COLLEGE OF PHARMACY
UNIVERSITY OF UTAH

L. S. SKAGGS PHARMACY INSTITUTE

UTAH MEDICAID P&T REPORT
SEPTEMBER 2022

HYPNOTICS
(NON-BENZODIAZEPINES, NON-BARBITURATES)

Doxepin (Silenor)
Eszopiclone (Lunesta)
Ramelteon (Rozerem)
Suvorexant (Belsomra)
Lemborexant (Dayvigo)
Daridorexant (Quviviq)
Zaleplon (Sonata)
Zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist)
Tasimelteon (Hetlioz, Hetlioz LQ)

Report finalized: August 2022
Report presented: September 2022

Drug Regimen Review Center

Monet Luloh, PharmD, Clinical Pharmacist
Valerie Gonzales, PharmD, Clinical Pharmacist
Lauren Heath, PharmD, MS, BCACP, Clinical Pharmacist
Kristin Knippenberg, MFA, Administrator and Editor
Jacob Crook, MS, Data Analyst
Joanne LaFleur, PharmD, MSPH, Director and Associate Professor

University of Utah College of Pharmacy, Drug Regimen Review Center

CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

The following list contains abbreviations used throughout the body text of this report:

AASM	American Academy of Sleep Medicine
AAT	auditory awakening threshold
ACP	American College of Physicians
ADHD	Attention Deficit Hyperactivity Disorder
AEs	adverse events
AGS	American Geriatrics Society
AHRQ	Agency for Healthcare Research and Quality
ARCI PCAG	Addiction Research Center Inventory for the Pentobarbital-chlorpromazine-alcohol Group
ASD	Autism Spectrum Disorder
BAP	British Association for Psychopharmacology
BDI-II	Beck Depression Inventory-II
CBT-I	cognitive behavioral therapy for insomnia
CNS	central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CRSWD	Circadian Rhythm Sleep-Wake Disorders
CYP	cytochrome
DDIs	drug-drug interactions
DoD	Department of Defense
DSST	Digit Symbol Substitution Test
DST	Digit Span Test
ER	extended-release
ESRS	European Sleep Research Society
FDA	Food and Drug Administration
GAD-7	Generalized Anxiety Disorder 7
ICER	Institute for Clinical and Economic Review
ICSD-3	International Classification of Sleep Disorders, Third Edition
IR	immediate-release
ISI-J	Japanese version of the Insomnia Severity Index
LPS	latency to persistent sleep
MAOIs	monoamine oxidase inhibitors
MDD	Major Depressive Disorder
MeSH	Medical Subject Headings
N24SWD	Non-24 Hour Sleep-Wake Disorder
nBH	non-benzodiazepine, non-barbiturate hypnotic
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NNH	number needed to harm
NNT	number needed to treat
OAA/S	Observer's Assessment of Alertness/Sedation
ORAs	orexin receptor antagonists

OSA	Obstructive Sleep Apnea
P&T	Pharmacy and Therapeutics
PDL	Preferred Drug List
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRISMS	Parents and Researchers Interested in Smith-Magenis Syndrome
PSG	polysomnography
PSQI-J	Japanese version of the Pittsburgh Sleep Quality Index
RCTs	randomized controlled trials
SMS	Smith-Magenis Syndrome
SRMAs	systematic review meta-analyses
SRs	systematic reviews
TEAEs	treatment-emergent adverse events
TST	total sleep time
US	United States
VA	Veterans Affairs
VAS	visual analog scale
WASO	wake-after-sleep onset

EXECUTIVE SUMMARY

Background:

This report reviews the non-benzodiazepine, non-barbiturate hypnotic (nBH) medications and serves as an update to our previous Pharmacy and Therapeutics (P&T) report on these agents, which was completed in 2019.[1] Agents in this drug class are approved for insomnia (sleep onset and/or sleep maintenance), and 1 agent (tasimelteon) is approved for 2 rare disorders: non-24 hour sleep-wake disorder (N24SWD), and Smith Magenis Syndrome (SMS).

