two treatment sequences comprising 8-night treatment periods (washout ≥ 14 days) with lemborexant 10 mg or placebo. Peripheral oxygen saturation (SpO2; primary endpoint), apnea-hypopnea index, objective sleep parameters and sleep architecture measures were assessed after single (Day 1) and multiple (Day 8) doses.
Results: There was no significant difference in least-squares mean SpO2 after a single dose of lemborexant (91.1%) versus placebo (91.5%). Although a statistically significant difference in SpO2 was observed after multiple doses (least-squares mean: lemborexant, 91.3%; placebo, 90.8%) favouring lemborexant, this was not considered clinically meaningful. Apnea-hypopnea index was not significantly different between treatments after single or multiple doses. Total sleep time and total rapid eye movement sleep were significantly greater on Days 1 and 8 with lemborexant versus placebo. Treatment-emergent adverse events were reported in five (16.7%) subjects when taking lemborexant and four (13.3%) subjects when taking placebo; treatment-emergent adverse events were mostly mild.
Conclusion: Lemborexant was well tolerated and did not adversely impact SpO2 or apnea-hypopnea index after single and multiple doses relative to placebo in subjects with moderate-to-severe chronic obstructive pulmonary disease.

Appendix 3: Medline Search Strategy

	Ovid MEDLINE(R) ALL 1946 to November 21, 2025	
1	exp Melatonin/	25487
2	exp Zolpidem/	1847
3	exp Eszopiclone/	150
4	zaleplon.mp.	474
5	ramelteon.mp.	601
6	exp Diphenhydramine/	4606
7	exp Doxylamine/	414
8	exp Doxepin/	871
9	exp Flurazepam/	783
10	exp Temazepam/	682
11	exp Triazolam/	1251
12	exp Estazolam/	124
13	lemborexant.mp.	225
14	suvorexant.mp.	514
15	daridorexant.mp.	144
16	exp Midazolam/	10367
17	exp Sleep Aids, Pharmaceutical/	9476
18	exp Orexin Receptor Antagonists/	701
19	exp Benzodiazepines/	72318
20	tasimelteon.mp.	108
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	107884
22	exp "Sleep Initiation and Maintenance Disorders"/	20787
23	exp Sleep Wake Disorders/	122671
24	22 or 23	122671
25	21 and 24	5541
26	limit 25 to yr="2022 -Current"	632
27	limit 26 to (english language and humans)	562
28	limit 27 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review")	188

Appendix 4: Key Inclusion Criteria

Population	Patients with insomnia
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1 or placebo
Outcomes	Outcomes Sleep latency (SL) Total sleep time (TST) Wake after sleep onset (WASO) Quality of sleep (QOS) Sleep efficiency (SE) Number of awakenings (NOA)
Timing	4 weeks or longer
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Sedatives

Goals:

- Encourage use of cognitive behavioral therapy for insomnia.
- Prevent inappropriate long-term use of sedatives.
- Prevent concomitant use of sedatives, including concomitant use with benzodiazepines or opioids.
- Permit use of melatonin in children and adolescents 18 years of age or younger.

Length of Authorization:

- 1 month to 12 months (criteria-specific)

Requires PA:

- Non-preferred products
- Preferred sedatives when:
    - There is history of a recent opioid in the past 30 days OR
    - Long-term use beyond 4 weeks every 120 days (except melatonin in children and adolescents).
- Melatonin is not covered for adults over 18 years of age.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org

- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for melatonin in an adult over 18 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #3
3. Is the patient currently engaged in cognitive behavioral therapy focused on insomnia treatment (CBT-I) or Brief behavioral treatment for insomnia [BBT-I], failed to have benefit in symptoms after at least 4 CBT or BBT interventions, OR have inability to access CBT-I or BBT-I? Note: CBT-I or BBT-I may be offered through telehealth or with provider or patient-directed, internet-based apps.	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for long-term therapy beyond 30 days?	**Yes:** Go to #5	**No:** Go to #6
5. Is this request for continuation of therapy previously approved by the fee-for-service pharmacy program?	**Yes:** Go to **Renewal Criteria.**	**No:** Go to #6
6. Is there documentation that the prescriber plans to reassess the patient for medication efficacy and adverse effects within 2-4 weeks of initiation OR for patients already started on treatment, documentation of reassessment 2-4 weeks after initiation? Note: Sedative medications should be prescribed only if necessary and for limited duration. (<4 weeks)	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
7. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes:** Inform prescriber of preferred alternatives in class. Go to #8	**No:** Go to #8
8. Is the patient being treated under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for 5 years	**No:** Go to #9
9. Has the patient been treated with a different non-benzodiazepine sedative, benzodiazepine, or opioid within the past 30 days?	**Yes:** Go to #10	**No:** Go to #12
10. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Go to #12 Document reason for switch.	**No:** Go to #11
11. Is concurrent sedative therapy part of a plan to switch and taper off a long-acting benzodiazepine (such as diazepam, clonazepam, or chlordiazepoxide) AND has the provider included a detailed strategy to taper? Note: a documented taper strategy should include planned dose reductions and length of time between each dose modification for at least the next few weeks. It should also include a documented follow-up plan to monitor progress and manage withdrawal symptoms (regular check-ins are essential for a successful taper). Triazolam may be discontinued without a taper in most cases (2-hour half-life prevents physical dependence).	**Yes:** Approve duplicate benzodiazepine therapy for the duration specified in the taper plan (not to exceed 6 months).	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the request for treatment of chronic insomnia disorder?	**Yes:** Go to #13	**No:** Go to #14

Approval Criteria		
13. Is there documentation or provider attestation that the patient **<u>does not</u>** have any contraindications to therapy? Contraindications could include: ○ Narcolepsy ○ Untreated obstructive sleep apnea (OSA) ○ Suicidal ideation or high suicide risk ○ Severe hepatic impairment (e.g. Child-Pugh C) ○ Active substance use disorder	**Yes:** Approve for 30 days.	**No:** Pass to RPh. Deny; medical appropriateness.
14. RPh only: Is the request for an FDA-approved indication or is there medical evidence of benefit for the prescribed sedative?	**Yes:** Document supporting literature and approve for 30 days with subsequent approvals dependent on follow-up and documented response.	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #15
15. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #16 Document baseline severity	**No:** Pass to RPh. Deny; medical necessity.
16. Is the request for a melatonin agonist (e.g., melatonin, ramelteon, tasimelteon) for treatment of one of the following circadian rhythm sleep-wake disorders: • People with delayed sleep-wake phase disorder • Adults with non-24 hour sleep-wake disorder • Children and adolescents with neurologic disorders and irregular sleep-wake rhythm disorder?	**Yes:** Approve for approve 30 days with subsequent approvals dependent on follow-up and documented response.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for a slow taper plan?	**Yes:** Approve for duration of taper (not to exceed 3 months). Subsequent requests should document progress toward discontinuation	**No:** Go to #2
2. Is the request to treat insomnia disorder and has the patient already received 1 month of treatment with a sedative hypnotic?	**Yes:** Go to #3	**No:** Go to #4
3. Has the patient been evaluated by a sleep specialist?	**Yes:** Go to #4	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; medical appropriateness. If eligible for EPSDT review: Go to #5
4. Is there documentation based on medical records that the patient and provider have discussed whether benefits of ongoing therapy (hospitalizations, function, quality of life) continue to outweigh risks (memory problems, dementia, cognitive impairment, daytime sedation, falls, fractures, dependence, and reduced long-term efficacy)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is there documentation of improvement (e.g., of symptoms, function, quality of life, etc) since treatment was started?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: *02/26(DE);12/22; 8/22; 12/20; 7/18; 3/17; 11/14, 3/14, 5/06, 2/06, 11/05, 9/05, 2/04, 2/02, 9/01*
Implementation: *3/1/26; 1/1/24; 10/1/22; 1/1/21; 8/15/18; 1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05*