

Drug Class Update with New Drug Evaluation: Sedatives

Date of Review: December 2020

Date of Last Review: March 2017

Generic Name: lemborexant

Dates of Literature Search: 1/1/2017 - 4/23/2020

Brand Name (Manufacturer): DAYVIGO (Eisai Inc.)

Dossier Received: yes

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

To review updated evidence for the sedatives drug class, including a new drug evaluation for DAYVIGO (lemborexant), in order to inform policy and placement of drugs on the Preferred Drug List (PDL) in the Oregon Health Plan (OHP) fee-for-service (FFS) population.

Research Questions:

1. What is the comparative evidence of efficacy or harms between sedatives when used for treatment of sleep disorders or for outpatient procedural sedation?
2. Are sedatives more effective or associated with more harms than no treatment when used for treat sleep disorders or for outpatient procedural sedation?
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:

- Six high-quality systematic reviews, two high-quality clinical practice guidelines, and one new drug approval were identified since the last drug class update in March 2017.
- Overall, there is still insufficient evidence of comparative efficacy and safety between specific drugs within this drug class.
- A systematic review found no improvement in sleep outcomes with eszopiclone or zolpidem in children with attention-deficit hyperactivity disorder (ADHD), with no improvement in ADHD symptoms, based on low-quality evidence.¹ While these drugs had higher frequency of some adverse events such as dizziness and hallucinations, the evidence was insufficient to draw conclusions.¹ Several trials identified in the review also provide low-quality evidence that melatonin may improve sleep latency and sleep duration in children, but evidence is insufficient to draw conclusions on improvements in nighttime awakenings or functional outcomes, or on increased frequency of some adverse events (e.g., dizziness, daytime drowsiness, and bed-wetting).¹ Children with autism or other neurodevelopmental disorders had the largest improvement in sleep outcomes with melatonin nightly.

- A systematic review found that with the possible exception of melatonin, there is insufficient evidence for the use of sedatives in children with ADHD for treatment of sleeping disorders such as insomnia.² It was also found in this population that zolpidem and eszopiclone do not show significant improvement in different sleep parameters when compared with placebo but are associated with adverse effects.²
- A systematic review that evaluated sedatives for sleep disorders at high altitudes concluded that non-benzodiazepine sedatives were safe and superior to placebo in improving sleep quality at high altitudes based on moderate-quality evidence.³ Patients who received zaleplon or zolpidem reported improvement in subjective sleep quality.³ As measured by polysomnography (PSG), both zaleplon and zolpidem improved the total sleep time, sleep efficiency, and stage 4 sleep duration, whereas they decreased waking after sleep-onset without impairing ventilation.³ In contrast, temazepam was not superior to placebo in terms of quicker onset of sleep and better sleep quality based on low-quality evidence.³
- A systematic review was performed to evaluate the efficacy and safety of the non-benzodiazepine sedatives eszopiclone, zaleplon, and zolpidem for sleep disorders in patients with schizophrenia.⁴ Investigators concluded that eszopiclone may be useful for the treatment of insomnia symptoms in patients with schizophrenia, but the overall evidence is low quality.⁴ Eszopiclone did not improve schizophrenia symptoms in any of the 3 studies.⁴ They also advised against the use of other non-benzodiazepine drugs in this population because they have not been studied.⁴
- Two recent systematic reviews evaluated the association of sedative use and fractures: the objectives of one review⁵ were to investigate the association between benzodiazepine use and benzodiazepine receptor agonist (BZRA) use and hip fracture risk; the second review⁶ assessed the association between exposure BZRA use and the risk for fractures, falls and injuries. These systematic reviews found an increase in the association between both benzodiazepine and BZRA with hip fracture, general fractures, falls and injuries based on moderate quality evidence.^{5,6} The risk of fracture depended on the length of time people used the drugs, with new users of these drugs at greatest risk of hip fracture.^{5,6} There appears to be little difference in the findings between benzodiazepine and BZRAs based on low quality evidence.^{5,6}
- The efficacy and relative efficacy of conscious sedation agents for behavior management in pediatric dentistry was evaluated in a systematic review. Meta-analysis of the available data from the primary outcome (behavior) was only possible for studies that investigated oral midazolam versus placebo.⁷ From this meta-analysis, the investigators found moderate-quality evidence that the use of oral midazolam is associated with more cooperative behavior compared to placebo.⁷ The investigators found insufficient evidence to draw any conclusions from studies that evaluated two or more sedatives for children needing dental care.⁷
- Cognitive Behavioral Therapy (CBT) is highly recommended as first-line therapy for chronic insomnia by both the American Academy of Sleep Medicine⁸ and the European Sleep Research Society⁹ based on high-quality evidence. A sedative can be offered if CBT is not effective or not available.^{8,9} Orexin receptor antagonists (suvorexant), benzodiazepines (triazolam and temazepam only), BZRAs (eszopiclone, zaleplon, zolpidem), doxepin, and ramelteon are all weakly recommended to treat sleep onset and/or sleep maintenance insomnia based on low-quality evidence.⁸ However, long-term treatment of chronic insomnia with a sedative is not recommended because of lack of evidence and possible adverse effects based on low-quality evidence.⁹ Trazodone, and diphenhydramine are not recommended due to adverse effects and lack of efficacy, and there is insufficient evidence for use of melatonin in adults.⁸
- The U.S. Food and Drug Administration (FDA) applied black boxed warning labeling to BZRAs for complex sleep behaviors, including sleepwalking, sleep-driving, and engaging in other activities while not fully awake, which can lead to serious injuries, including death.¹⁰
- Lemborexant, an orexin receptor antagonist similar to suvorexant, was approved by the FDA in December 2019 for the treatment of insomnia in adults.¹¹ One trial found the decrease from baseline in latency to persistent sleep (LPS) as measured by PSG was larger and statistically significant for both lemborexant 5 mg (-19.5 min) and 10 mg (-21.5 min) doses compared to zolpidem extended-release (ER) 6.25 mg (-7.5 min) and placebo (-7.9 min).¹² A second trial found the decrease from baseline in subjective sleep onset latency (sSOL) was larger and statistically significant for both lemborexant 5 mg (-21.8 min) and 10 mg (-28.2 min) doses compared to placebo (-11.4 min).¹³ These similar primary endpoints both provide low-quality evidence of efficacy for improved sleep onset, but it is important to note that secondary endpoints also found benefit in sleep maintenance outcomes.^{12,13} The most common

adverse effect found with lemborexant was somnolence (8-13%), but most adverse events were mild in severity and did not appear to differ based on specific demographic characteristics of the study participants.¹²

Recommendations:

- Add melatonin as a preferred agent to the PDL restricted to children and adolescents 18 years of age or younger based on relative evidence for safety and efficacy versus other sedatives in children with neurodevelopmental disorders.
- Update clinical prior authorization criteria in **Appendix 6**.
- After review of comparative drug costs in the executive session, melatonin tablets were preferred. Lemborexant will remain a non-preferred product.

Summary of Prior Reviews and Current Policy

- There is insufficient comparative evidence that assesses differences in efficacy or effectiveness between sedative classes or between individual sedative agents.
- Similar improvement in total sleep time was found with short-term use of benzodiazepines, non-benzodiazepine sedatives, and sedating antidepressants compared to placebo based on moderate-quality evidence.
- Sleep onset latency was improved in adults taking eszopiclone, zolpidem, ramelteon, suvorexant, and doxepin compared to placebo, but the mean sleep latency remained greater than 30 minutes in most trials.
- In elderly patients, there is low quality evidence that eszopiclone improves total sleep time and wake time after sleep onset compared to placebo. Sleep onset latency is improved with zolpidem and ramelteon compared to placebo in this population based on low quality evidence. Evidence also supports efficacy of doxepin for the treatment of insomnia in patients over 65 years of age.
- There is insufficient evidence to assess efficacy or safety of long-term use of sedatives. Few randomized control trials for non-benzodiazepine sedatives examine outcomes beyond 3 months, and study durations of benzodiazepines beyond 14 days were rare. Evidence from observational studies indicates long-term sedative use may be associated with increased risk of fractures and dementia. In addition, the FDA has recently updated warnings for non-benzodiazepine sedatives that emphasize the risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions.
- There is also 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.
- Uncomplicated insomnia is an unfunded condition under the OHP unless it exacerbates or worsens a concomitant condition funded under the OHP. Current policy also prevents concomitant use of benzodiazepines, opioids or sedatives. Quantity limits apply for this class, including dose limits for zolpidem which is the only preferred drug in this class.

Background:

Insomnia is defined as dissatisfaction with sleep quantity or quality and is associated with difficulty initiating or maintaining sleep and early-morning waking with inability to return to sleep.¹⁴ Approximately 6-10% of adults suffer from chronic insomnia, with most cases occurring in females and older adults.^{9,14} Older adults are more likely to report problems with waking after sleep onset (WASO) (the sum of wake times from sleep onset to the final awakening [i.e., difficulty maintaining sleep]) than they are to report problems with sleep onset latency (SOL) (time to fall asleep). Sleep problems also occur in children, affecting about

25% of individuals during childhood, with a rate that is significantly higher in children with neurodevelopmental disorders, with prevalence estimates as high as 86%.¹

Chronic insomnia poses substantial economic burdens on society.⁸ Direct costs are attributed to significantly higher utilization of emergency and office health care visits as well as greater cost for prescription drugs.⁸ Indirect costs are found in the form of work absenteeism, loss of productivity, and insomnia-related accidents.⁸

Insomnia is a risk factor for cardiovascular disease and has been associated with arterial hypertension, myocardial infarction and chronic heart failure.⁹ Besides insomnia itself, there is evidence suggesting that short sleep duration (sleeping less than 6 hours on average) is a risk factor for obesity, type 2 diabetes, hypertension and cardiovascular diseases.⁹

Insomnia is also associated with increased risk for the development of major depressive disorder (odds ratio 2.1) and there are relationships between documented insomnia and suicidal ideation, suicide attempts and completed suicides.⁹ Mental disorders, especially depression, bipolar disorder or psychosis frequently accompany sleep-onset or sleep-maintenance difficulties.⁹ The presence of mental disorders should be examined in individuals complaining about insomnia. **Table 1** summarizes major somatic and mental co-morbidities of insomnia.⁹

Table 1. Major Co-morbidities of Insomnia.⁹

Psychiatric	Medical	Neurological	Substance Use/Dependence
Bipolar disorders	Chronic kidney diseases	Cerebrovascular diseases	Alcohol
Depressive disorders	Chronic pain	Fatal familial insomnia	Amphetamine
GAD	COPD	Multiple sclerosis	Caffeine
Panic disorder	Diabetes mellitus	Neurodegenerative diseases	Cocaine
PTSD	HIV	RLS	Designer drugs
Schizophrenia	Malignancy	Traumatic brain injury	Marijuana
	Rheumatic disorders		Nicotine
	Sleep apnea		Opioids

Abbreviations: COPD = chronic obstructive pulmonary diseases; HIV = human immunodeficiency virus infection; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder; RLS = restless leg syndrome.

The Pittsburgh Sleep Quality Index (PSQI) can be used to assess subjective sleep; however, it is not a specific tool for diagnosing insomnia and should not be used for that purpose.⁹ The Insomnia Severity Index (ISI) has been developed to assess the severity of the disorder, and has also been shown to be a reliable and valid instrument to detect patients with insomnia.⁹ If indicated, actigraphy or PSG can be considered.⁹ A meta-analysis of PSG-based studies showed that patients with insomnia have a significantly reduced total sleep time (TST), significantly prolonged SOL, and an increased number of nocturnal awakenings and amount of time awake during the night.⁹ Furthermore, slow-wave sleep and REM sleep percentages are reduced compared with good sleepers.⁹

The goal of treatment for insomnia is to provide meaningful improvements in distress or dysfunction caused by the disorder.¹⁴ The ISI and the PSQI also measure the distress and dysfunction associated with insomnia.¹⁵ Sleep measures are based on specific sleep variables that can be assessed subjectively by patient-

reported sleep diaries or objectively in a sleep laboratory with PSG or actigraphy.¹⁵ These include SOL, WASO, TST and sleep efficiency (percentage of time spent in bed sleeping; it is calculated as (TST / time in bed) × 100). **Table 2** addresses clinically meaningful outcomes for chronic insomnia.

Table 2. Clinically Meaningful Outcomes for Chronic Insomnia (Adapted from the American Academy of Sleep Medicine).⁸

Outcome (units)	Minimum Clinically Important Difference Versus Placebo [^]		
	Polysomnography (PSG)	Actigraphy	Subjective
Sleep Onset Latency (min)	10	10	20
Total Sleep Time (min)	20	20	30
Wake After Sleep Onset (min)	20	20	30
Quality of Sleep (varies*)	Varies	Varies	Varies
Sleep Efficiency (%)	5	5	10
Number of Awakenings (n)	2	2	0.5

[^]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.

Sleep onset latency, when measured by PSG, may be reported as time to onset of first epoch of N1 (Stage 1) sleep, or, in more recent studies, as latency to persistent sleep (LPS), or time to onset of first 10 consecutive minutes of sleep.⁸ Total sleep time, as mentioned earlier, is defined as the total time spent in bed, minus SOL and WASO.⁸ Quality of sleep is a patient-reported measure, the definition of which varies by measurement tools and patient perceptions.⁸ Lastly, the number of awakenings is defined as the number of awakenings after sleep onset, excluding the final awakening.⁸

Assessment of the efficacy of a given agent for the treatment of chronic insomnia is challenging, and it remains unclear which are the most important variables for defining drug efficacy.⁸ More specific efficacy endpoints for both patient-reported and objective outcomes have been utilized in studies recently (e.g., self-reported and PSG-based SOL, WASO and TST), but substantial variability in data reporting is not uncommon.⁸ Several unresolved issues remain: first, investigators have not fully agreed upon the relative importance of subjective versus objective data; secondly, it is unknown whether sleep quality endpoints are better evaluated using subjective or objective means, and if sleep quality is more meaningful than measures of SOL, TST or WASO; thirdly, an additional issue is whether efficacy is better reflected by measures of daytime alertness and cognitive, emotional, and psychomotor function than by measures of sleep.⁸ Lastly, insomnia disorder is generally treated on the basis of patient-reported sleep-associated distress in clinical practice, not laboratory assessment.¹⁵

The standard of treatment for insomnia is CBT, but pharmacotherapy is also frequently used to treat insomnia.⁸ Although FDA-approved medication indications often focus on specific sleep variables, it is not known how frequently primary care physicians target medications to specific or global measures of insomnia or prescribe them long-term.¹⁵ Many patients may also self-treat using medications or substances like alcohol which have not shown to be effective in management of insomnia or have significant potential for harm.⁸ About 3.5% to 7% of individuals are prescribed drugs for sleep disturbances, but there continues to be significant knowledge gaps and anxieties about the proper use of these drugs among providers.⁸ A summary of the PDL for this drug class is in **Appendix 1**. Sedatives used in clinical practice, but not included in this drug class, are the antidepressants trazodone and mirtazapine, the antipsychotics olanzapine and quetiapine, and the supplement melatonin.

In the second quarter of 2020 (4/1/2020 to 6/30/2020), there were 348 patients with a FFS request for an agent in the sedative PDL class. Fifty percent of patients (n=176) had requests for a non-preferred agent. The most common non-preferred agents included triazolam (n=27) and first-generation antihistamines

doxylamine or diphenhydramine (n=44). Approximately 36% of patients (n=125) had no delay in therapy, and up to 48% of patients (n=167) had a paid claim within 90 days, with the majority of paid claims for preferred zolpidem products. Of the patients with paid claims for a sedative, 4 requests were for adolescents 13 to 17 years of age, and 2 requests were for children (ages 2 and 5 respectively). Fifty-two percent of patients never received a paid claim for a sedative. In patients without a subsequent paid claim, 31% were transferred into a coordinated care organization, 5% lost eligibility, and 34% had other insurance which may have paid for their claims. For 28% of patients (n=51), a PA was never requested by their provider.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (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, and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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.

Systematic Reviews:

Sedatives in Children with Insomnia

The Drug Review Effectiveness Project systematically reviewed the evidence of sedatives in children with insomnia.¹ Randomized, head-to-head or placebo-controlled trials of at least 1-week duration or systematic reviews that evaluated sedatives in children and adolescents (age <18 years) with sleep disorders were eligible for inclusion.¹ Drugs included: 1) melatonin agonists ramelteon and melatonin; 2) non-benzodiazepine sedatives eszopiclone, zaleplon and zolpidem; and 3) orexin receptor antagonist suvorexant. Efficacy outcomes of interest included: 1) sleep latency; 2) sleep duration; 3) number of awakenings; and 4) functional status (e.g. daytime alertness, missed school).¹ Safety outcomes of interest included: 1) study withdrawals due to adverse events; 2) serious adverse events, and 3) specific adverse events (e.g. sleep walking, rebound insomnia, cognitive impairment).¹ Studies conducted in sleep labs were excluded.¹

Twenty-one placebo-controlled RCTs were identified that provide evidence for eszopiclone (n=1), zolpidem (n=1) and melatonin (n=19).¹ No head-to-head comparative evidence of sedatives in children with sleep disorders were found.¹ Six trials identified children with a diagnosis of chronic sleep-onset insomnia, although many of the participants had comorbid conditions like ADHD.¹ The remaining trials included children with both sleep problems and a specific co-morbid diagnosis: 3 studies enrolled children with ADHD, 4 studies included children with autism spectrum disorders with other neurodevelopmental disorders, 2 studies enrolled children with epilepsy, and one trial included children with atopic dermatitis.¹ Study durations ranged from 1 week to 12 weeks.¹ Two studies enrolled adolescents, while the mean age in the other studies was 9 years.¹ The two studies that evaluated eszopiclone and zolpidem included 201 and 468 participants, respectively.¹ The trials that evaluated melatonin were smaller, ranging from 8 to 160 children.¹ The daily dose of melatonin ranged widely, from 2 to 12 mg.¹

The manufacturers for eszopiclone and zolpidem funded both studies, and both were conducted in the U.S.¹ The studies enrolled children 6 to 17 years of age who had insomnia and an ADHD diagnosis.¹ Children were taking psychostimulants for ADHD symptoms.¹ Sleep outcomes were measured by PSG and actigraphy, while outcomes for behavior were based on subjective child and parent assessments.¹ Neither eszopiclone nor zolpidem improved sleep or ADHD

outcomes, although Clinical Global Impression score for Improvement (CGI-I), which is a 7-point scale that assesses improvement from baseline, did favor both drugs.¹ More children who received zolpidem (7.4%) withdrew from the study early compared to placebo (0%).¹ Dizziness, headache, hallucinations, and anxiety were reported with zolpidem more frequently than with placebo, while somnolence, dizziness, and hallucinations were reported more frequently with eszopiclone.¹ The investigators graded the evidence for these findings as low for sleep outcomes and ADHD ratings, and insufficient for adverse events.¹

Melatonin improved sleep outcomes more than placebo across several fair- and good-quality studies.¹ Sleep latency (time to fall asleep) improved by 11 to 51 minutes (median 33.75 minutes), and most of these studies found a statistically significant difference.¹ Sleep duration also improved, by a median of 23 minutes (range, 13 to 93 min), with 67% of studies finding the difference to be statistically significant.¹ Children with autism had the largest improvement in sleep outcomes (reduced sleep latency by 38 minutes, longer sleep duration by 5.5 minutes) with 3 mg to 10 mg of melatonin nightly.¹ Other specific populations found benefit with melatonin: sleep latency improved by 21 minutes in children with chronic sleep-onset insomnia, 24 minutes in children with other neurodevelopmental disorders including ADHD, 11 minutes in children with epilepsy, and 21 minutes in children with atopic dermatitis.¹ Sleep duration improved by 36.7 and 33.4 minutes with other neurodevelopmental disorders and ADHD, 23.2 and 24.8 minutes with epilepsy and atopic dermatitis, and 15.5 minutes with chronic sleep onset insomnia.¹ The number of nighttime awakenings was not improved across 8 studies that evaluated that outcome, but WASO was improved from 8.2 to 31.9 minutes based on evidence from 4 studies (3 studies found a statistically significant difference).¹ Melatonin did not consistently improve functional outcomes across 7 studies that evaluated these outcomes.¹ However, these outcomes were more favorable in children with autism or other neurodevelopmental disorders.¹ Adverse events with melatonin were infrequent, but those events that were more common with melatonin than placebo included dizziness, daytime drowsiness or reduced alertness, and bed-wetting complaints.¹ No differences in early study withdraw due to adverse events were found between children treated with melatonin and those treated with placebo.¹ The investigators graded the evidence for these findings as low for sleep latency and sleep duration, but insufficient for outcomes related to nighttime awakenings, functional outcomes, and adverse events.¹

Sedation of Children Undergoing Dental Treatment

Sedation may be used to relieve anxiety and manage behavior in children undergoing dental treatment.⁷ In 2005, the Cochrane Collaboration identified a need to determine from published research which sedatives, dosages and regimens are effective, which was subsequently first updated in 2012 and updated again in 2018.⁷ The objective of this 2018 systematic review was to evaluate the efficacy and relative efficacy of conscious sedation agents and dosages for behavior management in pediatric dentistry.⁷

Studies were selected if they were a RCT of conscious sedation that compared two or more drugs, the same drug with different dosages, or a single drug controlled by placebo or another technique to manage behavior.⁷ Drugs had to be administered by a dentist or anesthetist in an outpatient setting or dental office.⁷ The following pediatric population was specifically reviewed:

- Children and adolescents aged 0 to 16 years of age (including children with specific medical or behavioral problems); and
- Simple dental restorative treatment with local anesthesia (e.g. fillings, stainless steel crowns), simple extractions or management of dental trauma (e.g. repositioning of tooth, splinting, removal of nerve from tooth).⁷

The primary outcome was behavior, which is measured by a range of different indices.⁷ Secondary outcomes included dental treatment completion, postoperative anxiety, and adverse events.⁷ Dichotomous outcomes such as treatment completion were compared by calculating risk ratios (RR) along with 95% confidence intervals (CI).⁷ Continuous outcomes (e.g. Frankl behavior scale) were reported as mean and standard deviations (SD) in each group.⁷ Because of the wide range of scales used to measure sedation in studies, the Houpt Scale was taken as the standard when ranking behavior (i.e. higher values equal better behavior).⁷ Where scales ran in the reverse order, values were transformed so that higher values equaled better behavior (e.g. anxiety scores as measured on

the Venham scale were transformed by subtracting the mean score per group from the maximum possible score).⁷ Where dosage studies were analyzed, the lowest dose was compared to the highest dose.⁷ Results from the lowest dosage were listed first.⁷ The certainty of the evidence was assessed using GRADE methodology.⁷

The 50 included studies were undertaken in 16 different countries with the greatest proportion of studies (n = 12, 24%) from the US.⁷ Age of participants included in the trials ranged from 1 year to 16 years.⁷ Mean age for all studies was 4.8 years.⁷ The mean number of participants per study was 74.08 (standard deviation (SD) = 109) with a total of 3704 children randomized in the 50 included trials.⁷ Forty studies (81%) were at high risk of bias, 9 studies (18%) were at unclear risk of bias, and just one study was assessed at low risk of bias.⁷ There were 34 different sedatives used with or without inhalational nitrous oxide.⁷ Dosages, mode of administration and time of administration varied widely.⁷ Studies were grouped into placebo-controlled, dosage comparisons and head-to-head comparisons.⁷ In most of the studies (n = 39, 78%), patients were reported as being uncooperative or anxious at the beginning of the study based on the Frankl behavioral rating scale often used to measure baseline behavior.⁷

Of the outcome measures proposed for this review (difference in behavior, completion of treatment, difference in postoperative anxiety, and adverse events), meaningful data could only be extracted on behavior.⁷ Postoperative anxiety was rarely mentioned, and in most of the studies almost all the participants completed treatment.⁷ Outcome variables reported in the studies were mostly ordinal (e.g. 5-point scale for increasing movement) or dichotomous (e.g. success/failure).⁷ Measures of behavior or level of sedation scales were commonly used (Haupt or modified versions of Haupt were used most frequently).⁷ Adverse events were recorded but this was not done in a uniform manner between studies.⁷

There were 12 placebo-controlled studies which investigated oral midazolam, oral chloral hydrate, oral diazepam, melatonin, intranasal dexmedetomidine, intramuscular meperidine, intravenous midazolam, midazolam/ketamine, and inhaled nitrous oxide.⁷ Ten studies compared different dosages or routes of administration of sedative agents: one used hydroxyzine and the other studies used various dosages and methods of administration of midazolam.⁷ A summary of the findings of oral agents utilized on the PDMP are in **Table 3** and **Table 4**.