According to the International Classification of Sleep Disorders, Third Edition (ICSD-3), insomnia is defined as trouble initiating or maintaining sleep that results in symptoms while awake, and occurs despite a suitable sleep environment and adequate opportunity to sleep.[2,3] Insomnia may occur independently, or comorbidly with other conditions (eg, sleep apnea, anxiety, depression, chronic pain).[4,5] N24SWD occurs when an individual is unable to maintain entrainment between their endogenous circadian clock and the 24-hour environment, often due to the inability to perceive light, a key entrainment cue.[6-8] SMS is a rare, genetic neurodevelopmental disorder that often results in sleep disturbances, potentially related to altered melatonin production.[9,10]

Since we completed our 2019 P&T report,[1] 2 new orexin receptor antagonists (ORAs) have been approved by the US Food and Drug Administration (FDA): daridorexant (Quviviq) and lemborexant (Dayvigo).[11,12] Additionally, a new dosage form of tasimelteon (a melatonin receptor agonist) has been approved: Hetlioz LQ, oral suspension.[13] These new products are reviewed in this report, along with the following products previously included in the 2019 P&T report[1]:

- Three non-benzodiazepines (z-drugs): zolpidem (Ambien, Ambien CR, Intermezzo, Edluar, Zolpimist), eszopiclone (Lunesta), and zaleplon (Sonata)
- One low-dose H_1 antihistamine antidepressant: doxepin (Silenor)
- One ORA: suvorexant (Belsomra)
- Two melatonin receptor agonists: ramelteon (Rozerem) and tasimelteon (Hetlioz)

Zolpidem is available in a variety of formulations: sublingual tablet, immediate-release (IR) tablet, controlled-release tablet, and oral spray.[14-18] The remaining products approved for insomnia are available as a single oral formulation, and the recommended dose, including initial dosage for some of these agents, varies by age and/or sex.[11,12,19-23] All of these agents except tasimelteon are FDA-approved for the treatment of insomnia in adults, but the indication varies according to the insomnia subtype (ie, sleep onset and/or sleep maintenance) and may differ between formulations of the same active ingredient.[11-23]

- All of the nBH agents indicated for insomnia are approved for sleep onset insomnia, except doxepin[11,12,14-23]
- The ORAs, controlled-release zolpidem, doxepin, and eszopiclone are approved for sleep maintenance insomnia[11,12,15,19,20,22]
- A sublingual formulation of zolpidem, Intermezzo, is uniquely indicated for trouble falling back asleep after awakening in the middle of the night[17]

- Tasimelteon, oral capsule (Hetlioz), is the only FDA-approved agent for the treatment of N24SWD in adults.[8,24,25] It is also approved for the treatment of sleep disturbances in SMS for patients 16 years of age and older,[26] and as an oral suspension (Hetlioz LQ) for children ages 3 to 15 years[13,27]

In terms of administration, all of these agents are taken orally once per night, before bedtime, except Intermezzo, which is used as-needed upon middle-of-the-night awakening.[11-23] Zaleplon may be taken either immediately prior to bedtime or after going to bed with difficulty falling asleep.[21] All of the reviewed nBH agents should not be taken with or immediately after food, which slows absorption and can potentially delay the onset of effect.[11-23]

Guideline Recommendations:

Insomnia: Several guidelines recommend cognitive behavioral therapy for insomnia (CBT-I) as the primary first-line treatment.[5,28-31] However, the American Academy of Sleep Medicine (AASM) recognizes that some patients may not benefit from CBT-I and recommends hypnotic pharmacotherapy either alone or in combination with CBT-I.[2]

Most clinical guidelines that provide guidance on agent selection recommend ramelteon, low-dose doxepin, the z-drugs (ie, zolpidem, zaleplon, and eszopiclone), and suvorexant for the treatment of chronic insomnia in adults.[2,5,28,30,31] The 2017 AASM guideline does not generally recommend one medication over another, but rather provides recommendations according to the particular insomnia subtype (onset or maintenance)[2]; it recommends the z-drugs and ramelteon for sleep onset insomnia, and eszopiclone, zolpidem, doxepin, and suvorexant for sleep maintenance insomnia, which in some cases differs from the FDA-approved indication.[2]

Across reviewed US guidelines, the strength of recommendations in favor of using these agents tends to be *weak*, signifying that the treatment approaches may not be applicable to all patients due to a lack of certainty about their appropriateness.[2,28] In such cases, treatment selection should be guided by physician clinical judgement in the context of patient preferences and values.[2,28] Nonetheless, this should not be interpreted as a lack of evidence for drug efficacy in the management of insomnia-related symptoms; nor does it imply that the recommendations are irrelevant to patient care.[2,28]

No recommendations for the use of daridorexant (approved 2022) or lemborexant (approved 2019) to treat insomnia were found in the included guidelines, as they all predate market approval of these agents.

N24SWD: Although tasimelteon was FDA-approved in 2014 for N24SWD, the 2 reviewed guidelines (2019 British Association for Psychopharmacology [BAP] and 2015 AASM) that address N24SWD do not include recommendations for or against its use.[7,13,31]

SMS: The single guideline identified for the management of patients with SMS, the Parents and Researchers Interested in Smith-Magenis Syndrome (PRISMS) 2018 guideline,[32] predates the 2020 approval of tasimelteon for use in patients with SMS and thus does not comment on its use.

Head-to-head Comparisons:

We conducted a systematic search of 3 bibliographic databases (Ovid MEDLINE, Epistemonikos, and Embase) for systematic reviews (SRs) of randomized controlled trials (RCTs) reporting head-to-head

comparisons between any agents addressed in this review. To supplement the SR searches, Ovid MEDLINE and Embase were also searched for RCTs published from 2019 to present.

In populations with insomnia, we identified the following head-to-head individual RCTs:

- A phase 3 RCT (SUNRISE 1) of lemborexant 5 and 10 mg compared to the lower dosage of extended-release (ER) zolpidem 6.25 mg in older adults (represented among 3 publications)[33-35]
- A small RCT of switching from benzodiazepines to suvorexant versus eszopiclone in patients with major depressive disorder (MDD) and benzodiazepine-resistant insomnia[36]
- Two older RCTs (published prior to 2019) of various dosages of zaleplon or eszopiclone compared to zolpidem IR in older adults or the general adult population[37,38]

No relevant head-to-head studies published since 2019 were found for tasimelteon, doxepin, daridorexant, or ramelteon versus any other agent of interest for their approved indications.

We also included safety comparisons from 4 studies in patients *without* insomnia (ie, healthy individuals, recreational sedative drug users); please refer to **page 28** for details.

Lemborexant vs zolpidem ER tablet: Evidence from SUNRISE 1, a phase 3 trial (n=1006), showed that lemborexant 5 and 10 mg is more effective than zolpidem ER (6.25 mg) for the treatment of insomnia in older adults (women ≥55 years of age; men ≥65 years of age), with statistically significant findings for the following endpoints[35]:

- Objective latency to persistent sleep (LPS) after only 1−2 nights and persisting for as long as 1 month on treatment[35]
- Objective sleep efficiency and wake-after-sleep onset (WASO) at the beginning and the end of the treatment period[35]
- Subjective sleep onset latency during the first 7 nights and at the end of the month[35]

In terms of safety, numerically more somnolence occurred in lemborexant-treated patients compared to zolpidem-treated patients (7.1% lemborexant 10 mg, 4.1% lemborexant 5 mg, 1.5% zolpidem ER),[35] with a number needed to harm (NNH) of 39 and 18 ($p<0.05$) for lemborexant 5 and 10 mg, respectively, compared to zolpidem ER.[33]

Switching from benzodiazepines to suvorexant vs eszopiclone: Suvorexant (15 or 20 mg) and eszopiclone (2 or 3 mg) performed similarly to each other for improving insomnia severity, sleep quality, and symptoms of depression and anxiety in a small RCT (n=18) of patients with benzodiazepine-unresponsive insomnia and MDD.[36]

In terms of drug-specific adverse events, unpleasant taste was reported only in eszopiclone-treated patients, with no reports occurring in suvorexant-treated patients (4 vs 0, respectively).[36]

Zaleplon vs zolpidem IR tablet: Our previous 2019 P&T report[1] included two meta-analyses[39,40] that showed sleep onset latency significantly improved with zolpidem 10 mg compared to the lower-end dosage of zaleplon (5 mg).[39,40] A separate short-duration RCT (n=549) that was not included in either meta-analyses showed that zaleplon 10 mg (but not 5 mg) improved subjective sleep latency compared to the lower-end dosage of zolpidem (5 mg) in older adults (≥65 years of age).[38] However, subjective total sleep time (TST) significantly improved with zolpidem 5 mg compared to zaleplon 5 mg.[38]

In terms of safety, the incidence of somnolence was numerically higher with zolpidem 5 mg versus zaleplon 5 mg (10% vs 4%, respectively); the incidence of somnolence with zaleplon 10 mg was not reported.[38]

Eszopiclone vs zolpidem IR tablet (n=65): Zolpidem 10 mg was more effective than eszopiclone 1 mg at improving LPS and sleep efficiency in adults with insomnia.[37] A dose-response relationship was observed with higher doses of eszopiclone (eg, 2−3 mg), resulting in comparable efficacy to zolpidem 10 mg.[37]

Rates of unpleasant taste were reported more frequently in eszopiclone-treated patients, whereas rates of dizziness and hallucinations were higher in patients treated with zolpidem.[37] Overall, central nervous system (CNS)-related adverse events were reported more frequently in the zolpidem arm (23.4%) compared to eszopiclone (6.2–12.5%, depending on the dose).[37]

Safety warnings and precautions:

Label warnings and precautions for the z-drugs, doxepin, ramelteon, and ORAs include the following[11,12,14-23]:

- Recommendation to re-evaluate for potential comorbid conditions if insomnia fails to remit after 7–10 days on pharmacotherapy
- Recommendation to evaluate for worsening depression or suicidal ideation
- Elevated risk of next-day impairment, especially when used in combination with CNS depressants (eg, opioids, alcohol, benzodiazepines)
- Elevated risk of complex sleep behaviors (eg, sleep-driving, sleep walking)

While the development of complex sleep behaviors is included as a label warning for most of the reviewed agents,[11,12,14-23] only the z-drugs have it listed as a **black box warning**.[14-18,20,21] Only the z-drugs also carry a warning for the possibility of withdrawal symptoms, which may occur upon drug discontinuation or rapid dose reductions.[14-18,20,21] Doxepin, ramelteon, tasimelteon, and the ORAs do not carry warnings for withdrawal effects and do not appear to induce physical dependence; however, of these, the ORAs are known to have abuse potential.[11-13,19,22,23] The z-drugs and ORAs are classified as Schedule IV controlled substances.[11-23]

The z-drugs, doxepin, and ramelteon have a warning for the potential development of behavioral changes (eg, decreased inhibition, depersonalization, agitation, hallucinations) and abnormal thinking.[14-18,20-23] Unique drug warnings include (1) the potential risk of sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms (with ORAs)[11,12,19]; and (2) the potential risk of altered reproductive hormone concentrations (with ramelteon).[23]

Tasimelteon carries a warning only for the risk of somnolence following administration.[13]

Summary:

No direct head-to-head evidence was found for tasimelteon, doxepin, daridorexant, or ramelteon versus any other agent of interest for their approved indications. For the comparison of lemborexant versus zolpidem, there is evidence from only 1 RCT (SUNRISE 1), which showed greater improvements in objective LPS, sleep efficiency, WASO, and subjective sleep onset latency with lemborexant 5 and 10 mg compared to zolpidem ER 6.25 mg in older adults with insomnia.[35] Nonetheless, it is unclear if the effect differences would be observed in younger adults with insomnia or with respect to other approved

dosages of zolpidem. A few efficacy differences between zolpidem versus zaleplon or eszopiclone were demonstrated when comparing low- to high-end dosages, but for the most part, agents performed similarly when comparing matched-end dosages (eg, low- vs low-end or high- vs high-end).[37,38] The exception was a single short-term study showing that zolpidem 5 mg was superior to zaleplon 5 mg for improving subjective TST at weeks 1 and 2 of treatment in elderly adults with insomnia.[38] No significant efficacy differences were reported among other nBH comparisons in RCTs of patients with insomnia.[36]

The safety profile of the reviewed nBH agents varies generally based on drug class.

Most clinical guidelines that provide guidance on agent selection recommend ramelteon, low-dose doxepin, the z-drugs (ie, zolpidem, zaleplon, and eszopiclone), and suvorexant for the treatment of chronic insomnia in adults[2,5,28,30,31]; however, the strength of recommendations in favor of using these agents tends to be weak across reviewed US guidelines.[2,28] The 2017 AASM guideline does not generally recommend one medication over another, but rather provides recommendations according to the particular insomnia subtype (onset or maintenance)[2]; it recommends the z-drugs and ramelteon for sleep onset insomnia, and eszopiclone, zolpidem, doxepin, and suvorexant for sleep maintenance insomnia, which in some cases differs from the FDA-approved indication.[2] The reviewed guidelines predate the regulatory approval of the newer ORAs, lemborexant and daridorexant, and the approval of tasimelteon for SMS. Notably, tasimelteon is *not* approved for insomnia. It is approved for patients ages 3 to 15 years (Hetlioz LQ) and patients 16 years of age and older (Hetlioz) with SMS-related sleep disturbances, and for adults with N24SWD (Hetlioz).[13] Clinical guidelines for N24SWD do not include recommendations for or against tasimelteon's use,[7,31] and the one guideline identified for SMS predated tasimelteon's approval within this patient population.[32]

Utah Medicaid Preferred Drug List (PDL) Considerations:

Regarding the Utah Medicaid PDL, the P&T Committee may consider the following recommendations:

A. Reaffirmation of our previous 2019 P&T board recommendation to have at least 1 hypnotic preferred for sleep onset insomnia and at least 1 agent preferred for sleep maintenance insomnia
B. Consider including at least 1 non-controlled hypnotic as preferred for sleep onset or sleep maintenance insomnia
    i. The z-drugs and ORAs are classified as Schedule IV controlled substances due to the potential increased risk of abuse.[11,12,14-21]
    ii. Ramelteon and doxepin are both non-controlled substances[22,23]; however, ramelteon is approved only for sleep onset insomnia in adults,[23] whereas low-dose doxepin formulations (6 mg or less; brand Silenor) are approved for sleep maintenance insomnia in adults.[22]
    iii. Higher strength formulations of doxepin (≥10 mg) are not approved for insomnia.[41]

1.0 INTRODUCTION

Insomnia is a common sleep disorder in the United States (US) with approximately 30−50% of the population affected with occasional short-term insomnia, and ≥5−10% of the population suffering from chronic insomnia (persistent symptoms for ≥3 months, with an occurrence of ≥3 times per week).[2,42] Insomnia is characterized as trouble initiating or maintaining sleep, or the inability to go back to sleep upon premature awakening that results in symptoms while awake.[2,4,28,43] Clinical manifestations during wakefulness consist of tiredness/fatigue, irritability, mood fluctuations, and difficulties with attention or cognition.[4] Insomnia may occur independently, or comorbidly with other conditions (eg, sleep apnea, anxiety, depression, chronic pain).[4,5]

The scope of this review consists of 9 non-benzodiazepine, non-barbiturate hypnotic (nBH) agents from various drug classes, including their unique formulations.[11-23] Recently-approved agents include the 2 oral orexin receptor antagonists (ORAs): lemborexant (Dayvigo) and daridorexant (Quviviq).[11,12] Older oral agents include the z-drugs: eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist); low-dose doxepin (Silenor), an H_1- antihistamine antidepressant; suvorexant (Belsomra), an ORA; and the melatonin receptor antagonists: ramelteon (Rozerem) and tasimelteon (Hetlioz).[13-23] The z-drugs and ORAs are classified as Schedule IV controlled substances due to the known risk of abuse.[11-23] Zolpidem is available in a variety of formulations: sublingual tablet, immediate-release (IR) tablet, controlled-release tablet, and oral spray.[14-18] The remaining products approved for insomnia are available as a single oral formulation.[11,12,19-23] All of these agents except tasimelteon are FDA-approved for the treatment of insomnia in adults, but the indication varies according to the insomnia subtype (ie, sleep onset and/or sleep maintenance) and may differ between formulations of the same active ingredient.[11-23] All of the nBH agents indicated for insomnia are approved for sleep onset insomnia, except doxepin.[11,12,14-23] The ORAs, low-dose doxepin, controlled-release zolpidem (Ambien CR), and eszopiclone are approved for sleep maintenance insomnia.[11,12,15,19,20,22] Unlike other hypnotics, a sublingual formulation of zolpidem, Intermezzo, is uniquely indicated for trouble falling back asleep after awakening in the middle of the night.[17]

Tasimelteon was approved in 2014 as an oral capsule for the rare sleep disorder, non-24 hour sleep-wake disorder (N24SWD) in adults.[13] In December 2021, the FDA approved tasimelteon, as an oral capsule, for the treatment of nighttime sleep disturbances related to a rare neurodevelopmental disorder, Smith-Magenis Syndrome (SMS) in patients 16 years of age and older, and an oral suspension (Hetlioz LQ) for children ages 3 to 15 years.[13,27] Notably, tasimelteon is *not* approved for insomnia. The FDA-approved indications for the nBH agents according to sleep disorder and/or insomnia subtype are summarized in **Table 1**.

Table 1. FDA-Approved Indications Based on Sleep Disorder and/or Insomnia Subtype[1]

Medication	Sleep Maintenance Insomnia	Sleep Onset Insomnia	Other
Z-Drugs			
Eszopiclone	✓	✓	
Zaleplon		✓	
Zolpidem	✓ for Ambien CR	✓ for Ambien, Ambien CR, Edluar, Zolpimist	✓ for Intermezzo- trouble retuning to sleep after awakening in the night[a]; as-needed
H_1-Antihistamine Antidepressant			
Doxepin	✓		
Orexin Receptor Antagonists			
Suvorexant	✓	✓	
Lemborexant	✓	✓	
Daridorexant	✓	✓	
Melatonin Receptor Agonists			
Ramelteon		✓	
Tasimelteon[b]			✓ N24SWD ✓ Nighttime sleep disturbances in SMS

Abbreviations: CR, controlled-release; FDA, Food and Drug Administrations; N24SWD, Non-24 hour sleep-wake disorder; SMS, Smith-Magenis Syndrome

[a] *Indicated for when there is ≥4 hours of bedtime remaining before the anticipated wake-up time*

[b] *Indicated for use in adults with N24SWD, and for the treatment of nighttime sleep disturbances related to SMS in patients 3 years of age and older (formulation is specific to age)*

The recommended dose, including initial dosage for some of these agents varies by age and/or sex. For example, labeling for zolpidem products (eg, Edluar, Zolpimist, Ambien) recommend a lower initiation dose for women due to the decreased clearance of the drug relative to men.[14-18] Drug exposure to suvorexant is increased in women compared to men, and among obese patients requiring additional consideration when increasing the dose, especially in obese women.[19] Although the suvorexant prescribing information does not recommended an initial lower dose for women, a variety of dosage strengths are available allowing clinicians to have the flexibility to use a lower initiation dose.[19] For older adults (≥65 years of age), a lower initial dose of doxepin is recommended,[22] and the maximum recommended doses are reduced for the z-drugs (ie, zaleplon, zolpidem, and eszopiclone).[14-18,20,21]

In terms of administration, all of these agents are taken orally once per night, before bedtime, except Intermezzo which is used as-needed upon middle-of-the-night awakening.[11-23] Eszopiclone, zolpidem, and lemborexant should be taken immediately before bedtime, with at least 7 hours of expected sleep remaining.[11,14-18,20] Zaleplon may be taken either immediately prior to bedtime or after going to bed with difficulty falling asleep.[21] Ramelteon, doxepin, suvorexant, and daridorexant should be taken within 30 minutes prior to bedtime, with the ORAs requiring at least 7 hours of anticipated sleep.[12,19,22,23] Either formulation of tasimelteon (ie, capsule or suspension) should be taken one hour prior to bedtime, at the

same time each night.[13] All of the agents should not be taken with or immediately after food, which slows absorption and can potentially delay the onset of effect.[11-23]

A research objective of this report is to ascertain whether there is new head-to-head evidence comparing the effects of the 9 hypnotics in **Table 2** for their approved indications since our previous Pharmacy and Therapeutics (P&T) report on these agents, which was completed in 2019.[1] The Utah Medicaid Preferred Drug List (PDL), published August 1, 2022, includes the following products as preferred within the nBH drug class: eszopiclone (generic), ramelteon (brand Rozerem), zaleplon (generic), zolpidem tablet (generic), and zolpidem CR (generic).[44] Non-preferred products are zolpidem (brand Ambien, Ambien CR, Edluar, Zolpimist, Intermezzo), suvorexant (brand Belsomra), lemborexant (brand Dayvigo), daridorexant (brand Quviviq), doxepin tablet (generic and brand Silenor), tasimelteon (brand Hetlioz), ramelteon (generic), and eszopiclone (brand Lunesta).[44] Of note, the formulation of doxepin as the higher strength capsules (10–150 mg) and the oral concentrate are approved for depression, but not insomnia,[41] and are listed as preferred under the antidepressant drug class on the PDL.[44] The approved indication of Silenor (low-dose doxepin) is not interchangeable with the higher-dose generic capsules/concentrate.

Table 2 provides details for the approved indications, dosing recommendations, and available formulations for the nBH agents.

Table 2. FDA-Approved Sedative Hypnotics (Non-benzodiazepines, Non-barbituarates)[1,45]

Generic Name **Brand** (approval year) and Preparation **Controlled substance class**	**Labeled Indication & Dosing Recommendations**
Z-Drugs	
Eszopiclone **Lunesta**[20] (2004) Film-Coated Oral Tablet: 1 mg, 2 mg, 3 mg **Class IV CS**	Indicated for the treatment of insomnia. Reduced sleep latency and improved sleep maintenance in clinical studies (duration of clinical studies: ≤6 months) Dosing: • Adults: Start at 1 mg PO once daily, dose may be increased to 2 or 3 mg PO once daily if lower dose is ineffective, but may increase the likelihood of next-day impairment • Max dose: 3 mg PO once daily • