Utah Medicaid Pharmacy and Therapeutics Committee

Drug Class Review

Hypnotics
(Non-Benzodiazepines, Non-Barbiturates)

- Doxepin (Silenor)
- Eszopiclone (Lunesta and generics)
- Ramelteon (Rozerem)
- Suvorexant (Belsomra)
- Tasimelteon (Hetlioz)
- Zaleplon (Sonata and generics)
- Zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist, generics)

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Executive Summary

The non-benzodiazepine, non-barbiturate hypnotics (nBHs) approved for the treatment of insomnia in adults include the benzodiazepine receptor agonists, eszopiclone, zaleplon, and zolpidem (also referred to as the Z-drugs); the orexin antagonist, suvorexant; the melatonin receptor agonist, ramelteon; and the low-dose formulation of the H1-antihistamine antidepressant, doxepin. Indications of these agents differ according to the nature of insomnia (eg, difficulty with sleep initiation vs. sleep maintenance) and drug formulation (considering the various zolpidem formulations). Of these hypnotics, zolpidem is the only active ingredient available in multiple formulations: immediate-release (IR) tablets, sublingual tablets, and oral spray; a controlled-release tablet; and a low-dose sublingual formulation. Except for doxepin, nearly all hypnotics for insomnia are approved for sleep onset including eszopiclone, ramelteon, suvorexant, zaleplon, and the Ambien, Ambien controlled-release (CR), Edluar, and Zolpimist formulations of zolpidem. For sleep maintenance insomnia, low-dose doxepin, eszopiclone, suvorexant, and the Ambien CR formulation of zolpidem are approved. Intermezzo, the low-dose, IR, sublingual formulation of zolpidem is indicated for middle-of-night awakening with difficulty returning to sleep. The melatonin agonist, tasimelteon, is an orphan drug approved for the rare disorder, non-24 hour sleep wake disorder (N24SWD).

Zaleplon can be administered after the patient has tried falling asleep; whereas, other Z-drugs and suvorexant, approved for sleep onset insomnia, must be taken immediately before bedtime or within 30 minutes of going to bed and with at least 7 to 8 hours remaining before the planned time of awakening. Ramelteon should be taken within 30 minutes of going to bed. For zaleplon and ramelteon, product labeling does not specify a certain recommended duration from administration to the planned time of awakening. With a short duration of action, zaleplon has been used for middle-of-the night awakening with difficulty returning to sleep as long as 5 hours before planned awakening remains. The product specifically approved for middle-of-the night awakening is Intermezzo, a low-dose, sublingual zolpidem formulation. Intermezzo can be taken once per night as long as 4 hours of sleep remains following administration. While the CR formulation of zolpidem yields slightly higher plasma concentration-time profiles in the middle of the night compared to the IR formulation, it is unclear whether this pharmacokinetic adjustment translates into clinically significant effect differences with respect to sleep maintenance. The formulations of zolpidem branded Edluar (sublingual tablet) and Zolpimist (oral spray) are bioequivalent with Ambien in terms of Cmax (peak concentration) and AUC (area under the plasma-drug concentration curve).

Once the decision for initiation of pharmacotherapy has been made, prescribers must consider the characteristics of hypnotics (eg, duration of action, side-effect risks, efficacy per sleep parameter) while tailoring the choice of therapy to the nature of the patient’s insomnia complaint and patient-specific factors (eg, co-morbidities, prior response to sedatives, adverse-effects experienced, or abuse potential). Pharmacotherapy is used alone or in combination with cognitive behavioral therapy for insomnia (CBT-I). While CBT-I should be used in conjunction with pharmacotherapy whenever possible, the 2017 American Academy of Sleep Medicine (AASM) guideline advised that prescription pharmacotherapies should be made available regardless of participation in CBT-I. For sleep onset insomnia, AASM recommends eszopiclone, ramelteon, temazepam, triazolam, zaleplon, and zolpidem. Recommended options for sleep maintenance insomnia include doxepin, eszopiclone, temazepam, suvorexant, and zolpidem (based on trials of zolpidem IR 10 mg formulation). Despite the FDA approval
of suvorexant for sleep onset and/or sleep maintenance, the AASM guideline recommends this agent only for sleep maintenance since clinically significant improvement in sleep onset was demonstrated in RCTs with the highest dose (20 mg) but not with the lower dosages (5 mg, 10 mg, or 15 mg). While the labeling for the IR zolpidem formulations does not include approval for sleep maintenance, the AASM guideline recommends zolpidem as an option for sleep maintenance since RCTs support its efficacy (outcomes primarily based on zolpidem 10 mg studies). The 2019 Beers Criteria recommends that the Z-drugs be avoided in the elderly population.

Regarding the rare-disease indication for tasimelteon, N24SWD is a type of circadian rhythm sleep-wake disorder that occurs when there is mismatch of the sleep-wake cycle to the 24 hour/day cycle. This type of disorder is usually observed in blind individuals with loss of light perception. The 2015 AASM guideline for the treatment of N24SWD recommended use of melatonin for the treatment of N24SWD in blind adults versus no treatment, and did not provide a recommendation for or against the use of tasimelteon (approved in 2014) since there was not convincing evidence that tasimelteon was any better than melatonin.

Upon reviewing published literature, we found several systematic reviews (SRs) published in the last 4 years describing an absence of comparative randomized-controlled trial (RCT) evidence (nBH vs. nBH) for doxepin, eszopiclone, ramelteon, and suvorexant. There was limited evidence regarding zaleplon versus zolpidem from 2 RCTs with moderate risk of bias (reported by 2 SRs). Zaleplon 10 mg and zolpidem 10 mg reduced the time to sleep onset similarly. Meta-analyses showed no significant differences between zaleplon (5-20 mg) and zolpidem 10 mg for self-reported improvement in sleep quality, withdrawals related to adverse effects, or the number of participants with at least 1 adverse event.

Product labeling of these agents, with exception of tasimelteon for N24SWD, warns of the potential risk for abnormal thinking (eg, hallucinations), worsening of depression, behavioral changes, decreased inhibition, or other complex behaviors (eg, sleep-driving). Residual daytime somnolence may be modified by lowering the dose, ensuring the timing of administration with respect to hours left of sleep is in line with product labeling, or by choosing a medication with shorter half-life. Caution is advised when using hypnotics concurrently with other CNS-depressants due to the potential for additive CNS-depressive effects. Eszopiclone, suvorexant, zaleplon, and zolpidem are class 4 DEA-controlled substances with the potential to cause dependence and possible withdrawal upon abrupt discontinuation. Labeling for zaleplon states that tolerance to the sleep onset effect or withdrawal upon discontinuation were not evident in clinical studies. RCT evidence does not support a strong association with withdrawal or tolerance to any sleep parameter with eszopiclone therapy or with the non-controlled agents, doxepin, and ramelteon.

Table 7 of the report summarizes the most common adverse reactions. Meta-analyses reported eszopiclone significantly increased the risk of unpleasant taste, dry mouth, somnolence, and dizziness; zolpidem 10 mg significantly increased risk of amnesia, dizziness, and somnolence; and ramelteon and doxepin 6 mg increased the risk of next-day somnolence. The most common adverse reaction of suvorexant therapy (at 15 and 20 mg dosing) in clinical trials was somnolence, and was significantly more common compared to placebo; frequency of other adverse effects (AEs) were similar. There is recommendation against driving or engagement in other activities requiring complete mental alertness for patients taking the suvorexant 20 mg dosage. The medication has not been associated with rebound
insomnia or withdrawal upon discontinuation and was well tolerated with a discontinuation rate of less than 3% at 3 months in the phase 3 studies.\textsuperscript{11,12} The most common adverse effects reported in clinical trials with zaleplon were headache, abdominal pain, dyspepsia, nausea, ataxia, dizziness, incoordination, nervousness, and somnolence; but, occurred at a similar frequency as in the placebo group.\textsuperscript{13} Zaleplon caused minimal to no residual psychomotor impairment and is not associated with rebound insomnia.\textsuperscript{13} Common AEs of the low-dose zolpidem formulation, Intermezzo, include nausea, headache, and fatigue. Tasimelteon adverse reactions, with and incidence >5% and twice that of the placebo group, included headache, elevated alanine aminotransferase, nightmares or unusual dreams, and upper respiratory or urinary tract infection.\textsuperscript{14}

Overall, treatment decisions should be patient-guided with consideration of the pharmacodynamics and kinetics of the options available (eg, duration of action, side effect risks, efficacy per sleep parameter). Adverse effects can be mitigated by initiating therapy at lower doses, especially for more vulnerable populations. Upon observing the patient’s response to therapy, a switch to a shorter duration of action of agent or to a lower dosage may be considered if there is residual daytime somnolence. For the purpose of the Medicaid Preferred Drug List, the panel may wish to indicate that at least one nBH for sleep onset and sleep maintenance be listed as preferred. Considering the Beer’s criteria, a non-Z-drug for sleep maintenance may be specified for patients ≥65 years and older.
Introduction

The non-benzodiazepine, non-barbiturate hypnotic (nBH) group includes medications from various pharmacological classes. The Z-drugs, eszopiclone, zaleplon, and zolpidem, are benzodiazepine receptor agonists. Suvorexant antagonizes orexin receptors. These agents are Drug Enforcement Administration (DEA) schedule IV controlled substances (CIV) with potential for abuse. Patient prescription-fill patterns for these substances may be reviewed by prescribers on the Utah Controlled Substance Database (CSD). Non-controlled nBHs include ramelteon, a melatonin receptor agonist, and low-dose doxepin, an H1-antihistamine antidepressant. While these aforementioned agents are indicated for insomnia, their indications vary according to the insomnia problem (i.e., sleep initiation versus maintenance) and are specific to the drug formulation. Tasimelteon, a melatonin agonist, is only indicated for the rare sleep disorder, non-24 hour sleep wake disorder (N24SWD), which is a different type of sleep disorder than insomnia. N24SWD is common among the blind, as circadian rhythm dis-synchronization occurs due to the loss of light perception. Table 1 summarizes the FDA-approved indications for the nBH medications and Table 2 provides more detailed information about the available formulations, indications, and dosing. The safety and effectiveness of these agents have not been established in the pediatric population per product labeling.

Table 1. FDA-Indications According to Sleep Disorder

<table>
<thead>
<tr>
<th></th>
<th>Sleep Onset Insomnia</th>
<th>Sleep Maintenance Insomnia</th>
<th>Other</th>
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<tbody>
<tr>
<td>Doxepin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suvorexant</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tasimelteon</td>
<td></td>
<td></td>
<td>✓ Non-24 Hour Sleep Wake Disorder</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem</td>
<td>✓ for Ambien, Ambien CR, Edluar, Zolpimist</td>
<td>✓ for Ambien CR</td>
<td>Middle of night awakening with difficulty returning to sleep</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>✓ for Intermezzo</td>
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Abbreviations: CR, controlled release

Dosing for several of these agents is specified according to sex and age. For instance, a lower initiation dose of zolpidem is recommended for women since they generally eliminate zolpidem slower compared to men. Suvorexant carries a warning for potential increased exposure in women. Although there is not an explicit labeled recommendation for lowered dosing in women, there are several strengths of suvorexant available, allowing prescribers to initiate at a lower dose based on their clinical judgment. For the elderly, lower initial doses are recommend for doxepin, and reduced maximum doses are recommend for eszopiclone, zaleplon, and zolpidem.