Meta-analysis of the available data from the primary outcome (behavior) was only possible for studies that investigated oral midazolam versus placebo.⁷ From this meta-analysis, the investigators found moderate-certainty evidence from 6 small, clinically heterogeneous studies at high or unclear risk of bias, that the use of oral midazolam in doses between 0.25 mg/kg to 1 mg/kg is associated with more cooperative behavior compared to placebo; the standardized mean difference (SMD) favored midazolam (SMD 1.96; 95% CI, 1.59 to 2.33, p<0.0001, I² = 90%; 6 studies; 202 participants).⁷ It was not possible to draw conclusions regarding the secondary outcomes due to inconsistent or inadequate reporting.⁷

Table 3. Sedative Compared to Placebo in Children Needing Dental Care (adapted from Cochrane).⁷

Drug and Outcome	Anticipated Absolute Effects* (95% CI)		Relative Effect (95% CI)	Number of Participants	Certainty of Evidence (GRADE)	Comments
	Risk with Placebo	Risk with Sedative				
Midazolam, oral Houpt/other behavioral score SD units: investigators measure behavior using different scales – higher values mean better behavior	1.96 SDs higher (1.59 to 2.33 SDs higher) than the placebo group		-	202 (6 RCTs)	MODERATE	As a rule of thumb, 0.2 SD represents a small difference, 0.5 a moderate difference, and 0.8 a large difference. Adverse events: vomiting/hiccupping reported in one study. Amnesia reported in one study. Oral midazolam probably improves behavior
Diazepam, oral Houpt/other behavioral score	0.62 SDs higher (0.28 lower to 1.53 higher) than the placebo group		-	20 (1 RCT)	VERY LOW	No adverse events reported. Uncertain whether oral diazepam improves behavior.
Chloral hydrate, oral Good or better behavior	533 per 1000	709 per 1000 (427 to 1000)	RR 1.33 (0.8 to 2.22)	60 (1 RCT)	VERY LOW	Adverse events: associated with airway problems. Uncertain whether chloral hydrate improves behavior.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Abbreviations: CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio; SD: standard deviation; SMD = standardized mean difference.

Table 4. Sedative Compared with Different Dosage of the Same Sedative for Children Needing Dental Care.⁷

Drug and Outcome	Number of Participants (studies)	Certainty of Evidence (GRADE)	Comments
Midazolam (any route of administration) Any behavioral score	394 (10)	VERY LOW	There is insufficient evidence to determine whether any specific dose of intranasal midazolam is more effective than another. There is weak evidence from two trials that oral midazolam at a dose of 0.5 mg/kg to 0.75 mg/kg is effective. One trial administered both nitrous oxide and midazolam, so it is difficult to attribute benefit to midazolam alone.
Any behavioral score – hydroxyzine	30 (1)	VERY LOW	There is insufficient evidence to determine whether any specific dose of hydroxyzine is effective.

No studies that compared two or more sedatives of the same intervention found similar effect.⁷ Overall, there was insufficient evidence to draw any conclusions from studies that evaluated two or more sedatives for children needing dental care.⁷

Sedatives for Treatment of Behavioral Insomnia in Children with Attention-Deficit Hyperactivity Disorder

A systematic review that assessed the safety, tolerability and efficacy of the most commonly used drugs to treat behavioral insomnia associated with ADHD was performed.² The review focused on sleep-onset insomnia (SOI), total sleep duration and number of awakenings during the night.² Observational and interventional studies that investigated the effects of melatonin, zolpidem, and eszopiclone on behavioral insomnia in children with ADHD were included.² ADHD was defined according to criteria outlined by the Diagnostic and Statistical Manual (DSM) of Mental Disorders, the American Academy of Child and Adolescent Psychiatry, the Diagnostic Interview Schedule for Children Version IV, or parents' and teachers' report on the child symptom inventories.² In order to ensure methodological quality and to avoid the bias caused by dependence on investigators agreeing to provide data from unpublished studies, only published, peer-reviewed studies were included.² Twelve studies, either observational studies or RCTs, met the inclusion criteria for this systematic review.²

In one good-quality, placebo-controlled melatonin trial, mean SOL and TST improved by both objective and subjective measurements in children with ADHD who did not respond adequately to sleep hygiene measures.² The mean SOL improved by about 16 minutes and TST improved by about 15 minutes, with melatonin versus placebo.² Open-label follow-up did not show a significant improvement in SOL; however, the improvement in sleep duration by 23 minutes continued with the melatonin treatment.² Another good-quality RCT found a difference in TST of about 33 minutes between melatonin and placebo.² Compared with placebo, the melatonin group had a statistically significant decrease in SOL ($p = 0.001$), increase in sleep efficiency ($p = 0.01$) and decrease in nocturnal restlessness ($p = 0.03$).² Observational studies have also found improvement in SOL with melatonin in children with ADHD based on subjective measurements.² One study found that mean SOL decreased with melatonin versus placebo at week 8 (26 min vs. 18 min, respectively), and mean TST increased with melatonin by about 0.5 hours but decreased with placebo by about 0.5 hours.² In another study, almost 90% of parents were satisfied with melatonin for the improvement of sleep-onset problems, 70.8% were satisfied with melatonin for improved daytime behaviors, and 60.9% for improvement of mood.² These studies have found that melatonin improves chronic behavioral insomnia in children with ADHD only as long as treatment is continued, but did not cure it, as relapse was common once treatment stopped.² Adverse events with melatonin have usually been mild and similar to those with placebo; however, studies have not been powered adequately to allow any definitive evaluation of safety related to melatonin.²

No statistically significant differences in LPS or TST between the zolpidem and placebo was detected at week 4 by actigraphy (objective) measures in children with ADHD-associated insomnia based on a good-quality RCT.² At week 4, the baseline-adjusted least square mean difference \pm standard error for TST (i.e. TST minus baseline TST) was 2.77 ± 14.23 min ($p = 0.8461$), and for LPS was 1.55 ± 110.37 min, ($p = 0.8884$).² Treatment-emergent adverse events (TEAE) were reported in 62.5% and 47.7% of children treated with zolpidem and placebo, respectively.² Treatment discontinuation occurred in 10 children in the zolpidem group versus none in the placebo group, the primary adverse event being hallucinations, which occurred in 10 of 136 total patients. Other adverse events included dizziness and headache.²

No statistically significant differences between eszopiclone and placebo at week 12 were found in PSG-measured LPS in an excellent quality RCT in children with ADHD-associated insomnia.² Secondary subjective measures (patient/parent reports on SOL, TST, WASO, number of awakenings after sleep onset and sleep quality) revealed no statistically significant differences on hierarchical statistical analysis.² The most common TEAE in this study were headache, dysgeusia and dizziness, which were reported more commonly in the eszopiclone groups (about 60% versus 46% with placebo).² Of interest, several patients discontinued treatment due to hallucinations (2.3%) and suicidal ideation (1%) in the eszopiclone-treated groups.²

The results from these RCTs and observational studies indicate that the quality of most of the available studies for the drugs treating behavioral insomnia in children with ADHD is not very high.² With the possible exception of melatonin, there is insufficient evidence for the use of sedatives in treating sleep-related

disturbances such as insomnia in ADHD.² It was also found that zolpidem and eszopiclone did not show significant improvement in different sleep parameters when compared with placebo but were associated with TEAEs.²

Benzodiazepine Receptor Agonist Sedatives for Improving Sleep Quality in Patients with Schizophrenia

About 44% of patients with schizophrenia suffer from sleep disturbances.⁴ This systematic review and meta-analysis was performed to inform clinical practice on the efficacy and safety of the benzodiazepine receptor agonists (BZRA) eszopiclone, zaleplon, and zolpidem for schizophrenia.⁴ Outcomes of importance were: 1) improvement in overall schizophrenia symptoms; 2) improvement in insomnia symptoms; 3) discontinuation rate; and 4) individual adverse events.⁴ Only RCTs of Z-drugs for patients with schizophrenia were included in this study.⁴ Non-blinded randomized trials were not excluded in order for the investigators to obtain as much information as possible.⁴ If outcome data were reported by at least 2 RCTs, a meta-analysis was performed to combine pooled data of these drugs versus placebo).⁴ The primary outcome measure was all-cause study discontinuation.⁴ Secondary outcomes for efficacy were improvement in the overall schizophrenia symptoms [Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Symptom Scale (PANSS) scores], total sleep time, and WASO.⁴ Secondary outcomes for safety were discontinuation due to adverse events and individual adverse events (incidence of at least one adverse event and sedation).⁴ To combine studies, the random effects model was used, which is more conservative than the fixed effects model and produces a wider CI.⁴ For dichotomous data, the risk ratio (RR) was estimated with 95% CIs.⁴ For continuous outcomes, SMDs were used.⁴

In total, only 3 eszopiclone RCTs were identified, two blinded placebo-controlled (n=60) trials and one open-label acupuncture-controlled trial (n=96).⁴ No drugs were identified for other FDA-approved BZRA sedatives.⁴ All studies were conducted among adults with schizophrenia.⁴ The two eszopiclone placebo-controlled trials were conducted in the USA and were sponsored by the pharmaceutical industry.⁴ A 10-week, double-blind placebo-controlled RCT on the augmentation of antipsychotics with eszopiclone versus that of antipsychotics with placebo found that eszopiclone was superior to placebo in improving the Insomnia Severity Index score; however, no difference was observed in the improvement in PANSS scores and other sleep-related outcomes between the groups.⁴ Six patients (31.6%) in the eszopiclone group and 3 patients (17.6%) in the placebo group did not complete the study.⁴ The most common adverse events in both treatment groups were sedation (eszopiclone = 42.1%, placebo = 41.2%).⁴ A one-week, double-blind placebo-controlled RCT on the augmentation of antipsychotics with eszopiclone versus that of antipsychotics with placebo did not find statistically significant differences in sleep-related outcomes and did not evaluate improvement in psychiatric symptoms.⁴ Lastly, an 8-week, open-label, Chinese RCT on the augmentation of antipsychotics with eszopiclone versus that of antipsychotics with shallow needling (a form of acupuncture) for the treatment of patients with schizophrenia did not find statistically significant differences in the improvement of PANSS scores and Pittsburgh Sleep Quality Index score between the groups.⁴

Based on the evidence of this review, eszopiclone may be useful for the treatment of insomnia symptoms in patients with schizophrenia, but the overall evidence is mixed and is low quality.⁴ Eszopiclone did not improve schizophrenia symptoms in either of the 3 studies.⁴ The use of other BZRAs is not advised because they have not been studied in this population.⁴

Risk of Falls and Hip Fractures with Benzodiazepine and Benzodiazepine Receptor Agonist Sedatives

There is a well-established association between benzodiazepines and fracture risk, but the association of BZRAs (zolpidem, zaleplon and zopiclone) is less clear.^{5,6} Two recent systematic reviews have evaluated these associations in more depth: the objectives of one review⁵ were to investigate the association between benzodiazepine or BZRA use and hip fracture risk; the second review⁶ assessed the association between BZRA use and the risk for fractures, falls and injuries.

Studies in the Donnelly, et al. review were included if all of the following criteria applied: 1) RCT, cohort or case-control study; 2) reported outcome was hip fracture or fragility fracture (within which outcome $\geq 70\%$ of fractures were hip fractures); 3) patients were prescribed either a benzodiazepine or BZRA, or were

matched as a non-exposed control population; and 4) the study population was at least 50 years of age or older with a mean age over 65 years.⁵ Exposure was categorized into two main subgroups: exposure to a benzodiazepine versus non-exposure; and exposure to a BZRA versus non-exposure.⁵ Benzodiazepine exposure was defined as patients prescribed diazepam, lorazepam, chlordiazepoxide, oxazepam, temazepam or clobazam.⁵ Exposure to BZRA was defined as patients prescribed zaleplon, zolpidem or zopiclone.⁵ Length of use was defined from the first prescription date, provided there was at least one preceding hypnotic-free month.⁵ Short-term use was defined as up to 14 days, medium-term use was defined as 15 days to 30 days, and long-term use was longer than one month; mixed use was a combination of medium and long-term users.⁵ The risk of hip fracture in those exposed to one of these drug classes was compared to patients not taking these medications.⁵ The measure of effect was the adjusted relative risk (RR) with the associated 95% CI.⁵ Included comparisons were studies of: people using benzodiazepine compared to those not exposed; and people using a BZRA compared to those not exposed.⁵ Non-randomized study designs were described narratively and only pooled into a meta-analysis if the investigators determined their context, population, medication (including delivery) were clinically similar.⁵ Statistical heterogeneity was summarized using an I^2 statistic.⁵ Where I^2 was reported higher than 75%, subgroups were explored to explain the heterogeneity.⁵

No RCTs were identified; overall, 18 studies were included: 9 case control studies and 9 cohort studies.⁵ Studies were compared for differences in the context of their setting including of location, design, fracture type, mean age, sample size, length of drug exposure and adjustment for confounders with attention to dose.⁵ The included sample sizes ranged from 500 to 906,422 participants.⁵ The mean age in the studies ranged from 72.0 to 84.3 years.⁵

Eighteen of the studies assessed the effect of benzodiazepine use compared to non-exposure.⁵ There was an associated increase in hip fracture risk with benzodiazepine use (RR 1.52; 95% CI, 1.37 to 1.68; $p < 0.001$; $I^2 = 67\%$).⁵ Severe heterogeneity was explained by the varying length of use; therefore, the risk of fracture was dependent on the length of use.⁵ Short-term use carried a 140% increased risk of hip fracture (RR 2.40; 95% CI, 1.88 to 3.05; $p < 0.001$; $I^2 = 27\%$).⁵ Medium-term use carried 53% increased risk (RR 1.53; 95% CI, 1.22 to 1.92; $p < 0.001$; $I^2 = 0\%$) and long-term use carried 20% increased risk (RR 1.20; 95% CI, 1.08 to 1.34; $p < 0.001$; $I^2 = 0\%$).⁵ The mixed length of use subgroup carried a 52% increased risk (RR 1.52; 95% CI, 1.35 to 1.71; $p < 0.001$; $I^2 = 59\%$), but given the high heterogeneity of this group, the investigators cautioned any interpretations of this finding.⁵

Six of the studies assessed the effect of BZRA use compared to non-exposure.⁵ There was an associated increased risk of hip fractures with BZRA use (RR 1.90; 95% CI, 1.68 to 2.13; $p < 0.001$; $I^2 = 26\%$).⁵ Short-term use carried a 139% increased risk of hip fracture (RR 2.39; 95% CI, 1.74 to 3.29; $p < 0.001$; $I^2 = 26\%$).⁵ Mixed use carried an 80% increased risk (RR 1.80; 95% CI, 1.60 to 2.02; $p = 0.001$; $I^2 = 0\%$).⁵

Studies in the Treves, et al. review were eligible if they evaluated adults (age ≥ 18 years) who received a BZRA and a control group who were not treated with a BZRA.⁶ The control group could include participants treated with other sedatives. Studies were only selected if they reported on fractures, falls or injuries.⁶ No restriction was placed on how these outcomes were defined in order to perform a more comprehensive evaluation.⁶ The possible impact of variation in terminology and study design was addressed by measuring heterogeneity and utilizing random-effects models and subgroup analyses.⁶

A total of 14 studies, including 5 cohort studies and 9 case-control studies were included in the systematic review.⁶ The analysis concerning fractures included 10 studies with 830,877 participants (including 146,678 exposed to a BZRA).⁶ A statistically significant increased risk for fractures was found with BZRA use, with evidence of significant heterogeneity (odds ratio [OR] 1.63; 95% CI, 1.42 to 1.87; $I^2 = 90\%$).⁶ Estimates obtained from case-control studies were similar to those obtained from cohort studies.⁶ When 3 studies contributing most to the heterogeneity were excluded, a similar risk was found, while the heterogeneity decreased (OR 1.52; 95% CI, 1.39 to 1.66; $I^2 = 58\%$, $n = 191,598$ participants).⁶ Subgroup analyses did not find any differences in risk of fracture between the BZRA sedatives.⁶ When the effect of insomnia was considered as a confounder, a subgroup analysis of studies with control groups diagnosed with insomnia still

resulted in statistically significant increased risk for fractures with BZRA exposure (OR 1.28; 95% CI, 1.08 to 1.53; $I^2 = 71\%$).⁶ The analysis concerning falls included 3 studies with 19,505 participants.⁶ The BZRAs were not associated with a statistically significant increased risk for falls; however, the trend suggests an increased risk and there was evidence of significant heterogeneity (OR 2.40; 95% CI, 0.92 to 6.27; $I^2 = 95\%$).⁶ The analysis concerning injuries included 2 studies with 160,502 participants (78,322 were exposed to zolpidem).⁶ A statistically significant increased risk for injuries was also found with BZRA use, with no evidence of heterogeneity (OR 2.05; 95% CI, 1.95 to 2.15; $I^2 = 0\%$).⁶

These systematic reviews found an increase in the association between both benzodiazepine and BZRA use with hip fracture, general fractures, falls and injuries.^{5,6} There appears to be little difference in the findings between benzodiazepine and BZRA sedatives.^{5,6} The risk of fracture depended on the length of time people used their medication, and newly prescribed users of these drugs were at the greatest risk of hip fracture.^{5,6}

After further review, two systematic reviews were excluded due to lack of adequate comparator (e.g. only eligible studies were placebo-controlled trials of a single drug)^{16,17} and one systematic review was excluded due to lack of applicability (use of sedatives at high altitudes).³

New Guidelines:

High Quality Guidelines:

The American Academy of Sleep Medicine (2017)

The purpose of this guideline was to establish clinical practice recommendations for the pharmacologic treatment of chronic insomnia in adults.⁸ The relative benefits of pharmacotherapy to CBT, which is already recognized as the standard of therapy, was not addressed.⁸ The guideline task force recognized, however, that despite the favorable benefit to risk ratio of CBT, not all patients with an insomnia disorder can derive benefit from CBT alone.⁸ Pharmacotherapy, alone or in combination with CBT, should be considered as a treatment option for insomnia.⁸

The guideline included a systematic review and meta-analyses which provided the basis for the conclusions and recommendations. The GRADE approach (Grades of Recommendation, Assessment, Development and Evaluation) was used for the assessment of quality of evidence. The task force assessed the following 3 factors to determine the direction and strength of a recommendation: quality of evidence, balance of beneficial and harmful effects, and patient values and preferences.⁸ First, quality of evidence was based exclusively on the studies that could be included in the meta-analyses. The task force determined their overall confidence that the estimated effect found in the studies was representative of the true treatment effect that patients would see, based on the following criteria: overall risk of bias (randomization, blinding, allocation concealment, selective reporting, and author disclosures); imprecision (when 95% CI crosses the clinical significance threshold); inconsistency (I^2 cutoff of 75%); indirectness (study population); and risk of publication bias (funding sources).⁸ Second, the task force determined if the beneficial outcomes of the intervention outweighed any harmful adverse effects based on what was reported in the studies and the clinical expertise of the task force.⁸ Thirdly, the task force determined if patient values and preferences would be generally consistent, and if patients would use the intervention based on the body of evidence reviewed.⁸

Taking these major factors into consideration and adhering to GRADE recommendations, the task force assigned a direction (for or against) and strength (strong or weak) for each recommendation statement.⁸ Additional contextual remarks were provided with each recommendation, which were based on the evidence evaluated during the systematic review.⁸

A STRONG recommendation is one that clinicians should, under most circumstances, always be following when pharmacological treatment is indicated (i.e., something that might qualify as a quality measure).⁸ A WEAK recommendation reflects a lower degree of certainty in the appropriateness of the patient-care strategy and requires that the clinician use their clinical knowledge and experience, and refer to the individual patient’s values and preferences to determine the best course of action.⁸

This guideline made two major recommendations. The first recommendation is that all patients with chronic insomnia should receive CBT as the initial and primary intervention.⁸ They graded this recommendation as a strong recommendation based on moderate-quality evidence.⁸ The second recommendation is that a shared decision-making approach be employed by clinicians in determining whether pharmacotherapy should be initiated for those patients who do not achieve adequate response with CBT.⁸ This second major recommendation was graded as a weak recommendation based on low quality evidence.⁸

The systematic review found that very few comparative efficacy studies have been conducted among these agents so the guideline provides a recommendation and evidence base for each individual drug as summarized in **Table 5**.⁸

Table 5. Summary of Clinical Practice Recommendations for Adults with Chronic Insomnia (Adapted from the American Academy of Sleep Medicine).⁸

Treatment	Recommendation	Strength of Recommendation	Quality of Evidence	Benefits and Harms Assessment	Summary of Clinically Meaningful Outcomes
Orexin Receptor Agonists					
Suvorexant <i>Based on 10, 15, 20 mg doses</i>	Suvorexant is suggested as a treatment for sleep maintenance insomnia (versus no treatment).	WEAK	LOW	Benefits outweigh harms	Efficacy: Total sleep time: Mean improvement was 10 min longer, compared to placebo (95% CI: 2 to 19 min improvement); Wake after sleep onset: Mean reduction was 16–28 min greater vs. placebo (95% CI: 7 to 43 min reduction); Quality of sleep: Not reported. Harm: Overall frequency of adverse events not significantly increased vs. placebo. No evidence of daytime residual or withdrawal symptoms.
Benzodiazepine Receptor Agonists					
Eszopiclone <i>Based on 2, 3 mg doses</i>	Eszopiclone is suggested as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment).	WEAK	VERY LOW	Benefits outweigh harms	Efficacy: Sleep latency: Mean reduction was 14 min greater vs. placebo (95% CI: 3 to 24 min reduction); Total sleep time: Mean improvement was 28–57 min longer vs. placebo (95% CI: 18 to 76 min improvement); Wake after sleep onset: Mean reduction was 10 –14 min greater vs. placebo (95% CI: 2 to 18 min reduction); Quality of sleep*: Moderate-to-large improvement vs. placebo. Harm: Limited or no consistent evidence of adverse events in excess of placebo, with possible exception of unpleasant taste.
Zaleplon <i>Based on 10 mg dose</i>	Zaleplon is suggested as a treatment for sleep onset	WEAK	LOW	Benefits outweigh harms	Efficacy: Sleep latency: Mean reduction was 10 min greater vs. placebo (95% CI: 0 to 19 min reduction);

	insomnia (versus no treatment).				Quality of sleep*: No improvement in quality of sleep vs. placebo. <u>Harm:</u> No statistical evidence of adverse events in excess of placebo, but some treatment-emergent adverse events were numerically more prevalent than placebo.
Zolpidem <i>Based on 10 mg dose</i>	Zolpidem is suggested as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment).	WEAK	VERY LOW	Benefits outweigh harms	<u>Efficacy:</u> Sleep latency: Mean reduction was 5-12 min greater vs. placebo (95% CI: 0 to 19 min reduction); Total sleep time: Mean improvement was 29 min longer vs. placebo (95% CI: 11 to 47 min improvement); Wake after sleep onset: Mean reduction was 25 min greater vs. placebo (95% CI: 18 to 33 min reduction); Quality of sleep*: Moderate improvement in quality of sleep vs. placebo. <u>Harm:</u> Limited evidence of mild adverse events in excess of placebo, with the possible exception of excessive sleepiness following administration of higher doses (10 mg) less than 8 hours prior to awakening.
Benzodiazepines					
Triazolam <i>Based on 0.25 mg dose</i>	Triazolam is suggested as a treatment for sleep onset insomnia (versus no treatment).	WEAK	HIGH	Benefits approximately equal to harms	<u>Efficacy:</u> Sleep latency*: Mean reduction was 9 min greater, compared to placebo (95% CI: 4 to 22 min reduction); Quality of sleep*: Moderate improvement vs. placebo. <u>Harm:</u> Insufficient data available for meta-analyses. Speech disorder was significantly more frequent than placebo in one report.
Temazepam <i>Based on 15 mg dose</i>	Temazepam is suggested as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment).	WEAK	MODERATE	Benefits outweigh harms	<u>Efficacy:</u> Sleep latency: Mean reduction was 37 min greater vs. placebo (95% CI: 21 to 53 min reduction); Total sleep time: Mean improvement was 99 min longer vs. placebo (95% CI: 63 to 135 min improvement); Wake after sleep onset: Not reported; Quality of sleep*: Small improvement vs. placebo. <u>Harm:</u> Insufficient data available for meta-analyses. Limited or no consistent evidence of adverse events in excess of placebo but daytime impairment has been noted.
Melatonin agonists					
Ramelteon <i>8 mg dose</i>	Ramelteon is suggested as a treatment for sleep onset insomnia (versus no treatment).	WEAK	VERY LOW	Benefits outweigh harms	<u>Efficacy:</u> Sleep latency: Mean reduction was 9 min greater vs. placebo (95% CI: 6 to 12 min reduction); Quality of sleep*: No improvement vs. placebo. <u>Harm:</u>

					Relatively low frequency of adverse effects overall and none which were significantly different than placebo.
Heterocyclics					
Doxepin 3, 6 mg doses	Doxepin is suggested as a treatment for sleep maintenance insomnia (versus no treatment).	WEAK	LOW	Benefits outweigh harms	<u>Efficacy:</u> Total sleep time: Mean improvement was 26–32 min longer vs. placebo (95% CI: 18 to 40 min improvement); Wake after sleep onset: Mean reduction was 22–23 min greater vs. placebo (95% CI: 14 to 30 min reduction); Quality of sleep*: Small-to-moderate improvement vs. placebo. <u>Harms:</u> Minimal evidence of adverse events in excess of placebo.
Trazodone 50 mg dose	Trazodone is not recommended as treatment for sleep onset or sleep maintenance insomnia (versus no treatment). This recommendation is based on the perception of trazodone as a “safer” sleep-promoting agent by many physicians despite absence of significant efficacy and paucity of information regarding harms.	WEAK	MODERATE	Harms outweigh benefits	<u>Efficacy:</u> Sleep latency*: Mean reduction was 10 min greater vs. placebo (95% CI: 9 to 11 min reduction); Wake after sleep onset: Mean reduction was 8 min greater vs. placebo (95% CI: 7 to 9 min reduction); Quality of sleep*: No improvement in quality of sleep vs. placebo <u>Harms:</u> Trazodone associated with significantly more adverse events vs. placebo, mostly headache and somnolence (based on one trial)
Over-the-Counter Products					
Diphenhydramine 50 mg dose	Diphenhydramine is not recommended as treatment for sleep onset or sleep maintenance insomnia (versus no treatment). This recommendation is based on the absence of evidence for clinically significant improvement.	WEAK	LOW	Benefits approximately equal to harms	<u>Efficacy:</u> Sleep latency: Mean reduction was 8 min greater vs. placebo (95% CI: 2 min increase to 17 min reduction); Total sleep time: Mean improvement was 12 min longer vs. (95% CI: 13 min reduction to 38 min improvement); Quality of sleep*: No improvement vs. placebo. <u>Harms:</u> No meta-analyses of adverse effects possible with minimal evidence of adverse events in excess of placebo.
Melatonin 2 mg dose	Melatonin is not recommended as treatment for sleep onset or sleep maintenance insomnia (versus no treatment). This recommendation is based on its availability and the widespread perception of melatonin as a benign sleep aid despite paucity of evidence for the 2 mg dose in adults.	WEAK	VERY LOW	Benefits approximately equal to harms	<u>Efficacy:</u> Sleep latency: Mean reduction was 9 min greater vs. placebo (95% CI: 2 to 15 min reduction); Quality of sleep*: Small improvement vs. placebo. <u>Harms:</u> No meta-analyses of adverse effects possible with minimal evidence of adverse events in excess of placebo.

Note: All reported measures are based on polysomnographic data, unless otherwise noted.

*Based on subjective reporting

Using the GRADE approach, quality of evidence for randomized clinical trials began at HIGH and were downgraded progressively for heterogeneity, imprecision or potential publication bias.⁸ Therefore, since most studies were industry-sponsored, the quality of evidence for nearly all of them was reduced from HIGH to MODERATE.⁸ The extent to which this downgrading of evidence is warranted due to actual publication bias is unknown, but under the GRADE system the task force chose to adopt a conservative approach and assume risk of bias.⁸ When heterogeneity and imprecision were accounted for, the quality of evidence for many treatments considered was LOW or VERY LOW.⁸ Heterogeneity and imprecision are not uncommon for these studies due to substantial variability in sleep outcome variables across studies and confidence intervals that frequently overlap the clinical thresholds for significance.⁸ Thus, the recommendations were graded as WEAK, in that they are based on relatively limited and low quality evidence.⁸

Most medications included in the meta-analyses are FDA-approved drugs for treatment of insomnia.⁸ The task force was aware that FDA approval rests on the demonstration of *statistically* significant changes in both subjective and objective outcomes.⁸ The task force recognized that many agents have been shown in one or more studies to be *statistically significantly superior* to placebo for a given outcome, but are nonetheless not recommended for treatment of chronic insomnia in this guideline.⁸ The task force emphasized the importance of understanding the discrepancy which results from different criteria employed by the FDA and individual studies versus GRADE.⁸ The GRADE approach establishes evidence quality ratings and *clinical* significance thresholds that are not employed in individual clinical trials and FDA assessment for approval.⁸

The task force also noted that it is important for clinicians to understand that a recommendation against use, particularly when associated with low quality evidence, is not equivalent to a demonstration of ineffectiveness.⁸ Rather, it is often an indication that the available evidence is insufficient and fails to provide convincing support in favor of use by GRADE standards.⁸

Of note, tasimelteon (a melatonin agonist), doxylamine (an over-the-counter antihistamine) and midazolam (a benzodiazepine) were not included in the guideline, although these drugs are included in the OSHP FFS PDL sedative drug class.

The European Sleep Research Society (2017)

This European guideline for the diagnosis and treatment of insomnia was developed to provide clinical recommendations for the management of adult patients with insomnia for physicians and clinical psychologists who diagnose and treat patients with insomnia, including insomnia co-morbid with somatic or mental disorders.⁹ The guideline is based on a systematic review of relevant meta-analyses from 1966 to 2016.⁹ The GRADE approach was used for the assessment of quality of evidence and to inform recommendations.⁹ The published evidence was rated as high quality if the examined meta-analyses suggested it to be very unlikely that further research would change the guideline task force's confidence in the estimate of effect.⁹ In contrast, evidence was rated as low quality when the meta-analyses suggested that any estimate of effect was uncertain.⁹ Two grades of recommendations were used: 'strong' and 'weak'.⁹ Recommendation grades were based on a consensus between members of the guideline task force from the body and quality of evidence.⁹

The grading of recommendations from the guideline are summarized in **Table 6**.

Table 6. Recommendations from the European Sleep Research Society.⁹

<p>Diagnostic management of insomnia and its co-morbidities</p> <ul style="list-style-type: none">• Diagnostic procedure for insomnia should include an evaluation of the current sleep–wake behavior, sleep history, somatic and mental disorders, a physical examination, the use of sleep questionnaires and sleep diaries, and additional tests, if indicated (blood test, ECG, EEG, CT/MRT, circadian markers). (strong recommendation, moderate- to high-quality evidence).• The clinician should ask for medication and other substance use (alcohol, caffeine, nicotine, illegal drugs), which may disturb sleep (strong recommendation, high-quality evidence).• Sleep diaries or actigraphy can be used in case of clinical suspicion of irregular sleep–wake schedules or circadian rhythm disorders (strong recommendation, high-quality evidence), and actigraphy can be used to assess quantitative sleep parameters (weak recommendation, high-quality evidence).• Polysomnography is recommended when there is clinical suspicion of other sleep disorders, like periodic limb movement disorder, sleep apnea or narcolepsy, treatment-resistant insomnia, insomnia in occupational at-risk groups, or suspicion of a large discrepancy between subjectively experienced and polysomnographically measured sleep (strong recommendation, high-quality evidence).
<p>Treatment of Insomnia</p> <p>In the presence of co-morbidities, clinical judgement should guide whether insomnia or the co-morbid condition is treated first, or whether both are treated at the same time.</p> <p><i>CBT</i></p> <ul style="list-style-type: none">• CBT is recommended as first-line treatment for chronic insomnia in adults of any age (strong recommendation, high-quality evidence).• A pharmacological intervention can be offered if CBT is not effective or not available. <p><i>BZD and BZRA</i></p> <ul style="list-style-type: none">• BZDs and BZRAs are effective in the short-term treatment of insomnia (≤ 4 weeks; high-quality evidence).• The newer BZRAs are equally effective as BZDs (moderate-quality evidence).• BZDs or BZRAs with shorter half-lives may have less adverse effects concerning sedation in the morning (moderate-quality evidence).• Long-term treatment of insomnia with a BZD or BZRA is not generally recommended because of a lack of evidence and possible adverse effects (strong recommendation, low-quality evidence). In patients using medication on a daily basis, reduction to intermittent dosing is strongly recommended (strong recommendation, low-quality evidence). <p><i>Sedating Antidepressants</i></p> <ul style="list-style-type: none">• Sedating antidepressants are effective for short-term treatment of insomnia; contraindications have to be carefully considered (moderate-quality evidence). Long-term treatment of insomnia with sedating antidepressants is not generally recommended because of a lack of evidence and possible adverse effects (strong recommendation, low-quality evidence). <p><i>Antihistamines</i></p> <ul style="list-style-type: none">• Because of insufficient evidence, antihistamines are not recommended for insomnia treatment (strong recommendation, low-quality evidence). <p><i>Antipsychotics</i></p> <ul style="list-style-type: none">• Because of insufficient evidence and in light of their adverse effects, antipsychotics are not recommended for insomnia treatment (strong recommendation, very low-quality evidence). <p><i>Melatonin</i></p> <ul style="list-style-type: none">• Melatonin is not generally recommended for the treatment of insomnia because of limited efficacy (weak recommendation, low-quality evidence). <p><i>Phytotherapy</i></p> <ul style="list-style-type: none">• Valerian and other phytotherapeutics are not recommended for the treatment of insomnia because of poor evidence (weak recommendation, low-quality evidence). <p><i>Light therapy and exercise</i></p> <ul style="list-style-type: none">• Light therapy and exercise regimes may be useful as adjunct therapies (weak recommendation, low-quality evidence). <p><i>Complementary and alternative medicine</i></p>

- Acupuncture, aromatherapy, foot reflexology, homeopathy, meditative movement, moxibustion and yoga are not recommended for the treatment of insomnia because of poor evidence (**weak recommendation, very low-quality evidence**).

Abbreviations: BZD = benzodiazepine; BZRA = benzodiazepine receptor agonist; CBT = cognitive behavioral therapy for insomnia; CT = Computed Tomography; ECG = electrocardiogram; EEG = electroencephalogram; MRT = Magnetic Resonance Tomography.

Additional Guidelines for Clinical Context:
No other new guidelines were identified.

New Formulations or Indications:

No new formulations or indications identified.

New FDA Safety Alerts:

Table 7. Description of New FDA Safety Alerts^{10,18}

Generic Name	Trade Name	Month / Year of Label Change	Location of Labeling Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Eszopiclone	LUNESTA	8/2019	Boxed Warning	COMPLEX SLEEP BEHAVIORS including sleepwalking, sleep-driving, and engaging in other activities while not fully awake may occur following use of eszopiclone. Some of these events may result in serious injuries, including death. Eszopiclone must be discontinued immediately if a patient experiences a complex sleep behavior.
Zaleplon	SONATA	8/2019	Boxed Warning	COMPLEX SLEEP BEHAVIORS including sleepwalking, sleep-driving, and engaging in other activities while not fully awake may occur following use of zaleplon. Some of these events may result in serious injuries, including death. Zaleplon must be discontinued immediately if a patient experiences a complex sleep behavior.
			Warnings and Precautions	Use in Patients with Depression: In primarily depressed patients treated with sedative-hypnotics, worsening of depression, including suicidal thoughts and actions (including completed suicides), have been reported.
		2/2019	Warnings and Precautions	Because zaleplon can cause drowsiness, patients, particularly the elderly, are at higher risk of falls.
Zolpidem	AMBIEN; AMBIEN CR; EDLUAR; INTERMEZZO	8/2019	Boxed Warning	COMPLEX SLEEP BEHAVIORS including sleepwalking, sleep-driving, and engaging in other activities while not fully awake may occur following use of zolpidem. Some of these events may result in serious injuries, including death. Zolpidem must be

				discontinued immediately if a patient experiences a complex sleep behavior.
Suvorexant	BELSOMRA	3/2020	Warnings and Precautions	Use in Patients with Depression: <ul style="list-style-type: none"> In primarily depressed patients treated with sedative-hypnotics, worsening of depression, including suicidal thoughts and actions (including completed suicides), have been reported.
		2/2019	Warnings and Precautions	<ul style="list-style-type: none"> Because zaleplon can cause drowsiness, patients, particularly the elderly, are at higher risk of falls.
ALL BENZODIAZEPINES Alprazolam Chlordiazepoxide Clobazam Clonazepam Clorazepate Diazepam Estazolam Flurazepam Lorazepam Oxazepam Quazepam Temazepam Triazolam		9/2020	Boxed Warning	To address the serious risks of abuse, addiction, physical dependence, and withdrawal reactions: The Boxed Warning will be updated to the prescribing information for all benzodiazepines. This information will describe the risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions consistently across all the medicines in the class. Other changes are also being required to several sections of the prescribing information, including to the Warnings and Precautions, Drug Abuse and Dependence, and Patient Counseling Information sections.
Triazolam	HALCION	10/2019	Contraindications	<ul style="list-style-type: none"> Patients with known hypersensitivity to triazolam, any of component of triazolam, or other benzodiazepines. Reactions consistent with angioedema (involving the tongue, glottis, or larynx), dyspnea, and throat closing have been reported and may be fatal. Concomitant administration of strong cytochrome P450 (CYP 3A) enzyme inhibitors (e.g., ketoconazole, itraconazole, nefazodone, lopinavir, ritonavir).
		10/2019	Adverse Reactions	Post-marketing Experience: <ul style="list-style-type: none"> General disorders and administration site conditions: Paradoxical drug reaction, chest pain and fatigue Gastrointestinal disorders: Tongue discomfort, glossitis, stomatitis Hepatobiliary disorders: Jaundice Injury, poisoning and procedural complications: Falls Psychiatric disorders: Confusional state (disorientation, derealization, depersonalization), mania, agitation, restlessness, irritability, sleep disorder and libido disorder,

				hallucination, delusion, aggression, somnambulism, and abnormal behavior
		2/2019	Warnings and Precautions	<ul style="list-style-type: none"> • Because triazolam can cause drowsiness, patients, particularly the elderly, are at higher risk of falls. • Advise patients that increased drowsiness and decreased consciousness may increase the risk of falls in some patients.
		12/2016	Boxed Warning	<p>WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.</p> <ul style="list-style-type: none"> • Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. • Limit dosages and durations to the minimum required. • Follow patients for signs and symptoms of respiratory depression and sedation.

Randomized Controlled Trials:

A total of 290 citations were manually reviewed from the initial literature search. After further review, all but 3 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 in the table below. Full abstracts are included in **Appendix 2**.

Table 8. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Hanna, et al. ¹⁹ SC DB RCT N=80	Midazolam syrup 0.5 mg/kg PO Zolpidem solution 0.25 mg/kg PO	Children 2-9 y undergoing elective inpatient procedure ≥2 h duration	Anxiety, measured by the modified Preoperative Anxiety Scale (mYPAS) at time of separation from parents	Midazolam: 26.7 Zolpidem: 30.0 Difference: NS Conclusion: No statistically significant difference in anxiety could be found between oral midazolam and zolpidem at time of surgery.
Impellizzeri, et al. ²⁰ SC DB RCT N=80	Midazolam syrup 0.5 mg/kg PO Melatonin solution 0.5 mg/kg PO	Children 8-14 y undergoing elective inpatient procedure	Anxiety, measured by the mYPAS) in preoperative room	Midazolam: 38.8 Melatonin: 36.3 Difference: NS Conclusion: No statistically significant difference in anxiety could be found between oral midazolam and melatonin at time of surgery.
Yu, et al. ²¹ SC DB PC PG RCT	Zolpidem 10 mg PO QHS + paroxetine 20 mg PO QAM	Adults with primary insomnia disorder	Change in PSG-defined SE (sleep time/time in bed × 100%), TST, SOL, and WASO	Zolpidem + paroxetine: SE = +18.3% (p<0.05 vs. control) SOL = -14.9 minutes (p=0.199 vs. control) WASO = -75.2 minutes (p<0.05 vs. control)

N=78	Zolpidem 10 mg PO QHS + placebo PO QAM		(baseline night and the night in week 8.	TST = +90.9 minutes (p<0.05 vs. control) Zolpidem + placebo: SE = +12.1% SOL = -14.2 minutes WASO = -44.7 minutes TST = +60.1 minutes Conclusion: zolpidem plus paroxetine improves sleep maintenance, but not sleep onset, compared to zolpidem alone in patients with primary insomnia.
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Abbreviations: DB = double blind; PO = orally; NS = not statistically significant; PC = placebo controlled; PG = parallel group; PSG = polysomnography; QAM = each morning; QHS = each bedtime; RCT = randomized controlled trial; SC = single-centered; SE = sleep efficiency; SOL = sleep onset latency; TST = total sleep time; WASO = week after sleep onset; y = years.

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Lemborexant, an orexin receptor antagonist similar to suvorexant, was approved by the FDA in December 2019 for the treatment of adults with insomnia, characterized by sleep onset or sleep maintenance.¹¹ The pharmacology and pharmacokinetic properties of lemborexant are summarized in **Table 9**.

Table 9. Pharmacology and Pharmacokinetic Properties of Lemborexant.¹¹

Parameter	
Mechanism of Action	Reversible competitive antagonist at orexin receptors 1 and 2 (greater affinity for orexin receptor 2). The orexin neuropeptide signaling system plays a role in wakefulness and blocking the orexin receptors is thought to suppress wake drive.
Oral Bioavailability	T _{max} = 1-3 hours High-fat, high calorie meal decreased C _{max} by 24%, AUC increased by 185 and Tmax was delayed by ~2 hours.
Distribution and Protein Binding	V _d = 1970 L Protein binding = 94% <i>in vitro</i>
Elimination	57.4% of the dose is recovered in the feces and 29.1% in the urine (<1% unchanged).
Half-Life	5 mg = 17 hours; 10 mg = 19 hours
Metabolism	Primarily metabolized by CYP3A4

Abbreviations: AUC = area under the curve; C_{max} = peak concentration; L = liters; T_{max} = time to peak concentration; V_d = volume of distribution.

Two Phase 3 clinical trials evaluated the efficacy and safety of lemborexant.^{12,13} Both studies were randomized, double-blind, parallel-group, placebo-controlled, studies sponsored by Eisai Inc.^{12,13} Study sites were primarily conducted in North America, Europe and Asia. Key participant inclusion and exclusion criteria for both studies were similar and are summarized in **Table 10**. Both trials required eligible participants to have a diagnosis of insomnia disorder based on *Diagnostic and Statistical Manual of Mental Disorders (5th Ed)* DSM-5 criteria; subjective wake-after-sleep onset (sWASO), defined as the estimated sum of time of wake during the night after initial sleep onset until the participant got out of bed for the day, for 60 minutes or longer at least 3 times per week; and a score 13 or higher,¹² or 15 or higher,¹³ on the ISI. After the initial screening periods in both trials, eligible patients received placebo for a 2-week run-in period to rule out placebo responders and to identify patients who did not adhere to sleep diary instructions. A summary of the populations studied in both trials can be found in **Table 10**.

The first trial was a 30-day study that evaluated lemborexant in older adults against placebo and zolpidem ER.¹² Older adults tend to have relatively more difficulty maintaining sleep, yet sedative hypnotics used in this population increase risk of adverse events, such as falls, hip fractures, and other injury.^{5,6} The investigators wanted to determine how lemborexant would compare with placebo and a long-acting BZRA. Efficacy outcomes included change from baseline in objective sleep onset and sleep maintenance at the beginning and end of treatment to 30 days, measured by PSG and averaged between days 1 and 2 and between days 29 and 30.¹² The primary efficacy endpoint was change in LPS as measured by PSG, defined as minutes from lights off to the first 10-minute consecutive period of nonwakefulness after 1 month of treatment.¹² Key secondary endpoints included sleep maintenance outcomes of sleep efficiency (proportion of time spent asleep per time in bed, calculated as TST/interval from lights off to lights on [standardized at 8 hours]), WASO, and WASO in the second half of the night (WASO2H; minutes awake from 240 minutes after lights off until lights on).¹² For primary endpoint comparison, LPS is known to be nonnormally distributed, so a log transformation was used in the LPS analysis, and statistical comparisons were made based on least squares geometric mean (LSGM) treatment ratios.¹²

At 30 days, the decrease from baseline in LPS as measured by PSG was larger and statistically significant for both lemborexant 5 mg and 10 mg doses compared to placebo and zolpidem ER (see **Table 10**).¹² These statistically significant differences were observed immediately on days 1 and 2, and throughout the 30-day treatment period. Key secondary endpoints, which objectively measured sleep maintenance outcomes by PSG, also resulted in statistically significant differences between lemborexant 5 mg and 10 mg compared to placebo and zolpidem ER (see **Table 10**).¹² Statistically significant differences for secondary endpoints were also observed immediately on days 1 and 2, and throughout the 30-day treatment period.¹²

The second trial was a 6-month placebo-controlled study with a 6-month extension in which all participants either continued lemborexant or were switched from placebo to lemborexant.¹³ Sleep onset and sleep maintenance endpoints were analyzed using data from electronic sleep diaries completed daily by each study participant.¹³ The primary efficacy endpoint was subjective sleep onset latency (sSOL), a sleep onset outcome.¹³ Key secondary endpoints evaluated sleep maintenance as measured by sWASO, subjective total sleep time (sTST), defined subjectively as the total time spent asleep during their time in bed, and subjective sleep efficiency (sSE), which was expressed as the proportion of sTST per subjective time in bed.¹³

At 6 months, the decrease from baseline in sSOL was larger and statistically significant (also assessed by the LSGM treatment ratio) for both lemborexant 5 mg and 10 mg doses compared to placebo (see **Table 10**).¹³ These differences were observed during the first week of treatment, and throughout the 6-month treatment period. Key secondary endpoints, which measured subjective sleep maintenance outcomes, also resulted in statistically significant differences between lemborexant 5 mg and 10 mg compared to placebo (see **Table 10**).¹³

Several limitations should be noted. Risk of bias and applicability assessments for both trials can be found in **Table 10**. In summary, both trials limited selection bias through the randomization process. Performance bias was also limited by blinding patients and all personnel involved with the conduct and interpretation of the studies. The 30-day trial¹² described a double-dummy design while the 6-month trial¹³ did not provide an adequate description of how blinding of treatment groups was assured. A true intention-to-treat analysis was also not performed which is important, especially when there is high attrition early in the study as observed in the 6-month trial.¹³ Rather, data analysis was limited to patients who had received at least one dose of study drug and had at least one post-dose primary efficacy measurement.^{12,13} Risk for attrition bias was high with the 6-month trial because of the overall high attrition (>20%) in all treatment arms.¹³ For the primary endpoint comparisons, it is also important to note that the clinical context of endpoints expressed as LSGMs can be difficult to interpret.^{12,13} In addition, both trials were funded by the drug sponsor (Eisai Inc.), who participated in the design and conduct of the studies; who were involved in data collection, data management, data analysis, and data interpretation; and who were involved in the preparation, review, and approval of the manuscript for publication.^{12,13}

Clinical Safety:

In the 6-month trial, drug exposure was similar across treatment groups, with 82.1%, 79.9%, and 73.9% of participants having at least 6 months of exposure for placebo, lemborexant 5 mg, and lemborexant 10 mg, respectively.¹³ A similar incidence of TEAEs was observed across both lemborexant doses and placebo treatment groups, with most of the TEAEs mild or moderate in severity.¹³ The most common TEAE was somnolence, which was reported in 1.6%, 8.6% and 13.1% of patients in the placebo, lemborexant 5 mg and lemborexant 10 mg treatment arms, respectively.¹³ The incidence of serious and severe TEAEs was low and similar across all treatment arms.¹³ More patients in the lemborexant 10 mg group (8.3%) discontinued the study early due to a TEAE compared with the 5 mg (4.1%) or placebo (3.8%) groups.¹³ The most common TEAE leading to study drug discontinuation was somnolence (placebo = 0.6%, lemborexant 5 mg = 1.0%, lemborexant 10 mg = 2.9%).¹³ The investigators could not find any correlation between baseline characteristics, including age, sex, race, ethnicity, region, and country, and participants who discontinued study treatment early due to somnolence.¹³

In the 30-day trial, the long-term safety of lemborexant therapy could not be evaluated.¹² The overall incidence of TEAEs was similar among treatment groups.¹² Six patients reported 8 serious adverse events (4 in zolpidem ER group; 2 in lemborexant 5 mg group) but none were deemed to be treatment-related.¹² Falls (with or without injury) were reported as a TEAE by 4 patients treated in the lemborexant 5 mg group.¹² Sleep paralysis was reported by 1 patient in the lemborexant 5 mg group and 3 patients in the lemborexant 10 mg group but were deemed mild in severity.¹²

In both trials, no deaths occurred, no complex sleep-related behaviors were reported, no evidence of suicidal ideation, suicidal behavior or self-injury was observed, and no clinically meaningful changes in clinical laboratory tests, vital signs, weight, or electrocardiograms were found.^{12,13} Overall mean values for these parameters were within normal range and dose-related trends were not observed.^{12,13} In addition, no evidence of withdrawal was found.^{12,13}

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Quality of life
- 2) Daytime Function
- 3) Sleep onset and maintenance
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoints:

- 1) Change in LPS (sleep onset outcome)
- 2) Change in subjective SOL (sleep onset outcome)

		<p>-AHI >15 episodes/hr as measured by PSG</p> <p>-PLMI >15 episodes/hr as measured by PSG</p> <p>-Depression (BDI-II score >19)</p> <p>-Anxiety (BAI score >15)</p> <p>-Habitually naps 3x/day</p> <p>-Female of child-bearing potential</p> <p>-H/o drug or alcohol dependency in past 2 y</p> <p>-Excessive caffeine use (subjective)</p> <p>-HIV, HepC, HepB</p> <p>-QTc >450 ms</p> <p>-Evidence of clinically significant disease (cardiac, respiratory, renal, psychiatric, malignancy, chronic pain, etc.)</p> <p>-Comorbid nocturia</p> <p>-Any concomitant tx for insomnia, including sedative, OTC drug, marijuana, or CBT</p>		<p>LSMD vs. ZOL:</p> <p>1. 3.9% (95% CI, 2.5 to 5.3) p<0.001</p> <p>2. 4.9% (95% CI, 3.5 to 6.3) p<0.001</p> <p>Δ Minutes of Wake from LPS until Lights On (WASO) from Baseline to Nights 29, 30:</p> <p>1. -43.9 min (SD 39.3)</p> <p>2. -46.4 min (SD 39.6)</p> <p>3. -36.5 min (SD 43.4)</p> <p>4. -18.6 min (SD 41.9)</p> <p>LSMD vs. PBO:</p> <p>1. -24.0 min (95% CI, -30.0 to -18.0) p<0.001</p> <p>2. -25.4 min (95% CI, -31.4 to -19.3) p<0.001</p> <p>3. -16.3 min (95% CI, -22.3 to -10.2) p<0.001</p> <p>LSMD vs. ZOL:</p> <p>1. -7.7 min (95% CI, -13.4 to -2.1) p=0.007</p> <p>2. -9.1 min (95% CI, -14.8 to -3.5) p=0.002</p>	<p>NA</p> <p>NA</p> <p>NA</p> <p>NA</p> <p>NA</p> <p>NA</p>	<p>4.0</p>		<p>Other Bias: (high) Study funded by Eisai Inc. Data analyzed by statisticians employed by Eisai Inc.</p> <p>Applicability:</p> <p>Patient: Study limited to patients at least 55 years of age. Patients with comorbid conditions were excluded. Patients receiving first-line CBT excluded. Mostly white females studied; inclusion criteria confirmed by sleep history, sleep diary and PSG (WASO mean ≥60 min on 2 consecutive PSGs, with neither night <45 min).</p> <p>Intervention: New drug studied to establish efficacy and short-term safety for FDA approval. Patients allocated to the 5 mg arm were not permitted to titrate to 10 mg if the 5 mg dose was ineffective, which conflicts with current prescribing information.¹¹</p> <p>Comparator: PBO used to establish efficacy; ZOL ER provides an active comparison, though suvorexant would have provided comparison against the only other Orexin Receptor Antagonist.</p> <p>Outcomes: Primary endpoint assessed sleep initiation and secondary endpoints assessed sleep maintenance.</p> <p>Setting: 67 outpatient sites in Europe and North America.</p>
<p>NCT02952820^{13,22}</p> <p>MC, DB, PG, PC, RCT</p> <p>Eisai Inc.</p>	<p>1. LEM 5 mg PO QHS</p> <p>2. LEM 10 mg PO QHS</p> <p>3. PBO PO QHS</p> <p>1:1:1</p> <p>Duration: 6 months; additional 6-month DL extension for LEM (at same</p>	<p>Demographics:</p> <p>Mean age: 54.5 y</p> <p>Age <65 y: 72.4%</p> <p>Female: 68.2%</p> <p>White: 71.5%</p> <p>Black: 8.0%</p> <p>Japanese: 17.0%</p> <p>Mean BMI: 27.3</p> <p>Mean ISI: 19.2</p> <p>Key Inclusion Criteria:</p> <p>-Age ≥18 y</p> <p>-DSM-5 criteria for insomnia disorder*</p> <p>-Confirmation of insomnia sxS from</p>	<p>ITT:</p> <p>1. 323</p> <p>2. 323</p> <p>3. 325</p> <p>PP:</p> <p>1. 254</p> <p>2. 235</p> <p>3. 261</p> <p>Attrition:</p> <p>1. 20.4%</p> <p>2. 26.3%</p> <p>3. 18.7%</p>	<p>Primary Endpoint:</p> <p>Δ sSOL from baseline to 6 months:</p> <p>1. -21.81 min</p> <p>2. -28.21 min</p> <p>3. -11.43 min</p> <p>LSGM Tx Ratio vs. PBO:</p> <p>1. 0.732 (95% CI, 0.636 to 0.843; p<0.0001)</p> <p>2. 0.701 (95% CI, 0.607 to 0.810; p<0.0001)</p> <p>Key Secondary Endpoints:</p> <p>Δ sSE from baseline to 6 months:</p>	<p>NA</p> <p>NA</p>	<p>Early Discontinuation from TEAE:</p> <p>1. 4.1%</p> <p>2. 8.3%</p> <p>3. 3.8%</p> <p>TEAE:</p> <p>1. 61.1%</p> <p>2. 59.6%</p> <p>3. 62.7%</p> <p>Severe TEAE:</p> <p>1. 4.1%</p> <p>2. 2.5%</p> <p>3. 1.6%</p>	<p>NA</p>	<p>Risk of Bias (low/high/unclear):</p> <p>Selection Bias: (low) randomization based on interactive computer-generated algorithm; stratified by age (≥64 y vs. younger)</p> <p>Performance Bias: (unclear) all personnel involved with the conduct and interpretation of the study, including investigators, site personnel and sponsor staff, were blinded to treatment allocation; however, method of blinding not described.</p> <p>Detection Bias: (high) data analyzed by mITT (participants were randomized and received ≥1 dose and had at least one post-dose primary efficacy measurement) with high early attrition in all arms.</p>

LEM dose, PBO randomized to 5 or 10 mg)	Sleep Diary which showed h/o sSOL ≥30 min or sWASO ≥60 min for ≥3 nights of past 7 nights -ISI score ≥15 -Reports 7-9 h spent in bed sleeping or trying to sleep -Reports habitual bedtime and waketime		<p>1. LSM 14.19% 2. LSM 14.31% 3. LSM 9.64%</p> <p>LSMD vs. PBO: 1. 4.55 (95% CI NR; p=0.0001) 2. 4.67 (95% CI NR; p<0.0001)</p> <p>Δ sWASO from baseline to 6 months: 1. LSM -46.75 min 2. LSM -41.95 min 3. LSM -29.28 min</p> <p>LSMD vs. PBO: 1. -17.47 min (95% CI NR; p=0.0005) 2. -12.67 min (95% CI NR; p<0.0105)</p> <p>Δ sTST from baseline to 6 months: 1. LSM 69.95 min 2. LSM 74.08 min 3. LSM 51.40 min</p> <p>LSMD vs. PBO: 1. 18.56 min (95% CI NR; p=0.0034) 2. 22.69 min (95% CI NR; p<0.0004)</p>	NA NA NA NA NA	<p><u>Somnolence</u></p> <p>1. 8.6% 2. 13.1% 3. 1.6%</p> <p><u>Headache:</u></p> <p>1. 8.9% 2. 6.7% 3. 6.6%</p> <p><u>Arthralgia:</u></p> <p>1. 4.5% 2. 1.0% 3. 2.8%</p>	<p><u>Attrition Bias:</u> (high) attrition rate >20% for both LEM arms with higher than PBO. <u>Reporting Bias:</u> See NCT02783729 above. <u>Other Bias:</u> See NCT02783729 above.</p> <p>Applicability: <u>Patient:</u> strictly defined exclusion criteria including sleep disorders other than insomnia limited study enrollment at screening, limit real-life applicability. <u>Intervention:</u> New drug studied to establish efficacy and safety for FDA approval. <u>Comparator:</u> PBO used to establish efficacy. <u>Outcomes:</u> assessed sleep onset and sleep maintenance subjectively by diaries completed by each participant. <u>Setting:</u> 119 sites in North America (n=45), Europe (n=34), Asia (n=35), and Oceania (n=5).</p>
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Abbreviations: AHI = Apnea-Hypoapnea Index; ARR = absolute risk reduction; avg = average; BAI = Beck Anxiety Index; BDI-II = Beck Depression Inventory; BMI = body mass index; CBT = cognitive behavioral therapy; CI = confidence interval; CPAP = continuous positive airway pressure; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders* (5th Edition); ER = extended release; FDA = Food and Drug Administration; LEM = lemborexant; h = hours; h/o = history of; HepB = active viral hepatitis B; HepC = active viral hepatitis C; h/o = history of; hr = hours; ISI = Insomnia Severity Index; ITT = intention to treat; LPS = latency to persistent sleep; defined as minutes from lights off to the first epoch of 20 consecutive 30-second epochs of nonwakefulness); LSGM = least squares geometric mean; LSMD = least square mean difference; min = minutes; mITT = modified intention to treat; ms = milliseconds; MUPS = Munich Parasomnia Scale; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OTC = over-the-counter; PBO = placebo; PLMI = Periodic Limb Movements Index; PP = per protocol; PSG = polysomnography; RLS = Restless Leg

Syndrome; SEA = serious adverse event; sSE = subjective sleep efficiency (the proportion of sTST per subjective time in bed); sSOL = subjective sleep onset latency (estimated time from attempt to sleep until sleep onset); sTST = subjective total sleep time (time spent asleep during their time in bed); sWASO = subjective wake-after-sleep onset (estimated sum of time of wake during the night after initial sleep onset until participant got out of bed for the day); sx = symptoms; TEAE = treatment emergent adverse event; tx = treatment; WASO = wake-after-sleep onset assessed by PSG; y = years; ZOL = zolpidem.

*Insomnia Criteria per DSM-5: 1) complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep; 2) frequency of complaint ≥ 3 times per week; 3) duration of complaint ≥ 3 months; and 4) associated with complaint of daytime impairment.

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Appendix 1: Current Preferred Drug List

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>PDL</u>
zolpidem tartrate	AMBIEN	TABLET	Y
zolpidem tartrate	ZOLPIDEM TARTRATE	TABLET	Y
diphenhydramine HCl	SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP TIME	CAPSULE	N
diphenhydramine HCl	Z-SLEEP	CAPSULE	N
diphenhydramine HCl	SLEEP AID	LIQUID	N
diphenhydramine HCl	SLEEP TIME	LIQUID	N
diphenhydramine HCl	Z-SLEEP	LIQUID	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP TABS	TABLET	N
doxepin HCl	DOXEPIN HCL	TABLET	N
doxepin HCl	SILENOR	TABLET	N
doxylamine succinate	SLEEP AID	TABLET	N
estazolam	ESTAZOLAM	TABLET	N
eszopiclone	ESZOPICLONE	TABLET	N
eszopiclone	LUNESTA	TABLET	N
flurazepam HCl	FLURAZEPAM HCL	CAPSULE	N
midazolam HCl	MIDAZOLAM HCL	SYRUP	N
ramelteon	RAMELTEON	TABLET	N
ramelteon	ROZEREM	TABLET	N
suvorexant	BELSOMRA	TABLET	N
tasimelteon	HETLIOZ	CAPSULE	N
temazepam	RESTORIL	CAPSULE	N
temazepam	TEMAZEPAM	CAPSULE	N
triazolam	HALCION	TABLET	N
triazolam	TRIAZOLAM	TABLET	N
zaleplon	ZALEPLON	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	INTERMEZZO	TAB SUBL	N
zolpidem tartrate	ZOLPIDEM TARTRATE	TAB SUBL	N

Appendix 2: Abstracts of Comparative Clinical Trials

Hanna AH, Ramsingh D, Sullivan-Lewis W, et al. A comparison of midazolam and zolpidem as oral premedication in children, a prospective randomized double-blinded clinical trial.

Background: Anxiety associated with pediatric surgery can be stressful. Midazolam is a well-accepted anxiolytic in this setting. However, there are cases in which this medication is not effective. Zolpidem is a short-acting nonbenzodiazepine hypnotic drug that is administered orally and has quick onset of action (~15 minutes), and 2-3 hour duration.

Aims: Based on the theory that impaired perception following oral zolpidem administration would suppress the development of anxiety, we sought to compare zolpidem to midazolam for pediatric preoperative anxiety.

Methods: This prospective randomized double-blinded clinical trial was designed to compare the effectiveness of oral midazolam and zolpidem for anxiety premedication. Eighty ASA class I-II pediatric patients between 2 and 9 years old, surgery >2 hours, and at least 23 hours postoperative admission were included in the study. Randomization was done with 0.5 mg/kg midazolam or 0.25 mg/kg zolpidem administered orally. The primary outcome measure was between group difference in patient anxiety at the time of separation using the Modified Yale Preoperative Anxiety Scale. Secondary outcomes included emergence delirium and mask acceptance at induction.

Results: There was no significant difference in Modified Yale Preoperative Anxiety Scale scores at separation between midazolam (median/interquartile range = 26.7/ 23.3-36.6) and zolpidem (median/interquartile range = 30.0/23.3-56.6) groups, difference 0.01 (95% CI, $-3E^{-2}$ to $3E^{-2}$; $p=0.07$). Mask acceptance score was significantly better in the midazolam group. There was no significant difference in emergence delirium scores between groups.

Conclusion: This study demonstrates that zolpidem, as dosed, was similar to midazolam with regard to anxiety scoring, and inferior with regard to mask acceptance scores.

Impellizzeri P, Vinci E, Gugliandolo MC, et al. Premedication with melatonin vs midazolam: efficacy on anxiety and compliance in paediatric surgical patients.

Preoperative anxiety is a major problem in pediatric surgical patients. Melatonin has been used as a premedicant agent and data regarding effectiveness are controversial. The primary outcome of this randomized clinical trial was to evaluate the effectiveness of oral melatonin premedication, in comparison to midazolam, in reducing preoperative anxiety in children undergoing elective surgery. As secondary outcome, compliance to intravenous induction anesthesia was assessed. There were 80 children undergoing surgery randomly assigned, 40 per group, to receive oral midazolam (0.5 mg/kg, max 20 mg) or oral melatonin (0.5 mg/kg, max 20 mg). Trait anxiety of children and their mothers (State-Trait Anxiety Inventory) at admission, preoperative anxiety and during anesthesia induction (Modified Yale Pre-operative Anxiety Scale), and children's compliance with anesthesia induction (Induction Compliance Checklist) were all assessed. Children premedicated with melatonin and midazolam did not show significant differences in preoperative anxiety levels, either in the preoperative room or during anesthesia induction. Moreover, compliance during anesthesia induction was similar in both groups. Conclusions: This study adds new encouraging data, further supporting the potential use of melatonin premedication in reducing anxiety and improving compliance to induction of anesthesia in children undergoing surgery. Nevertheless, further larger controlled clinical trials are needed to confirm the real effectiveness of melatonin as a premedicant agent in pediatric population.

Yu ZH, Xu XH, Wang SD, et al. Effect and safety of paroxetine combined with zolpidem in treatment of primary insomnia.

Purpose: Primary insomnia is a persistent and recurrent disorder as well as a risk factor for depression. The aim of this study was to determine whether the zolpidem combined with paroxetine would be effective in the treatment of patients with primary insomnia.

Methods: Ninety patients meeting DSM-IV criteria for primary insomnia were randomly assigned to 8 weeks of treatment with zolpidem combined with paroxetine (the combined treatment group, $n = 45$) or zolpidem combined with placebo (the control group, $n = 45$). Patients were assessed with the Pittsburgh

Author: Gibler

December 2020

Sleep Quality Index (PSQI), polysomnography (PSG), and the Treatment Emergent Symptom Scale (TESS). Results Compared with the control group, the combined treatment group was more significantly improved on wake time after sleep onset (WASO), total sleep time (TST), sleep efficiency (SE), and total PSQI scores, but not the sleep onset latency (SOL).

Conclusions: Eight weeks of the zolpidem combined with paroxetine treatment to patients with primary insomnia is more effective than zolpidem treatment only in sleep maintenance and early morning awakenings.

Appendix 3: Medline Search Strategy

Ovid MEDLINE, ALL: 1946 to April 23, 2020

1 exp Zolpidem/ 1589

2 exp Diphenhydramine/ 4382

3 exp Doxepin/ 822

4 exp Doxylamine/ 381

5 exp Estazolam/ 105

6 exp Eszopiclone/ 116

7 exp Flurazepam/ 780

8 exp Midazolam/ 8770

9 ramelteon.mp. 395

10 suvorexant.mp. 235

11 tasimelteon.mp. 75

12 exp Temazepam/ 668

13 exp Triazolam/ 1233

14 zaleplon.mp. 398

15 exp "Sleep Initiation and Maintenance Disorders"/ 13026

16 exp "Hypnotics and Sedatives"/ 122457

17 exp Sleep Wake Disorders/ 88013

18 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 19149

19 15 or 16 or 17 206256

20 limit 19 to (english language and yr="2017 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))

3063

21 18 and 19 and 20 290

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DAYVIGO safely and effectively. See full prescribing information for DAYVIGO.

DAYVIGO™ (lemborexant) tablets, for oral use, [controlled substance schedule pending]

Initial U.S. Approval: [pending controlled substance scheduling]

INDICATIONS AND USAGE

DAYVIGO is an orexin receptor antagonist indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. (1)

DOSAGE AND ADMINISTRATION

- Recommended dose is 5 mg taken no more than once per night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening. Dosage may be increased to 10 mg based on clinical response and tolerability. (2.1)
- The maximum recommended dose is 10 mg once daily. (2.1)
- Time to sleep onset may be delayed if taken with or soon after a meal. (2.1)
- Hepatic Impairment: (2.3)
 - Moderate hepatic impairment: Initial and maximum recommended dosage is 5 mg no more than once per night.
 - Severe hepatic impairment: Not recommended.

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg (3)

CONTRAINDICATIONS

DAYVIGO is contraindicated in patients with narcolepsy. (4)

WARNINGS AND PRECAUTIONS

- CNS Depressant Effects and Daytime Impairment: Impairs alertness and motor coordination including morning impairment. Risk increases with dose and use with other central nervous system (CNS) depressants. For patients taking DAYVIGO 10 mg, caution against next-day driving and other activities requiring complete mental alertness. (5.1)

- Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms: May occur with use of DAYVIGO. (5.2)
- Complex Sleep Behaviors: Behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur. Discontinue immediately if a complex sleep behavior occurs. (5.3)
- Compromised Respiratory Function: Effect on respiratory function should be considered. (5.4, 8.8)
- Worsening of Depression/Suicidal Ideation: Worsening of depression or suicidal thinking may occur. Prescribe the lowest number of tablets feasible to avoid intentional overdose. (5.5)
- Need to Evaluate for Co-morbid Diagnoses: Reevaluate if insomnia persists after 7 to 10 days of treatment. (5.6)

ADVERSE REACTIONS

The most common adverse reaction (reported in $\geq 5\%$ of patients treated with DAYVIGO and at least twice the rate of placebo) was somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong or moderate CYP3A inhibitors: Avoid concomitant use. (7.1)
- Weak CYP3A inhibitors: The maximum recommended dose is 5 mg. (2.2, 7.1)
- Strong or moderate CYP3A inducers: Avoid concomitant use. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2019

Appendix 5: Key Inclusion Criteria

Population	Patients diagnosed with primary chronic insomnia
Intervention	Diphenhydramine Doxepin Doxylamine Estazolam Eszopiclone Flurazepam Midazolam Ramelteon Suvorexant Tasimelteon Temazepam Triazolam Zaleplon Zolpidem [melatonin, tiagabine, trazodone]
Comparator	Active Intervention Above Placebo
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	At least 4 weeks
Setting	Outpatient

Appendix 6: Prior Authorization Criteria

Sedatives

Goals:

- Restrict use of sedatives to OHP-funded conditions. Treatment of uncomplicated insomnia is not funded; insomnia contributing to covered co-morbid conditions is funded.
- Prevent concomitant use of sedatives, including concomitant use with benzodiazepines or opioids.
- Limit daily zolpidem dose to the maximum recommended daily dose by the FDA.
- Permit use of melatonin in children and adolescents 18 years of age or younger.

Length of Authorization:

- Up to 12 months or lifetime (criteria-specific)

Requires PA:

- All sedatives except melatonin in children and adolescents 18 years of age or younger.

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/

Zolpidem Daily Quantity Limits

Generic	Brand	Max Daily Dose
Zolpidem	Ambien	10 mg
Zolpidem ER	Ambien CR	12.5 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for zolpidem at a higher dose than listed in the quantity limit chart?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #3

Approval Criteria		
<p>3. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product?</p> <p>Message: Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.</p>	Yes: Inform prescriber of preferred alternatives in class.	No: Go to #4
<p>4. 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?</p>	Yes: Approve for lifetime.	No: Go to #5
<p>5. Has the patient been treated with another non-benzodiazepine sedative, benzodiazepine, or opioid within the past 30 days?</p>	Yes: Go to #6	No: Go to #7
<p>6. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?</p>	Yes: Document reason for switch and approve duplication for 30 days.	No: Pass to RPh. Deny; medical appropriateness.
<p>7. Does the patient have a diagnosis of insomnia with obstructive sleep apnea?</p>	Yes: Go to #8	No: Go to #9
<p>8. Is patient on CPAP?</p>	Yes: Approve for up to 12 months.	No: Pass to RPh. Deny; medical appropriateness. Sedative/hypnotics are contraindicated due to depressant effect.

Approval Criteria

<p>9. Is the patient being treated for co-morbid:</p> <ul style="list-style-type: none"> • Depression; • Anxiety or panic disorder; or • Bipolar disorder? <p>AND Is there an existing claim history for treatment of the co-morbid condition (e.g., antidepressant, lithium, lamotrigine, antipsychotic, or other appropriate mental health drug)?</p>	<p>Yes: Approve for up to 12 months.</p>	<p>No: Pass to RPh; Go to #10</p>
<p>10. RPh only: Is diagnosis being treated a funded condition and is there medical evidence of benefit for the prescribed sedative?</p>	<p>Funded: Document supporting literature and approve up to 6 months with subsequent approvals dependent on follow-up and documented response.</p>	<p>Not Funded: Go to #11</p>
<p>11. RPh only: Is this a request for continuation therapy for a patient with a history of chronic benzodiazepine use where discontinuation would be difficult or unadvisable?</p>	<p>Yes: Document length of treatment and last follow-up date. Approve for up to 12 months.</p>	<p>No: Deny; medical appropriateness</p>

P&T/DUR Review:
Implementation:

12/20 (AG); 7/18 (JP); 3/17; 11/20/14, 3/27/14, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01
1/1/21; 8/15/18; 1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05