The research objective of this report is to determine whether there are key efficacy or safety differences between the nBHs listed in Table 2, for their respective FDA-approved indications. The Utah Medicaid Preferred Drug List (PDL) groups these products under “Hypnotics: Non Benzodiazepine, Non Barbiturates.” The following are listed as preferred products: generic zaleplon capsules and zolpidem tablets. Non-preferred products include Ambien, Ambien CR and its generics, Belsomra, Edluar, Hetlloz, Intermezzo and its generics, Lunesta and its generics, Rozerem, Silenor, Sonata, and Zolpimist.
<table>
<thead>
<tr>
<th>Active Ingredient (Approval date)</th>
<th>Indications and Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doxepin</strong>&lt;br&gt;(2010)&lt;br&gt;Immediate-Release Oral Tablet&lt;br&gt;Silenor: 3 mg, 6 mg</td>
<td>Indicated for the treatment of insomnia with sleep maintenance difficulties (the clinical trials were up to 3 months in duration)&lt;br&gt;Dosing&lt;br&gt;• 6 mg in adults &lt; 65 years&lt;br&gt;• Initiate at 3 mg for adults ≥ 65 years of age and may be increased to 6 mg if clinically indicated&lt;br&gt;Administer 30 minutes before bedtime; to avoid next day effects, avoid within 3 hours of a meal since this increases drug exposure</td>
</tr>
<tr>
<td><strong>Eszopiclone</strong>&lt;br&gt;(2004)&lt;br&gt;Film-coated Oral Tablet (CIV)&lt;br&gt;Lunesta: 1 mg, 2 mg, 3 mg generic available</td>
<td>Indicated for the treatment of insomnia (decreased sleep latency and improved sleep maintenance in clinical trials up to 6 months in duration); failed to demonstrate effectiveness in clinical studies of children with ADHD-associated insomnia&lt;br&gt;Dosing&lt;br&gt;• Initiate at 1 mg per evening in adults; may be increased to 2 mg or 3 mg if clinically indicated and if there is no next-day impairment (do not exceed 3 mg per evening)&lt;br&gt;• In geriatric patients, disabled patients, patients with severe hepatic impairment, or who are taking potent CYP3A4 inhibitors, the dose should not exceed 2 mg per evening&lt;br&gt;Administer immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening; reduced efficacy on sleep latency would be expected if the drug is administered with a high-fat meal (induces slower absorption)</td>
</tr>
<tr>
<td><strong>Ramelteon</strong>&lt;br&gt;(2005)&lt;br&gt;Film-coated Oral Tablet&lt;br&gt;Rozerem: 8 mg</td>
<td>Indicated for the treatment of insomnia with sleep onset difficulty&lt;br&gt;Dosing&lt;br&gt;• Should not exceed 8 mg per evening&lt;br&gt;• Avoid in patients with severe hepatic impairment, and use with caution during moderate hepatic impairment. Do not use in combination with fluvoxamine and use caution with concomitant drugs that inhibit CYP1A2.&lt;br&gt;Administer within 30 minutes of going to bed; avoid taking with or after a high-fat meal (induces slower absorption, which could reduce onset, and increases drug exposure)</td>
</tr>
<tr>
<td>Active Ingredient (Approval date)</td>
<td>Indications and Dosing Information</td>
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</tbody>
</table>
| **Suvorexant** (2014) Oral Tablet (CIV) **Belsomra**: 5 mg, 10 mg, 15 mg, 20 mg | Indicated for the treatment of insomnia with sleep onset and/or sleep maintenance difficulty  
Dosing  
- Initiate at 10 mg per evening; may increase to 20 mg per evening if the lower dose was well-tolerated but not effective (max dose is 20 mg per evening)  
- Initiate at 5 mg per evening if patient if taking moderate CYP3A inhibitors; the dose should not be increased beyond 10 mg. Use of suvorexant is not recommended with strong CYP3A inhibitors.  
- Use caution in women and obese patients since drug exposure is increased in these subpopulations; the increased risk of exposure-related adverse effects should be considered before increasing the dose, especially in obese women  
Administer within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening; avoid taking with or after a high-fat meal (induces slower absorption, which could reduce onset, and increases drug exposure) |
| **Tasimelteon** (2014) Oral Capsule **Hetlioz**: 20 mg | Indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (orphan-drug designation); expect the onset of the drug’s effectiveness to take several weeks or months.  
Dosing  
- 20 mg per evening  
- Avoid use with fluvoxamine of other strong CYP1A2 inhibitors; avoid use with rifampin or other strong CYP3A4 inhibitors  
Administer before bedtime; avoid taking with food |
| **Zaleplon** (1999) Oral Capsule (CIV) **Sonata**: 5 mg, 10 mg generic available | Indicated for the short-term treatment insomnia; has been shown to decrease the time to sleep onset for up to 30 days in controlled trials.  
Dosing  
- 10 mg per evening for non-elderly adults; may titrate up to 20 mg per evening  
- Consider 5 mg for low-weight individuals  
- 5 mg per evening is the recommended dose for elderly patients; doses over 10 mg are not recommended  
Administer immediately before bedtime or after going to bed and not being able to fall asleep; avoid taking with high-fat food since this is expected to delay the absorption and reduce effect on sleep latency |
| **Zolpidem tartrate** (1999 Ambien; 2005 Ambien CR; 2008 Zolpimist; 2009 Edluar; 2011 Intermezzo) Oral Tablet (CIV) **Ambien**: 5 mg, 10 mg generic available | Ambien  
Indicated for the short-term treatment of insomnia with difficulties of sleep initiation (clinical trials lasted 4 to 5 weeks).  
Dosing  
- 5 mg for women (due to lower drug clearance) and 5 to 10 mg for men, per night  
- For elderly or patients with hepatic insufficiency, the recommended dose is 5 mg  
Administer immediately before bedtime with at least 7 to 8 hours remaining before planned time of awakening |
Table 2. FDA-Approved Hypnotics (Non-benzodiazepines, Non-barbiturates)\textsuperscript{5,7,11,14-21}

<table>
<thead>
<tr>
<th>Active Ingredient (Approval date)</th>
<th>Indications and Dosing Information</th>
</tr>
</thead>
</table>
| Zolpidem tartrate | Ambien CR  
Indicated for the treatment of insomnia with difficulties of sleep onset and/or sleep maintenance (clinical trials were up to 24 weeks duration).  
**Dosing**  
- Initiate at 6.25 mg in women (due to lower drug clearance), and either 6.25 mg or 12.5 mg in men per night; may titrate up to 12.5 mg if the lower dose is not effective  
- The recommended dose in elderly or patients with mild to moderate hepatic impairment is 6.25 mg. Avoid use in patients with severe hepatic impairment.  
Administer immediately before bedtime with at least 7 - 8 hours remaining prior to planned awakening. |
| Oral Extended-Release Tablet (CIV) Ambien CR: 6.25 mg, 12.5 mg generic available | |
| Sublingual Tablet (CIV) Edluar: 5 mg, 10 mg Intermezzo: 1.75 mg, 3.5 mg generic available for Intermezzo | |
| Oral Solution, Spray (CIV) Zolpimist: 5 mg/ spray; supplied as either 30 actuations/4.4 mL or 60 actuations/7.7 mL | |

**Edluar**  
Indicated for the short-term treatment of insomnia with difficulties of sleep initiation (clinical trials lasted 4 to 5 weeks).  
**Dosing**  
- 5 mg for women (due to lower drug clearance) and 5 to 10 mg for men, per night  
- For elderly or patients with hepatic insufficiency, the recommended dose is 5 mg  
Administer immediately before bedtime with at least 7 to 8 hours remaining before planned time of awakening  

**Intermezzo**  
Indicated for use as needed for insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep and when there is at least 4 hours of bedtime remaining before the planned time of awakening.  
**Dosing**  
- Recommended maximum doses are 1.75 mg for women, geriatric patients, and for patients with hepatic impairment, up to once per night as needed  
- Up to 3.5 mg for men, up to once per night as needed  
Place under tongue and allow to disintegrate completely, do not swallow whole  

**Zolpimist**  
Indicated for the short-term treatment of insomnia with sleep initiation difficulty. Controlled trials up to 35 days showed effectiveness at reducing sleep latency.  
Use of Zolpimist use in the middle of the night is not recommended.  
**Dosing**  
- 5 mg for women, and 5 mg or 10 mg for men at bedtime; if the 5 mg dose is not effective, the dose can be titrated up to 10 mg  
- For elderly or patients with hepatic insufficiency, the recommended dose is 5 mg  
Administer immediately before bedtime, with at least 7-8 hours remaining before the planned time of awakening; the effect may be slowed if taken with or immediately after a meal  

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CIV, schedule 4 controlled substance; CR, controlled release; CYP, cytochrome
Methods

Systematic Literature Search

Search strategies were developed for the systematic reviews (SRs) in Ovid-Medline, Embase, and Epistemonikos; databases were searched up to March 11th, April 4th, and April 15th of 2019, respectively. Strategies in Medline and Embase consisted of controlled vocabularies such as Medical Subject Headings (MeSH), Emtree terms, and keyword phrases. The complete search strategies are available in Appendix A. A combination of independently derived filters and a McMaster University filter22 were used to identify SRs in Ovid-Medline; an independently derived filter was used in Embase for SRs; and the imbedded publication type filter for SRs was used in Epistemonikos. In Embase, we excluded conference abstracts and limited to English language.

After finding the thorough 2015 US Agency for Healthcare Research and Quality (AHRQ) Systematic Review2 on insomnia disorder treatments in Medline, the SR search in Embase and Epistemonikos was narrowed from 2015 onward to capture more recent evidence. A search for randomized controlled trials (RCTs) was conducted for the years of 2015 onward using publication filters for RCTs located in the Cochrane Collaboration Handbook for SRs (for Ovid-Medline)23 and on their website (for Embase).24 We also screened the reference lists and other relevant websites for further information:

1. For treatment guidelines addressing insomnia management, we searched the website of the College of Psychiatric and Neurologic Pharmacists which provides a compilation of treatment guidelines for various mental health disorders: https://cpnp.org/guideline/external.

2. For professional prescribing information (ie, product labeling), we searched the drug sponsor’s website for each brand product, or websites such as Drugs@FDA and dailymed.nlm.nih.gov if there was no sponsor website available

Screening

Two reviewers independently screened publication titles and abstracts for inclusion. Conflicts were resolved by consensus between reviewers. The full text for all citations receiving 2 inclusion votes were retrieved. The lead author made the final determination for inclusion upon full-text review. Figure 1 on page 20 shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart for the literature screening process.

Inclusion and Exclusion Criteria

For the section of this report, Direct-Comparative Evidence, we included evidence based on randomized controlled trials (RCTs) comparing active arms of treatments listed in table 1, reporting efficacy or safety outcomes for the treatment of patients with insomnia at FDA-approved dosing, and published from 2015 onward (to update the 2015 AHRQ SR).2 Direct pair-wise meta-analysis statistical data was included, while mixed- or indirect-comparative statistical data (ie, network meta-analyses) was excluded. Since outpatient management of chronic insomnia or N24SWD is the focus of this report, we did not include evidence regarding critical or hospital care settings, jet lag, or outcomes on psychomotor vigilance during forced awakenings for high-functioning operational jobs (eg, astronauts).
Disease Overview

Insomnia

Insomnia is defined in the 3rd edition of the International Classification of Sleep Disorders (ICSD-3)\(^8\) which is a collaborative work from international sleep societies. Insomnia is “...a complaint of trouble initiating or maintaining sleep which is associated with daytime consequences and is not attributable to environmental circumstances or inadequate opportunity to sleep.”\(^8\) Chronic insomnia is persistence of symptoms, occurring at least 3 times a week for at least 3 months. Symptoms that do not meet this threshold are referred to as short-term insomnia. Factors leading to perpetuation of insomnia may include “…anxiety about sleep, maladaptive sleep habits and the possibility of an underlying vulnerability in sleep-regulating mechanisms,” or persistence of pain-inflicting disorders such as cancer or arthritis.\(^25\)

About 30% to 50% of the population is estimated to experience occasional short-term insomnia and between 5% and 10% of the population suffers from chronic insomnia.\(^8\) Chronic insomnia is associated with reduced functional status, productivity, and quality of life; and is a risk factor for the development of mood disorders and relapse of depression or alcoholism.\(^8\) Insomnia may be precipitated by, or co-morbid, with other psychiatric disorders such as anxiety, depression, and bipolar disorder.\(^26\) Some patients may complain about insomnia, as the easier topic to discuss with a provider, while not revealing fully other emotional distress.\(^26\) It is important to adequately assess patients for possible underlying disorders and treat such disorder(s), which may help improve the insomnia complaint. Nonetheless, treatment of an underlying disorder may not fully attenuate the patient’s insomnia.\(^26\) Insomnia is considered a discrete disorder (versus the obsolete classifications of primary and secondary insomnia) requiring medical attention regardless of the suspected underlying cause.\(^4\) The American College of Physician’s guideline describes that complaints of sleep maintenance problems are more common in older adults than sleep onset problems.\(^27\)

The aim of treatment is to improve important sleep parameters and ultimately lessen daytime insomnia-related impairments and psychological distress.\(^28\) Sleep parameters (ie, outcomes) that are considered clinically relevant when establishing the efficacy of medications in clinical trials include total sleep time (TST), sleep efficiency (defined as percentage of time spent in bed asleep/ time spent in bed), sleep onset latency (SOL), time to first awakening after sleep onset (WASO), number of awakenings, and quality of sleep (QOS). Outcomes may be reported by subjective self-reporting or by objective-reporting via polysomnography (ie, a sleep study that tracks stages of sleep by assessing brain waves and other measures).\(^8\) The American Academy of Sleep Medicine recommends maintaining and assessing sleep diaries prior to and during treatment.\(^28\)

Pharmacotherapy for Insomnia

Pharmacotherapy is used alone or in combination with cognitive behavioral therapy for insomnia.\(^8\) The decision for initiation of pharmacotherapy depends on many factors including a thorough evaluation of the patient’s sleep history, bed-time routine/environment, symptoms, medical and psychiatric history, and potential sleep-interfering medications, diet, or substance-use disorders.\(^8\) Factors that clinicians take into account when choosing a medication should include the duration of action, side effect risks,
efficacy per sleep parameter, and patient-specific factors (eg, prior response to sedatives, adverse-
effects experienced, or abuse potential).

Guidelines published within the last 3 years for the pharmacological treatment of chronic insomnia
include those by the American Academy of Sleep Medicine (AASM), the European Sleep Research
Society, and the American College of Physicians. The 2017 AASM guideline provides recommendations
regarding pharmacotherapy options according to individual drug agents. Since there are key
pharmacokinetic differences between products within the same class (ie, zaleplon vs. zolpidem), the
AASM approach seems most helpful to distinguish which specific medication should be used according
to insomnia problem. Authors, however, do not go as far to recommend one drug over another.8 The
choice of therapy depends on patient-specific factors. The pharmacokinetic profile of the drug should be
matched to the needs of the patient (ie, complaint regarding sleep onset latency vs. sleep maintenance).
While cognitive behavioral therapy for insomnia (CBT-I) should be used in conjunction with
pharmacotherapy whenever possible, AASM advised that prescription pharmacotherapies should be
made available regardless of participation in CBT-I. Over-the-counter herbal sleep aids or antihistamines
are not recommended due to inadequate supportive evidence and safety concerns.8

Recommended pharmacologic options in the 2017 AASM include benzodiazepines (eg, temazepam and
triazolam) and the non-benzodiazepine, non-barbiturate hypnotics, eszopiclone, zolpidem, zaleplon,
ramelteon, low-dose doxepin, and suvorexant; agents are specified according to the type of insomnia
problem.8 All “recommended options” are proposed with a weak strength of recommendation meaning
that “…available evidence is insufficient and fails to provide convincing support in favor for (or against)
this patient care strategy (hypnotic medication), or that the balance of benefits versus harms and
patient values and preferences are such that the use of the hypnotic agent cannot be confidently
recommended for use in all patients.”29 Authors note that while their recommendations for the use of
these agents are all graded as “weak”, “[t]his should not be construed to mean that no sleep promoting
medications are clearly efficacious or indicated in the treatment of chronic insomnia.”8 It is further
described that “[h]ypnotic medications, along with management of comorbidities and non-
pharmacological interventions such as CBT, are an important therapeutic option for chronic insomnia.”8
Since the strength of evidence is low, the choice of therapy is dependent on the prescriber’s clinical
judgment.

Trazodone is an antidepressant that is commonly use off-label for the treatment of insomnia. AASM
suggests that this medication should not be used for the majority of patients with sleep onset or
maintenance insomnia (weak recommendation).8 Although trazodone received a weak strength of
recommendation against use, authors explain in a separate document that this should not be
interpreted as that trazodone should never be used.29 Prescribers may wish to try this medication if the
patient has depression as a coexisting disorder or can apply this medication based on their clinical
judgment considering other patient-specific factors.25 There is some limited RCT evidence showing
improvements in sleep parameters such as sleep latency, wake after sleep onset (WASO), number of
nocturnal awakenings, and sleep quality with trazodone.3,8,25

Table 3 compares the recommended medications for chronic insomnia according the 2017 AASM
guide with the FDA-approved indication for the nBH agents. The FDA approval for suvorexant
includes use for sleep onset and/or sleep maintenance. Nonetheless, the AASM guideline recommends
this agent only for sleep maintenance since improvement in sleep latency was demonstrated in RCTs when using the highest dose (20 mg) but not with the lower dosages (5, 10, or 15 mg). While the labeling for the IR zolpidem formulations does not include approval for sleep maintenance, the AASM guideline recommends zolpidem as an option for sleep maintenance since RCTs support its efficacy (outcomes primarily based on zolpidem 10 mg studies).8

Table 3. Medication Benefit According to Insomnia Problem, FDA vs. AASM 5,7,8,11,14-21

<table>
<thead>
<tr>
<th>Sleep Onset Insomnia</th>
<th>Sleep Maintenance Insomnia</th>
<th>Midnight awakening with difficulty returning to sleep</th>
<th>Summary of drug effect (vs. placebo) reported in the 2017 AASM Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin</td>
<td>rAASM</td>
<td>FDAi</td>
<td>Total sleep time: mean increase by 26 to 32 min (95% CI: 18, 40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wake after sleep onset: mean reduction of 22 to 23 min (95% CI: 14, 30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of sleep: Small-to-moderate improvement</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>rAASM</td>
<td>FDAi</td>
<td>Sleep onset: mean reduction of 14 min (95% CI: 3, 24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total sleep time: mean increase by 28 to 57 min (95% CI 18 to 76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wake after sleep onset: mean reduction of 10 to 14 min (95% CI 2, 18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of sleep: moderate-to-large improvement</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>rAASM</td>
<td>FDAi</td>
<td>Sleep onset: mean reduction of 9 min (95% CI 6, 12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of sleep: no improvement vs placebo</td>
</tr>
<tr>
<td>Suvorexant</td>
<td>rAASM</td>
<td>FDAi</td>
<td>Total sleep time: mean increase by 10 min (95% CI 2, 19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDAi</td>
<td>Wake after sleep onset: mean reduction of 16 to 28 min (95% CI 7, 43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of sleep: not reportable</td>
</tr>
<tr>
<td>zaleplon</td>
<td>rAASM</td>
<td>FDAi</td>
<td>Sleep onset: mean reduction of 10 min (95% CI 0, 19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of sleep: no improvement vs placebo</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>rAASM</td>
<td>FDAi for Intermezzo only</td>
<td>Sleep onset: mean reduction of 5 to 12 min (95% CI 0, 19)</td>
</tr>
<tr>
<td>(based on trials of zolpidem 10 mg and CR 12.5 mg)</td>
<td></td>
<td></td>
<td>Total sleep time: mean increase of 29 min (95% CI 11, 47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDAi for Ambien, Ambien CR, Edluar, Zolpimist</td>
<td>Wake after sleep onset: mean reduction of 25 min (95% CI 18, 33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDAi for Ambien CR</td>
<td>Quality of sleep: moderate improvement</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, US Food and Drug Administration; FDAi, FDA-approved indication; AASM, American Academy of Sleep Medicine Guideline; rAASM, recommended active ingredient (versus no treatment) by the 2017 American Academy of Sleep Medicine Guideline
Due to the concern about the risk of tolerance and dependence, Cochrane review authors described that there have been recommendations against long-term insomnia medications, especially benzodiazepines beyond 2 to 4 weeks, by the 1983 consensus from a panel of the National Institute of Health (NIH), the 1988 consensus from the UK Committee on Safety of Medicines, the Royal College of Psychiatrists, and the 2004 National Institute for Clinical Excellence (NICE) guidance. However, Cochrane authors describe that “[t]his view was not based on data demonstrating an unfavourable transition in the risk-benefit ratio after two to four weeks of treatment, but appeared to have emerged because no substantive placebo-controlled trials of hypnotics had been carried out for longer than a few weeks.” Nonetheless, there remains a clinical need for chronic insomnia treatment as many patients have persistence of symptoms that aren’t cured after 2 to 4 weeks of treatment. Further, studies suggested that the use of certain drugs (zolpidem, eszopiclone, ramelteon) for up to six months and use of temazepam for up to 2 months was not strongly associated with tolerance and withdrawal; therefore, Cochrane review authors have commented that “…the available evidence does not suggest there is an unfavourable risk/benefit transition at three to four weeks for any agent.”
Table 4. Guidelines, Pharmacotherapy Options for Management of Insomnia

<table>
<thead>
<tr>
<th>Professional Organization</th>
<th>Excerpts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>American Academy of Sleep Medicine</strong></td>
<td>This guideline is aimed at describing the safe and effective options of specific insomnia medications once the decision has already been made to start pharmacotherapy; however, is not intended to recommend one drug over another.</td>
</tr>
</tbody>
</table>

All patients should receive cognitive behavioral therapy; however, this may not be available to some patients, may be ineffective or only partially effective to particular patients, or patients may be unable or unwilling to participate in such therapy. Thus, authors comment that pharmacotherapies must be made available to use alone or in combination with cognitive behavioral therapy.

**Pharmacotherapy Recommendations**

The two immediate bullet points below are classified as “Weak” for the strength of recommendation. “Weak” is explained as, “available evidence is insufficient and fails to provide convincing support in favor of (or against) this patient care strategy (hypnotic medication), or that the balance of benefits versus harms and patient values and preferences are such that the use of the hypnotic agent cannot be confidently recommended for use in all patients.”

- **Recommended agents for sleep maintenance insomnia vs. no treatment** (Weak strength)
  - Doxepin (low quality evidence; benefits outweigh harms)
  - Eszopiclone (very low quality evidence; benefits outweigh harms)
  - Suvorexant (low quality evidence; benefits outweigh harms)
  - Temazepam (moderate quality evidence; benefits outweigh harms)
  - Zolpidem (very low quality evidence; benefits outweigh harms)

- **Recommended drugs to sleep onset insomnia vs no treatment** (Weak strength)
  - Eszopiclone (very low quality evidence; benefits outweigh harms)
  - Ramelteon (very low quality evidence; benefits outweigh harms)
  - Triazolam (high quality evidence; benefits outweigh harms)
  - Temazepam (moderate quality evidence; benefits outweigh harms)
  - zaleplon (low quality evidence; benefits outweigh harms)
  - Zolpidem (very low quality evidence; benefits outweigh harms)

Other prescribed medications that the Academy suggests not to use include trazodone (graded as a weak recommendation). Nonetheless authors comment in a separate guideline-explanatory publication that “a “WEAK” recommendation against a hypnotic agent is not a recommendation that the hypnotic agent should never be used; it too requires clinicians to use their knowledge and experience and evaluate the needs of the individual patient.”

Comments pertaining to long-term treatment:

“Some studies have shown that long-term treatment with at least newer generation BzRA hypnotics can be safe and effective under properly controlled conditions. However, chronic use should be reserved for those individuals for whom CBT is either inaccessible or ineffective, who have been appropriately screened for contraindications to such treatment, who maintain long-term gains with medication, and who are followed regularly. Patient preference must also be considered in the determination of treatment approach.”
<table>
<thead>
<tr>
<th>Professional Organization</th>
<th>Excerpts</th>
</tr>
</thead>
</table>
| **European Sleep Research Society** | This guideline is aimed at therapy for chronic insomnia as diagnosed according to the ICSD-3.  
- CBT-I is first-line and if not effective or not available, the following pharmacotherapies may be considered.  
- Benzodiazepines and benzodiazepine receptor agonists are effective for short-term treatment of insomnia (≤ 4 weeks; high-quality evidence).  
  • Agents with shorter half-lives may result in less sedation in the morning (moderate-quality evidence).  
  • It is recommended for patients who use sedatives on a daily basis to reduce use to intermittent dosing (strong recommendation, low-quality evidence).  
- Sedating antidepressants are effective for short-term treatment of insomnia (moderate-quality evidence).  
- Ramelteon and suvorexant were not approved in Europe at the time of writing this guideline.  
- Long-term treatment of insomnia with BZ, BZRA, or sedating antidepressants is not generally recommended because of a lack of evidence and possible side-effects/risks (strong recommendation, low-quality evidence). Antipsychotics, and antihistaminics are not recommended for insomnia treatment due to insufficient evidence. Nonetheless, the authors acknowledged that “…long-term treatment of insomnia using hypnotics is clinically relevant because insomnia typically returns following withdrawal.” |

<p>| European guideline for the diagnosis and treatment of insomnia, 2017 | |</p>
<table>
<thead>
<tr>
<th>Professional Organization</th>
<th>Excerpts</th>
</tr>
</thead>
</table>
| American College of Physicians                               | • Cognitive behavioral therapy for insomnia (CBT-I) is recommended for all patients with chronic insomnia (strong recommendation based on moderate quality evidence)  

**Pharmacotherapy**  
“ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful. (Grade: weak recommendation, low-quality evidence)”  
  
  • “Medications should ideally be used for no longer than 4 to 5 wk, and the skills learned in CBT-I can manage insomnia over the longer term.”  
  
  • “If, after a trial of CBT-I, a shared decision is made to continue medications for longer than 4 to 5 wk, clinicians should revisit the need for medication continuation at periodic intervals.”  
  
  • Authors conclude that there is not enough evidence to determine how drugs compare to one another in terms of efficacy or safety. Thus, there is no specific recommendations made for any particular agent or regarding the benefits versus harms of a particular therapy.  
  
  • Compared to placebo, authors describe drug efficacy in the general population as follows:  
    - Eszopiclone improved remission (low-quality evidence), and sleep onset latency, total sleep time, and wake after sleep onset (low- to moderate-quality evidence)  
    - Zolpidem improved sleep onset latency and total sleep time in the general population (Moderate quality evidence)  
    - Zolpidem taken “as needed” improved Clinical Global Impression scores (low-quality evidence), and sleep onset latency and total sleep time (moderate-quality evidence)  
    - Zolpidem extended-release improved Clinical Global Impression scores, sleep onset latency, total sleep time, and wake after sleep onset in the general population (low-quality evidence)  
    - Sublingual zolpidem reduced sleep onset latency after middle-of-the-night waking (low-quality evidence)  
    - Suvorexant increased treatment response and improved sleep onset (Moderate-quality evidence)  

Abbreviations: ICSD-3, International Classification of Sleep Disorders 3rd Edition of the American Academy of Sleep Medicine  

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While the table above outlines general guidelines for the management of insomnia, it’s important to note that individual patient needs and circumstances should be considered when formulating a treatment plan. This includes considering the patient’s overall health, potential side effects, and preferences. It is recommended that patients, particularly those with chronic insomnia, work closely with their healthcare provider to determine the most effective and safe treatment options for their specific condition.
Non-24 Hour Sleep-Wake-Disorder

Non-24 hour sleep wake disorder falls under Circadian Rhythm Sleep-Wake Disorders (CRSWD) of the ICSD-3. Non-24 hour sleep-wake disorder (N24SWD) occurs when there is mismatch of the sleep-wake cycle to the 24-hour cyclical day pattern, usually due to an inability to perceive light which influences wakefulness. For the diagnosis of a sleep-wake disorder, there must also be evidence of sleep-wake disturbance (ie, insomnia or excessive sleepiness) that is associated with considerable distress or impairment. The diagnosis of N24SWD requires a history of at least 14 days of progressively shifting sleep-wake times documented per sleep diary and/or actigraphy. Loss of light perception may be a congenital or trauma-induced disability, and may occur gradually during progression of diseases such as glaucoma, retinitis pigmentosa, or diabetic retinopathy. AASM notes N24SWD can occur in both sighted and blind individuals, with a least 50% of the fully blind experiencing this disorder.

In 2015, AASM published a guideline for the treatment of N24SWD. At that time, tasimelteon was approved, but the committee recommended that clinicians use “…strategically timed melatonin for the treatment of N24SWD in blind adults (versus no treatment).” Authors explained that while tasimelteon demonstrated safety and efficacy in blind patients with N24SWD (entrainment occurring in 20% of the treatment group versus 3% with placebo), the rate was considerably lower than the historical rate of 67% reported in a previous meta-analysis assessing melatonin versus placebo. This is an indirect comparison that did not account for differences in treatment settings, placebo performance, or populations, which diminishes the robustness of the conclusions. Additionally, the historical meta-analysis described was not cited by authors. Nonetheless, the authors do highlight the uncertainty in this indirect comparison approach, commenting that the apparent difference in efficacy between melatonin and tasimelteon may have been “…a product of the short duration of treatment with Tasimelteon prior to the assessment of entrainment…”, and “[c]onsistent with this hypothesis, higher rates of entrainment were [eventually] found during longer, open-label treatment with tasimelteon.” No recommendations were provided with regard to tasimelteon, other than that head-to-head comparison trials with melatonin were needed.

Pharmacology

The Z-drugs, zolpidem, and zaleplon, allosterically modulate GABA-A receptors, with preference for the alpha-1 subunit, thought to be responsible for sedation effects, compared to alpha 2 and 3 thought to be responsible for anxiolytic and antidepressant effects. By allosterically modulating GABA receptors, chloride channels open more frequently and inhibit neuronal excitation of the central nervous system. Eszopiclone non-specifically binds to GABA-A subtypes, but is thought to have greater affinity for alpha 1 and 2 subunits than benzodiazepines. Affinity for alpha 1, 2 and 3 may suggest “…that eszopiclone has both hypnotic and anxiolytic effects.” Peak plasma concentrations are obtained approximately 1 hour after taking eszopiclone, zaleplon, and zolpidem oral spray; between 1 to 2 hours with zolpidem immediate release (IR), controlled release (CR), and Edluar sublingual (SL) tablets; and between 35 to 75 minutes for the zolpidem Intermezzo SL tablet. A high-fat meal delays absorption of these agents, reducing effectiveness for sleep onset latency.
Zaleplon has a rapid onset and short duration, making useful for sleep latency problems. Rather than taking the medication prophylactically, with its short onset, it can be administered after the patient has tried falling asleep but whom experiences difficulties. Authors have also suggested that zaleplon can be used for middle-of-the-night awakening as long as 5 hours before planned awakening remains. The only other Z-drug that can be used for middle-of-the-night awakening is the Intermezzo, a low dose zolpidem sublingual tablet, which is specifically approved for this indication.

Zolpidem CR was formulated to immediately release 60% of the dose, then 40% over 4 hours in order to produce “...slightly higher plasma concentrations during the middle of the night...” for the goal of improving sleep maintenance. The FDA review further describes that “[t]he sponsor tried to preserve the elimination half-life from the immediate release formulation in order to prevent next-day residual effects,” thus, the half-lives of the IR and CR form are very similar. While the CR formulation clinically improved wake time after sleep onset between hours 0 to 6 upon sleep initiation (ie, sleep maintenance) compared to placebo, there was very limited information made available regarding the differences with respect to the IR version. Among the package insert there is a single pharmacokinetic graph from a study in 24 healthy males comparing zolpidem plasma concentration-time profiles of the 10 mg IR and 12.5 mg CR dosages. There is a slight increase in drug exposure from 2 hours post dose onwards; yet, it is unclear whether this pharmacokinetic adjustment translates into clinically significant treatment effect differences between these formulations.

Edluar (zolpidem) sublingual tablet and Zolpimist spay are bioequivalent to Ambien in terms of C_max and AUC. These products are rapidly absorbed and useful for improving sleep onset. Regulatory approval for Edluar and Zolpimist was largely based on bioequivalency to Ambien, and consideration that such formulations may be more convenient for some people. Similarly, the approval of Intermezzo SL (zolpidem) also relied on the safety profile of previously approved Ambien. Intermezzo was designed to help re-initiate sleep upon middle of the night awakenings, which is different from approved indications of any other non-benzodiazepine hypnotics. This medication can be taken up to once per night as long as 4-hours of sleep remains upon dosing.

The low-dosed tricyclic antidepressant, doxepin, is used for maintenance insomnia as it has a longer time to effect onset relative to other agents available. The sedating effect of doxepin is thought to be mediated through its antagonist action of histamine-1 receptors. Ramelteon has high affinity for melatonin receptors MT1 and MT2, activating a pathway involved in maintenance of circadian rhythm; is rapidly absorbed and useful for sleep onset latency. Labeling describes that in a small study of elderly patients, a single dose did not appear to affect balance, mobility, and memory function after middle of the night awakening. Tasimelteon, indicated for N24SWD, is also a melatonin agonist, with greater affinity for MT2 than MT1.

While the FDA approval for the orexin receptor antagonist, suvorexant, includes use for sleep onset and/or sleep maintenance, the AASM guideline only recommends this agent for the improvement of sleep maintenance since improvement in sleep latency was only seen in RCTs when using the highest dose of 20 mg and not with the other 3 lower dosages. Suvorexant blocks the effects of wake promoting neuropeptides (orexin A and B) that promote wakefulness by stimulation of the orexin neuropeptide signaling pathway.
Table 5 provides information regarding pharmacokinetic parameters. CYP enzymes are involved in the metabolism of all the agents listed in table 5; thus, labeling advises caution with use of strong CYP inducers or inhibitors. Product warnings that go beyond the exercise of caution apply to suvorexant and tasimelteon: avoid suvorexant in combination with strong CYP3A4 inhibitors and tasimelteon in combination with strong inducers or inhibitors of CYP1A2 or CYP3A4.11,35

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Tmax</th>
<th>T1/2 (hrs)</th>
<th>Metabolism</th>
<th>Excretion</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doxepin</strong> (Silenor)</td>
<td>3.5 hr Delayed -3 hrs if taken with high-fat meal</td>
<td>15</td>
<td>Hepatic: CYP2C19, CYP2D6, CYP1A2, CYP2C9; oxidation, demethylation</td>
<td>Renal: mainly as metabolites; less than 3% as the parent molecule or as nordoxepin</td>
<td><strong>Sleep Maintenance:</strong> FDAi; rAASM</td>
</tr>
<tr>
<td><strong>Eszopiclone</strong> (Lunesta)</td>
<td>1 hr Delayed-1 if taken with high-fat meal</td>
<td>6</td>
<td>Hepatic: CYP3A4 (major), CYP2E1 via demethylation and oxidation</td>
<td>Renal: 75% of dose, mainly as metabolites; less than 10% as the parent molecule</td>
<td><strong>Sleep Onset and/or Maintenance:</strong> FDAi; rAASM</td>
</tr>
<tr>
<td><strong>Ramelteon</strong> (Rozerem)</td>
<td>0.75 hr (range 0.5 to 1.5) Delayed by -0.75 hr with a high-fat meal</td>
<td>1 to 2.6</td>
<td>Hepatic: CYP1A2, CYP2C, CYP3A4 mediated oxidation, glucuronidation</td>
<td>Renal: 84% of dose, mainly as metabolites, and less than 0.1% as parent molecule 4% via feces</td>
<td><strong>Sleep Onset:</strong> FDAi; rAASM</td>
</tr>
<tr>
<td><strong>Suvorexant</strong> (Belsomra)</td>
<td>2 hr (range ½ hr to 6 hrs) Delayed- 1.5 hrs if taken with high-fat meal</td>
<td>12</td>
<td>Hepatic CYP3A (major), CYP2C19 Suvorexant, hydroxyl-suvorexant (inactive)</td>
<td>23% via renal 66% via feces</td>
<td><strong>Sleep Onset:</strong> FDAi <strong>Sleep Maintenance:</strong> FDAi; rAASM</td>
</tr>
<tr>
<td><strong>Tasimelteon</strong> (Hetlioz)</td>
<td>Tmax: 0.5-3 hr Tmax is delayed (by about 1.75 hrs) if taken with a high-fat meal</td>
<td>1.3 ± 0.4</td>
<td>Hepatic CYP1A2, CYP3A4 mediated oxidation and oxidative dealkylation (13-fold less active than tasimelteon), phenolic glucuronidation</td>
<td>Renal: 85% of dose, mainly as metabolites and less than 1% as the parent drug 4% via feces</td>
<td><strong>Non 24-hr Sleep Wake Disorder:</strong> FDAi</td>
</tr>
<tr>
<td><strong>Zaleplon</strong> (Generic only)</td>
<td>1 hr Delayed by about 2 hrs if taken with a high-fat meal</td>
<td>1</td>
<td>Aldehyde oxidase (major) and by CYP3A4 (minor) to inactive metabolites</td>
<td>70% via urine, mostly as metabolites 17% via feces, mostly as metabolites</td>
<td><strong>Sleep Onset:</strong> FDAi; rAASM</td>
</tr>
<tr>
<td>Generic Name (Brand Name)</td>
<td>$T_{\text{max}}$</td>
<td>$T_{1/2}$ (hrs)</td>
<td>Metabolism</td>
<td>Excretion</td>
<td>Indications</td>
</tr>
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<td>---------------------------</td>
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</tr>
<tr>
<td>Zolpidem tartrate IR Tablet (Ambien)</td>
<td>1.6 hr</td>
<td>~2.5</td>
<td>CYP3A4, CYP1A2, CYP2C9</td>
<td>Renal, primarily as inactive metabolites</td>
<td>Sleep Onset: FDAi for Ambien, Ambien CR, Edluar, Zolpimist; rAASM based on trials of zolpidem 10 and 12.5 mg</td>
</tr>
<tr>
<td>Zolpidem tartrate CR Tablet (Ambien CR)</td>
<td>1.5 hr</td>
<td>2.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem tartrate SL Tablet (Edluar)</td>
<td>1.4 hr</td>
<td>~3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem tartrate SL Tablet (Intermezzo)</td>
<td>35-70 min</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem tartrate Oral Spray (Zolpimist)</td>
<td>1 hr</td>
<td>~3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR, controlled release; FDAi, FDA-approved indication; IR, immediate release; MNA, Middle of night awakening with difficulty returning to sleep; SL, sublingual; SM, sleep maintenance; SOL, sleep onset latency; r-AASM, recommended active ingredient (versus no treatment) by the 2017 American Academy of Sleep Medicine Guideline;
Direct-Comparative Evidence for Hypnotic Effects in Patients with Insomnia

Our SR literature search yielded a total of 444 unique titles from which 2 systematic reviews (SRs) were included. Figure 1 displays the PRISMA flow chart for the publication screening process. Additional SRs published after the 2015 AHRQ SR were considered. Our RCT search from 2015 onward yielded 305 unique records; though, no additional head-to-head studies were found meeting our criteria. Appendix B provides a list of studies excluded in the full-text review stage.

Figure 1. PRISMA Flow Diagram for Publication Screening

Searches for Systematic Reviews
- Records identified from OvidMedline[all years], 252
  - Records identified in Embase[publication year 2015 onward], 181
    - (43 duplicates removed)
  - Records identified in Episemonikos[publication year 2015 onward],118
    - (64 duplicates removed)

Searches for RCTs
- Records identified from OvidMedline[2015 onward], 161
  - (23 duplicates removed)
- Records identified in Embase[2015 onward], 277
  - (110 duplicates removed)

Total Records Screened 749

Records Excluded 744

Full-text articles excluded, with reasons:
- Wrong comparator (11)
- Wrong study design (6)
- Wrong population (4)
- SRs reporting an absence of
- H-H evidence for certain hypnotics (3)
- Other (7)

Full-text articles assessed for eligibility 33

Publications included in qualitative synthesis reporting H-H evidence 2 SRs

See Appendix B for a list of excluded studies

Abbreviations: H-H, head-to-head randomized controlled trial
Zaleplon versus Zolpidem

Two head-to-head RCTs (Fry et al and Eli et al) of 4 weeks duration and with moderate risk of bias were reported among the 2015 AHRQ SR and the 2016 American College of Physician’s (ACP) SR. Only 1 RCT provided information that compared sleep onset latency (self-reported) between zaleplon and zolpidem. Zaleplon and zolpidem, both dosed at 10 mg per night, reduced sleep onset similarly. A significant difference was seen only when zaleplon was dosed lower, at 5 mg compared to zolpidem 10 mg; sleep onset was about 14 minutes less with zolpidem 10 mg (95% CI -25.1, -2.3) compared to zaleplon 5 mg. Meta-analyses calculated using 2 RCTs (N=965) available resulted in no significant differences between zaleplon (5 -20 mg) and zolpidem 10 mg for self-reported sleep quality improvements, overall withdrawals, withdrawals related to adverse effects, or the proportion of participants with at least 1 AE. Insufficient information was available to compare total sleep time or sleep efficacy.

Other SRs that searched for head-to-head evidence

Three additional systematic reviews were identified that searched for nHB vs. nHB comparisons, besides zaleplon versus zolpidem; however, they did not find any comparative studies meeting their inclusion criteria.

- Two 2018 Cochrane Review searched for RCTs with doxepin or eszopiclone of any treatment duration. For the eszopiclone SR (Rosner et al), only parallel-design studies were considered since a carry-over effect was a concern explained by authors who cite the potential for lasting sleep stabilizing effect with eszopiclone after discontinuation. Systematic reviews by the American College of Physicians (ACP) and the AHRQ (2015) are in agreement with the 2 Cochrane reviews, locating no nHB-comparator studies with doxepin or eszopiclone. They also reported no active comparator studies for ramelteon or suvorexant. Studies considered for inclusion by ACP and AHRQ were those lasting at least 4 weeks since authors view insomnia as a chronic condition.

- Regarding special populations, a 2019 SR (McDonagh et al) searched for information specifically regarding efficacy in the pediatric population; however, no comparative RCTs were found. Additionally, no head-to-head RCT information has been found in SRs for other pertinent populations such as the elderly or adults with dementia or Alzheimer’s disease.

Special Populations

Pediatric Patients

Insomnia is described as a common condition in children, especially in adolescence with a prevalence of 9.4% (2003) in a sampled US population of 13-16 year olds (diagnosis per the diagnostic and statistical manual of mental disorders 4th edition). Insomnia can co-occur with a variety of disorders such as epilepsy, neurodevelopmental disabilities (eg, ADHD, autism spectrum disorder (ASD), cerebral palsy), and respiratory diseases, etc.

The safety and effectiveness of the agents listed in table 1 have not been established for the pediatric population. Labeling for zolpidem products includes information from an 8-week controlled study in
pediatric patients suffering from insomnia associated with attention-deficit/hyperactivity disorder (ADHD). This study showed that zolpidem dosed at 0.25 mg/kg did not improve sleep latency compared to placebo. Treatment-emergent adverse reactions included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7% vs. 0%), for zolpidem versus placebo respectively. The Cochrane review concluded that only “... melatonin was useful in improving some sleep outcomes in the short term, particularly those with comorbid ASD [autism spectrum disorder] and neurodevelopmental disorders,” while other medications such as zolpidem and eszopiclone had inadequate evidence to support their routine use in the pediatric population.

A 2017 SR (Anand et al) for the pediatric population with ADHD and insomnia identified only 1 RCT each for zolpidem and eszopiclone and found no improvements over placebo. A 2013 SR by Cortese et al provided recommendations concerning the management of sleep disturbance in children with ADHD. If behavior strategies fail as first-line, then patients may try pharmacological treatment; the use of melatonin was supported by RCTs, and there was limited evidence for other medications.

### Older Adults

Cochrane SRs highlighted the need for studies on commonly used drugs for insomnia in patients with dementia and Alzheimer’s disease to clarify the risks and benefits, as evidence is lacking. In older adults, compared to younger adults, lower initial dosing is recommend with doxepin and lower maximum doses are labeled for eszopiclone, zaleplon, and zolpidem since this population is typically more sensitive to the effects of hypnotics. Exposure to tasimelteon was found to be higher in older adults compared to younger adults, by approximately 2-fold.

The 2019 Beers Criteria recommends that the Z-drugs be avoided. However, it is unclear what evidence (ie, trials or SRs) was considered for this decision since citations or evidence tables are not provided or easily retrievable. It should be considered whether conclusions are based on studies of mixed evidence with benzodiazepines or experience primarily with particular doses (ie, zolpidem 10 mg). Since there are key differences in duration of action with zaleplon vs. zolpidem and dose effects may be relevant, it would be useful if information was cited along with consideration for agents individually or according to the dosage (eg, zolpidem 5 mg vs. 10 mg). A meta-analysis proposing harms of Z-drugs outweigh the benefits, published by Glass et al 2005, grouped Z-drugs with benzodiazepines and did not stratify effects of individual agents. When looking only at the independent treatment effect reported in each trial with Z-drugs, each trial resulted in insignificant differences in cognitive and psychomotor adverse effects; yet authors of the meta-analysis summarized more broadly that the benefits of these drugs in the older population may not be justified. Other authors writing about studies of elderly patients treated with zaleplon note that the incidence of adverse-effects was similar to placebo. Ramelteon, suvorexant, and low-dose doxepin, are not listed among the potentially inappropriate list of the Beer’s Criteria.

### Labeled WARNINGS Regarding Other Special Populations

There is a warning of increased exposure to suvorexant in women and in obese patients. Dose increases should be approached with caution especially in obese women. While lower initial doses are not specifically recommended in the suvorexant labeling, this can be considered (eg, starting at 5 mg instead of 10 mg). Likewise, for zolpidem, lower initial doses are recommended for women since the
FDA described this population generally has lower zolpidem drug clearance compared to men. Nonetheless, authors more recently have critically appraised the evidence and argue that the available clinical evidence does not substantiate the FDA’s recommendation for lowering the zolpidem dose for females; the FDA’s concern seems to be based mostly on a theory of increased risk and not on actual published data.50,51 As authors are concerned for potential under dosing at 5 mg and the hazards of sub-optimally treated insomnia, the FDA labeling seems loose enough such that if patients (women or men) are not responding adequately to 5 mg or 6.5 mg nightly, then the dose can be increased.17

With tasimelteon, smokers can experience reduced drug efficacy since smoking induces the main enzyme responsible for the metabolism of tasimelteon (CYP1A2).14

**Table 6** provides additional information from the product labeling regarding pregnancy, renal/hepatic impairment, and geriatric patients.

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Pregnant Women</th>
<th>Geriatric Patients</th>
<th>Renal or Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doxepin</strong> (Silenor)</td>
<td>Pregnancy: May cause fetal harm based on animal data. Human data suggest low risk, but when used near term NAS is possible. Lactation: Excreted into human milk; potential toxicity.</td>
<td>Initiate at a lower dose (3 mg) and monitor prior to considering dose escalation.</td>
<td>Initiate at 3 mg in patients with hepatic impairment or tendency of urinary retention</td>
</tr>
<tr>
<td><strong>Eszopiclone</strong> (Lunesta)</td>
<td>Pregnancy: Toxicity in animal offspring occurred at the lowest dose tested of 200 times the usual human exposure. Lactation: Limited human data suggests potential toxicity.</td>
<td>Older adults (&gt;65 years) had longer elimination and higher exposure to eszopiclone. Therefore the dose should not exceed 2mg in elderly patients</td>
<td>The dose should not exceed 2mg/night in patients with severe hepatic impairment; no adjustment necessary with mild/moderate hepatic impairment</td>
</tr>
<tr>
<td><strong>Ramelteon</strong> (Rozerem)</td>
<td>Postmarketing data for use in pregnant women have not identified a drug-associated risk of negative maternal or fetal outcomes. Lactation: likely excreted into human milk; human data suggests potential toxicity.</td>
<td>No difference in effect was observed between elderly and younger adults. Clinical trials included elderly patients.</td>
<td>Exposure increased by 4 and by &gt;10 fold in patients with mild and moderate hepatic impairment, respectively. Use with caution in these patients and avoid use in patients with severe hepatic impairment</td>
</tr>
</tbody>
</table>

No dose adjustment is required with renal impairment.
<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Pregnant Women</th>
<th>Geriatric Patients</th>
<th>Renal or Hepatic Impairment</th>
</tr>
</thead>
</table>
| **Suvorexant (Belsomra)** | Pregnancy C: no human information; may cause fetal harm but animal data suggests low risk<sup>52</sup>  
  Lactation: it is unknown whether the drug is secreted into human milk; probably compatible<sup>52</sup> | There was no clinically meaningful difference in effect observed between elderly and younger adults | No dose adjustments are necessary in renal impairment or in mild or moderate hepatic impairment; not recommended for use in severe hepatic impairment |
| **Tasimelteon (Hetlioz)** | Pregnancy: no human data; animal studies suggests potential fetal harm. Use only if potential benefit justifies potential risk  
  Lactation: it is unknown whether drug is excreted into human milk | Exposure in older adults (>65) is increased by about 2-fold compared to that in younger adults; use with caution | Dose adjustments with mild or moderate hepatic impairment are not necessary. Avoid use in severe hepatic impairment |
| **Zaleplon (Generic only)** | Pregnancy: no human data; animal studies suggests potential fetal harm. Use only if potential benefit justifies potential risk  
  Lactation: it is unknown whether drug is excreted into human milk | Since elderly patients responded to a 5 mg/evening dose, it is recommended to start at this lower dose especially since old adults may be more sensitive to the effects of hypnotics | Use at doses up to 5 mg with mild or moderate hepatic impairment. Avoid use in severe hepatic impairment |
| **Zolpidem Tartrate (Ambien; Ambien CR; Edluar; Intermezzo; Zolpimist)** | Pregnancy: May cause respiratory depression and sedation in neonates with exposure late in the third trimester; reports on human data have not found a clear association with zolpidem use and major birth defects<sup>17</sup>  
  Lactation: drug is excreted into milk; potential for adverse events (eg, excess sedation, CNS depression) in nursing infant<sup>17</sup> | Elderly patients tend to be more sensitive to the effects of hypnotics. The recommended dose of zolpidem is lower for elderly compared to younger adults: 5 mg/dose of IR tablet, Edluar SL tablet, and oral spray; 6.25 mg/dose of CR tablet; 1.75 mg/dose of Intermezzo SL tablet | Lower doses are recommended with mild to moderate hepatic impairment (avoid use of Ambien products with severe hepatic impairment)  
  Dose adjustments are not necessary with renal insufficiency |

**Abbreviations:** CR, controlled release; IR, immediate release; NAS, neonatal abstinence syndrome; SL, sublingual
General Safety Information

Label precautions for all the agents approved for insomnia includes warnings for (a) potential risk of abnormal thinking (eg, hallucinations), behavioral changes, decreased inhibition, complex behaviors (eg, sleep-driving), or worsening of depression; (b) CNS-depressant effects and/or day-time somnolence; and (c) additive effects with other CNS depressants. While labeling warns of dependence and possible withdrawal upon abrupt discontinuation with eszopiclone and zolpidem some studies have suggested that use of eszopiclone up to six months was not associated with increased tolerance or withdrawal with eszopiclone. Withdrawal is not known to be a problem with zaleplon. Doxepin, ramelteon, and suvorexant are also not known to induce physical dependence or withdrawal symptoms.

Though an increased risk of dementia in observational studies has been found with the use of hypnotics (benzodiazepines and benzodiazepine receptor agonists), RCTs are needed to confirm this finding and whether it is a potential risk with other hypnotics (eg, doxepin, ramelteon, suvorexant). Dementia is listed as a rare event (occurring in less than 1/1000) reported during the pre-approval studies of Ambien involving treatment of 3,660 patients.

A Cochrane SR of all RCT evidence involving eszopiclone, available up to February 2018, found small but statistically significant differences in the risk of the following adverse events compared to placebo (evidence rated moderate quality): unpleasant taste (risk difference [RD] 0.18, 95% CI 0.14 to 0.21), dry mouth (RD 0.04, 95% CI 0.02 to 0.06), somnolence (RD 0.04, 95% CI 0.02 to 0.06), and dizziness (RD 0.03, 95% CI 0.01 to 0.05). Treatment- and placebo-group frequencies of serious adverse events (eg, suicide, accidental injury due to fall), hallucination, mood changes, memory impairment, or overall withdrawal symptoms were similar. The meta-analysis RD for other adverse events listed in the product labeling (headache, respiratory infection, dizziness, anxiety, and rash) was similar between treatment and placebo. Authors concluded that “[t]here was no or little evidence of harm if taken as recommended.”

Zaleplon is generally well tolerated. The most common adverse effect reported in clinical trials were headache, abdominal pain, dyspepsia, nausea, ataxia, dizziness, incoordination, nervousness, and somnolence; however, these did not occur significantly more frequently than in the placebo group. Zaleplon causes minimal to no residual psychomotor impairment and is not associated with rebound insomnia.

Labeling explains that there is a dose relationship for many zolpidem-related adverse effects, especially for CNS and gastrointestinal adverse events. Common AEs labeled with zolpidem 5 and 10 mg dosage forms include next day drowsiness, dizziness, diarrhea, drugged feelings, and headache. Common adverse effects with the low-dosage form designed for middle of the night awakenings, Intermezzo, include nausea, headache, and fatigue. Meta-analyses carried out for the AASM guideline on safety
outcomes resulted in a significant difference from placebo for increased risk of amnesia, dizziness and somnolence with zolpidem 10 mg.8

Based on the meta-analysis by Brasure et al (2015 AHRQ SR), of 2 RCTs of 4 weeks duration, there was no significant difference between zaleplon (5 -20 mg) and zolpidem 10 mg for overall withdrawals, withdrawals related to adverse effects, or the number of participants with at least 1 AE.1,2 A review of observational evidence explained that sleep walking is reported mostly with zolpidem as post-marketing reviews found the incidence rates in adults to be 0.5% and 1.1%.56 Two case reports of sleep-walking were found for the less often prescribed Z-drug, zaleplon, and no case reports were found with other drugs of our interest.56

Low-dose doxepin is well tolerated. RCTs from polysomnographic studies consistently showed similar dropout rates between doxepin and placebo treatment.57 Labeling reports AEs occurring in ≥ 2% of patients and more common than in the placebo group were somnolence, nausea, and upper respiratory tract infection. Meta-analyses carried out in the literature evaluation for the AASM guideline resulted in a significant difference from placebo for increased somnolence risk when doxepin was dosed at 6 mg. Other risks of AEs evaluated (eg, doxepin 3 mg and somnolence, diarrhea, and upper respiratory tract infection; doxepin 6 mg and headache) were not significantly elevated with doxepin.9

Labeling for ramelteon describes adverse effects reported with numerically higher frequency than in patients treated with placebo were somnolence, dizziness, fatigue, nausea, and exacerbated insomnia. A 2014 SR of placebo-controlled RCTs found patients receiving ramelteon were significantly more likely to report somnolence than those taking placebo (relative risk, 1.97; 95% CI 1.21, 3.20) and the relative risk of other AEs were not significantly different from the placebo arm.10

The most common adverse reaction of suvorexant therapy (at 15 and 20 mg dosing) in clinical trials was somnolence — significantly more common compared to placebo (7% vs. 3%).11,12 No other AEs occurred more often than in the placebo arm. Overall AE frequency of suvorexant treatment, in the 2 clinical trials, was not significantly different than placebo and daytime performance decrements or withdrawal effects were not evident.8 There is warning of a dose-response on next-day somnolence and cautionary advice against driving or other activities requiring complete mental alertness for patients taking the suvorexant 20 mg dosage. The medication has not been associated with rebound insomnia or withdrawal upon discontinuation and was well tolerated with the discontinuation rate at 3 months, in the phase 3 studies, of less than 3% of treated patients.11,12 Since the tolerability profile in elderly patients was congruent with that of younger adults, there is no recommendation for dose reduction (from the usual 10 mg imitation dosage) in the elderly. Prescribers do, however, have the option to start as low as 5 mg if they wish to use a “start low/go slow” approach.

Tasimelteon is the melatonin receptor agonist only indicated for Non-24-Hour Sleep Wake Disorder. Adverse reactions with and incidence >5% and twice that of the placebo group included headache, elevated alanine aminotransferase, nightmares or unusual dreams, and upper respiratory or urinary tract infection.14

Table 7 provides additional information from the drug product labeling regarding warnings, adverse reactions, and drug interactions.
Table 7. Warnings, Common Adverse Reactions, and Drug Interaction Information5,7,11,14-21

Contraindications

- Hypersensitivity to the active ingredient or any excipient of the formulation (all drugs)
- *Ramelteon (Rozerem):* contraindicated with strong inhibitors of CYP1A2 such as fluvoxamine
- *Doxepin (Silenor):* (1) Avoid use of monoamine oxidase inhibitors concurrently or if MAOIs have been used within the past two weeks, and (2) untreated narrow angle glaucoma or severe urinary retention
- *Suvorexant (Belsomra):* do not use in patients with narcolepsy

Warnings

Applies to all medications indicated for insomnia (with active ingredients DOX, ESZ, RAM, SUV, ZAL, and ZOL)

- Re-evaluate for co-morbid diagnoses if insomnia persists after 7 to 10 days of use
- Immediately evaluate and assess risk of abnormal thinking, behavioral changes, decreased inhibition, or other complex behaviors that arise during treatment: May induce "sleep-driving" and hallucinations.
- Depression: Worsening of depression or suicidal thinking may occur
- CNS-depressant effects/or day-time somnolence: may impair alertness and motor coordination. Avoid engaging in hazardous activities such as operating a motor vehicle or heavy machinery after taking drug.
- Caution for potential additive effects when used in combination with other CNS depressants or sedating antihistamines. Consider dose reductions. Avoid concomitant use with alcohol

Applies to a limited set of medications

- Severe anaphylactic/anaphylactoid reactions: do not re-challenge if such reaction occurs (ESZ, REM, ZAL, ZOL)
- Elderly: initiate and/or use at a lower maintenance dose due to increase sensitivity (DOX, ESZ, ZAL, ZOL)
- Effect on respiratory function should be considered in patients with respiratory disorders (SUV, ESZ, ZAL, ZOL); for patients with severe sleep apnea, generally not recommended (DOX, REM)
- Withdrawal effects: symptoms can occur with abrupt discontinuation (ESZ, ZOL)
- Use with caution in patient with hepatic impairment or hemodynamic responses (ESZ, ZAL); avoid use in patients with severe hepatic impairment (Ambien products)
- SL tablets should be placed under tongue and allowed to completely disintegrate (Intermezzo, Edluar)
- Reproductive effects: may reduce testosterone and increase prolactin levels (REM)
- Sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms: risk increases with dose (SUV)
- Induces somnolence: after taking suvorexant, limit activities to preparing for bed since patients may experience impaired mental alertness (TAS)
- Severe Injuries: drowsiness may lead to falls including severe injuries (Ambien products)

Labeled Adverse Reactions

- *Doxepin (Silenor):* Reported in ≥ 2% of patients treated with Silenor, and more commonly than in patients treated with placebo were somnolence/sedation, nausea, and upper respiratory tract infection
- *Eszopiclone (Lunesta):* Reported in ≥ 2% of patients treated with Lunesta were unpleasant taste, headache, somnolence, respiratory infection, dizziness, dry mouth, rash, anxiety, hallucinations, and viral infections
- *Ramelteon (Rozerem):* Reported in ≥ 3% of patients treated with Rozerem, and more commonly than in patients treated with placebo were somnolence, dizziness, fatigue, nausea, and exacerbated insomnia
- *Suvorexant (Belsomra):* Reported in ≥ 5% of patients treated with Belsomra and at least twice the placebo rate was somnolence
<table>
<thead>
<tr>
<th>Warnings, Common Adverse Reactions, and Drug Interaction Information</th>
</tr>
</thead>
</table>

- **Tasimelteon (Hetlioz):** Reported in ≥ 5% of patients treated with Hetlioz and at least twice the placebo rate were headache, increased alanine aminotransferase, nightmares or unusual dreams, and upper respiratory or urinary tract infection.
- **Zaleplon:** Reported in ≥ 5% of patients and at least twice the placebo incidence: abdominal pain.
- **Zolpidem (Ambien):** drowsiness, dizziness, diarrhea, drugged feelings.
- **Zolpidem CR (Ambien CR):** reported in ≥ 10% of patients: dizziness, headache, next day drowsiness.
- **Zolpidem low-dose SL (Intermezza):** reported in ≥ 1% of patients: nausea, headache, fatigue.
- **Zolpidem SL (Edluar):** next-day drowsiness and dizziness, diarrhea, headache, drugged feeling.
- **Zolpidem OS (Zolpimist):** next-day drowsiness and dizziness, diarrhea, headache, drugged feeling.

**Drug Interactions**

- **Doxepin:** MAO inhibitors, cimetidine, alcohol, CNS depressants (additive effect), tolazamide.
- **Eszopiclone:** CNS depressants (additive effect), rifampicin (strong CYP inducer), ketoconazole (strong CYP3A4 inhibitor).
- **Ramelteon:** rifampin, ketoconazole, fluconazole (strong CYP2C9 inhibitor), donepezil, doxepin, alcohol.
- **Suvorexant:** CYP3A inhibitors, strong CYP3A inducers, digoxin.
- **Tasimelteon:** avoid use with strong CYP1A2 inhibitors (eg, fluvoxamine) and strong CYP3A4 inducers (eg, rifampin).
- **Zaleplon:** CNS depressants, imipramine (decreased alertness and/or psychomotor performance observed), CYP3A4 inducers (eg, rifampin, St. John’s wort), ketoconazole (may increase effect).
- **Zolpidem:** CNS depressants, imipramine and chlorpromazine (decreased alertness and/or psychomotor performance observed), CYP3A4 inducers (eg, rifampin, St. John’s wort), ketoconazole (may increase effect).

Abbreviations: CR, controlled release; DOX, doxepin; ESZ, eszopiclone; RAM, ramelteon; OS, oral spray; SL, sublingual; SUV, suvorexant; TAS, tasimelteon; ZAL, zaleplon; ZOL, zolpidem.

**Other Safety-related Studies in Non-insomniacs**

Two studies were found comparing the effects of hypnotics in healthy adults during forced awakenings at the maximum concentration time-point of drug. One was a cross-over RCT investigating arousability and balance in healthy males (N=51) treated with a single dose of zolpidem 10 mg versus doxepin 6 mg. Doxepin treatment resulted in better balance scores (ie, surrogate for fall risk) and lower auditory awakening threshold upon forced awakening compared to the zolpidem arm. In an RCT on cognitive performance in healthy astronauts and flight controllers (N=34), zaleplon 5 mg and zolpidem 5 mg had similar and minimal effects on cognitive and psychomotor vigilance compared to placebo at the forced awakening; whereas zolpidem 10 mg was found to significantly affect cognitive throughput, psychomotor vigilance, working memory, and subjective sleepiness upon forced awakening. Nonetheless, it is unclear whether these findings should be generalized to patients with insomnia.
Summary

Indications of nBHs differ according to the nature of sleep disturbance and are specific to the drug formulation. Zolpidem is available in multiple formulations: immediate-release tablet, sublingual, and oral spray; a controlled-release tablet; and a low-dose sublingual formulation. The remaining products are available as one formulation type. Table 3 of the report compares the recommended medications for chronic insomnia according to the 2017 AASM guideline with the FDA-approved indication for the nBH agents. The 2017 AASM guideline does not go as far to recommend one drug over another within the two insomnia categories (agents for sleep onset and agents for sleep maintenance). For sleep onset insomnia, the recommended options include eszopiclone, ramelteon, temazepam, triazolam, zaleplon, and zolpidem. Recommended options for sleep maintenance insomnia include doxepin, eszopiclone, temazepam, suvorexant, and zolpidem (based on trials of zolpidem IR 10 mg formulation). The melatonin agonist, tasimelteon, is an orphan drug approved for the rare disorder, non-24 hour sleep wake disorder. The 2015 AASM guideline for the treatment of N24SWD recommended that clinicians use melatonin and did not provide a recommendation for or against the use of tasimelteon.

Once the decision for initiation of pharmacotherapy has been made, prescribers must consider the characteristics of hypnotics (eg, duration of action, side-effect risks, efficacy per sleep parameter) while tailoring the choice of therapy to the nature of the patient’s insomnia complaint and patient-specific factors (eg, co-morbidities, prior response to sedatives, adverse-effects experienced, or abuse potential). Residual daytime somnolence may be lessened by lowering the dose, ensuring the timing of administration with respect to hours left of sleep is in line with product labeling, or by choosing a medication with shorter half-life.

Upon reviewing published literature, we found several systematic reviews (SRs) published in the last 4 years describing an absence of comparative randomized-controlled trial (RCT) evidence (nBH vs. nBH) for doxepin, eszopiclone, ramelteon, and suvorexant. Two systematic reviews reported that there was limited evidence available for zaleplon versus zolpidem (2 RCTs with moderate risk of bias) showing that when agents were used at the same milligram dose (ie, 10 mg) they yielded similar improvements in sleep onset. Meta-analyses showed no significant differences between zaleplon (5-20 mg) and zolpidem 10 mg for self-reported improvement in sleep quality, withdrawals related to adverse effects, or the number of participants with at least 1 adverse event.

Currently preferred agents on the Utah Medicaid PDL include generic zaleplon capsules and zolpidem tablets. For the purpose of preferred status, the panel may wish to consider at least one agent indicated for sleep onset, one for sleep maintenance, and at least one that is a non-Z-drug for sleep maintenance (eg, doxepin or suvorexant), considering the Beer’s criteria pertaining to Z-drugs. Tasimelteon may be specified as non-preferred since it should be reserved for patients with the rare disorder N24SWD.
References


## Appendix A: Literature Search Strategies

Table 1. OvidMedline Search Strategy

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<th>Literature Search for Systematic Reviews Performed March 11, 2019</th>
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</tr>
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</table>

<table>
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<th>Literature Search for RCTs Performed April 18th, 2019</th>
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<td>Table 2. Embase Search Strategy</td>
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| #11 | #3 AND #6 AND #10 | 1,465 |
| #10 | #7 NOT (#8 OR #9) | 1,683,112 |
| #9  | 'conference abstract'/it OR 'conference paper'/it | 4,107,961 |
| #8  | ('nonhuman'/de OR 'animal'/de) NOT ('human'/exp AND ('nonhuman'/de OR 'animal'/de)) | 5,786,644 |
| #7  | 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((double*NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti | 2,392,407 |
| #6  | #4 OR #5 | 126,305 |
| #5  | ((sleep NEAR/2 (maintenance OR latency OR onset OR initiation OR disorder)):ti,ab,kw) OR insomni*:kw,ti,ab | 52,391 |
| #4  | 'insomnia'/exp OR 'sleep parameters'/exp OR 'circadian rhythm sleep disorder'/exp | 109,931 |
| #3  | #1 OR #2 | 19,456 |
| #2  | 'doxepin'/de OR 'eszopiclone'/de OR 'zolpidem'/de OR 'zolpidem tartrate'/de OR 'ramelteon'/de OR 'suvorexant'/de OR 'tasimelteon'/de OR ' zaleplon'/de | 18,969 |
| #1  | doxepin:ti,ab,kw OR eszopiclone:ti,ab,kw OR zolpidem:ti,ab,kw OR ramelteon:ti,ab,kw OR suvorexant:ti,ab,kw OR tasimelteon:ti,ab,kw OR zaleplon:ti,ab,kw | 5,916 |
We checked the searches above against 9 articles a pharmacist on the team found using a basic search in Episimonikos. There were two articles indexed in Embase, however, not found by our search since it seemed to appropriately weed them out: after reviewing the full text of these, it was verified that no head-to-head drug comparison RCTs are included.

The following articles were checked for their presence in the results from the Medline and Embase searches.

   - Found by the OVIDMedline search
   - Found by both Embase searches

   - Found by OVIDMedline search
   - Found by both Embase searches

   - Found by the OVIDMedline search
   - Found by the Embase search

   - Found by the OVIDMedline search
   - This was not found by the Embase search since for the drug class Mesh terms we used a drug subheading available in Embase for “drug comparison”. Deleting this subheading would have produced this article.
   - After reviewing the full-text, we found this is an article that does not present head-to-head drug comparison information; thus, the subheading worked to exclude such studies (placebo only comparisons) that don’t pertain to our main objective of identifying head-to-head drug comparison information

5. Liu et al. (2017) *Treatment of insomnia with tricyclic antidepressants: a meta-analysis of polysomnographic randomized controlled trials.*[^3]
   - Found by the OVIDMedline search
   - Found by the Embase search

   - Found by the OVIDMedline search
   - Found by the Embase search

   - Found by the OVIDMedline search
   - Found by the Embase search

8. Baandrup et al. (2013) *Treatment options for residual insomnia in schizophrenia.*
   - Found by the OVIDMedline search
   - This was not found in Embase mainly because no abstract was available and the title is very general (leaving out drug and drug class terms, systematic review methodology terms); moreover, there is no head-to-head comparison information of the drugs we are looking at so this article would not be included anyway.

9. AHRQ Brasure et al. (2015) *Management of Insomnia Disorder (Book)*
   - Found by the OVID search
   - Does not appear to be indexed in Embase
Table 4. Epistemonikos Search

<table>
<thead>
<tr>
<th>Query 04-15-2019</th>
<th>Notes</th>
</tr>
</thead>
</table>
| (title:(doxepin OR eszopiclone OR zolpidem OR ramelteon OR suvorexant OR tasimelteon OR zaleplon OR antidepressant* OR sedative* OR hypnotic* OR "orexin receptor antagonist" OR nonbenzodiazepin* OR non-benzodiazepin* OR z-drug* OR z-compound*)) OR abstract:(doxepin OR eszopiclone OR zolpidem OR ramelteon OR suvorexant OR tasimelteon OR zaleplon OR antidepressant* OR sedative* OR hypnotic* OR "orexin receptor antagonist" OR nonbenzodiazepin* OR non-benzodiazepin* OR z-drug* OR z-compound*)) AND (title:(insomnia* OR sleep) OR abstract:(insomnia* OR sleep)) | Results: Total SRs 914, Total Broad Syntheses 7  
Limited to 2015 onward: **118 SRs** and 1 BS  
- Uploaded 58 records into Covidence screening; 60 duplicates removed by Covidence and 4 duplicates additionally identified by screener (54 unique records) |
Appendix B: Excluded Studies for Direct-Comparative Evidence Section

Wrong Study Design

   • We are interested in the full review, not just a summary
   • Compares drug class vs. drug class based on indirect and direct comparative evidence

Wrong Comparators

   • This review also only searched 1 database
   • Authors focused on placebo comparison
   • The PICO defined by the authors shows placebo comparisons were the aim of this SR. Though this publication is not included in the direct-comparative evidence section, it is included in our guideline section.
   - Comparison information is based on observational data or indirect comparisons; nonetheless, since this publication represents expert opinion consensus, it was used as a background information but not in the direct-comparison section

Wrong Population

   - Included non-insomniacs; outcomes upon forced awakening


SRs that searched for head-to-head RCTs but did not locate any meeting their inclusion criteria


Other

a. Publication Type

   - Supplement abstract

   - Meeting abstract

   - Instead we included the primary SR publication that this guideline was based on for the direct comparative section; Qaseem et al report is included in the guideline section

b. SRs published prior to the 2015 AHRQ SR


• Updated SR available: see 2015 SR by Brasure et al. Nonetheless Liu et al findings are congruent with Brasure et al with respect to finding no head-to-head studies available for ramelteon versus hypnotics of interest for our review.


• Updated SR available: see Everett et al. Nonetheless Vande Griend et al findings are congruent with Everett et al with respect to finding no head-to-head low-dose doxepin studies versus hypnotics of interest for our review.
### Appendix C: Systematic Review Information

<table>
<thead>
<tr>
<th>First Author, Year of Publication</th>
<th>Title</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
</table>
| McDonagh, 2019 | Pharmacologic Treatments for Sleep Disorder in Children: A Systematic Review | Included RCTs lasting at least 1 week in patients 18 years old or younger comparing medications used for insomnia (except for benzodiazepines and tricyclic antidepressants) with placebo or an active comparator arm. Searched through June 2018 in CENTRAL, Medline, and PsycInfo | Authors found no head-to-head drug comparisons.  
- There was 1 study each for zolpidem (Blumer 2009) or eszopiclone (Sangal 2014) versus placebo. Both studies were in study populations suffering for co-morbid ADHD and neither resulted in improvements in sleep outcomes (measured by polysomnography and actigraphy) or in ADHD symptoms  
- 19 studies were found that evaluated melatonin versus placebo. With melatonin treatment, there were significant improvements in sleep latency (a median reduction by 28 minutes), sleep duration (a median reduction by 33 minutes), and wake time after sleep onset, however, not in the number of awakenings per night. |
<p>| Everitt, 2018 | Antidepressants for insomnia in adults | Included RCTs of adults with insomnia diagnosis, treated with any antidepressant as monotherapy compared with placebo or with an active comparator arm. Studies could be of any duration. Searched up to July 2015 in CENTRAL, Medline, Embase, and PsycInfo Protocol present | Authors found no head-to-head comparison RCTs with doxepin; all were versus placebo |</p>
<table>
<thead>
<tr>
<th>First Author, Year of Publication</th>
<th>Title</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
</table>
| Rosner, 2018<sup>4</sup> | Eszopiclone for insomnia (Review) | Objective: to compare the safety and effectiveness of eszopiclone with placebo and active comparators  
  Included RCTs of adults with insomnia diagnosis, treated with eszopiclone and comparator for the improvement of sleep. Cross-over RCTs were excluded since eszopiclone may have sleep stabilizing effects even after discontinuation (ie, possible carry over effect). Studies of any duration were considered.  
  Searched up to February 21<sup>st</sup> 2018 in CENTRAL, Medline, Emsbase, PsycInfo, PSYN-DEX, WHO trials and ClinicalTrials.gov | Authors found no head-to-head comparison RCTs with eszopiclone |
| Wilt, 2016<sup>1</sup> | Pharmacologic Treatment of Insomnia Disorder: An Evidence Report for a Clinical Practice Guideline by the American College of Physicians | Objective: to evaluate efficacy, comparative effectiveness, and harms of medications use for insomnia  
  Included RCTs of US available/approved medications regardless of the comparator (placebo, another medication, non-pharmacologic therapy) of adults patients with insomnia disorder, provided at least 4 weeks of follow-up, and reported global or sleep outcomes. Excluded studies with high risk of bias.  
  Searched from 2004 to 2015 in MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and PSYCinfo; Protocol present on Prospero | Authors found 2 RCTs comparing zolpidem and zaleplon (the same identified by the SR Brasure et al) which they rated as moderate risk of bias. Authors stated that these trails “...provided insufficient evidence about the comparative effectiveness of zaleplon versus zolpidem...”  
  - Meta-analysis showed that the the total withdrawals and the proportion of participants with at least 1 adverse effect were similar between zaleplon and zolpidem groups. |
<table>
<thead>
<tr>
<th>First Author, Year of Publication</th>
<th>Title</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brasure, 2015</td>
<td>Management of Insomnia Disorder</td>
<td>Included RCTs and SRs comparing medications for the treatment of insomnia compared to placebo or to each other. Studies must be at least 4 weeks duration. Searched Medline, Ovid PsycInfo, Embase, Cochrane Library, and clinicaltrials.gov from 2004 through January 2015. Authors used other SRs with search dates up to 2005 for more previous information.</td>
<td>Authors’ conclusions “…medical therapy with eszopiclone, zolpidem, and suvorexant improve global and sleep outcomes for insomnia disorder. Clinical significance, applicability, comparative effectiveness, and long-term efficacy, especially among older adults, are less well known. Effect sizes vary, and a large placebo response is sometimes observed.” Comparative effectiveness of medications for insomnia disorder (begins on page 99 of the review)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NS, non-significant; RCT, randomized controlled trial,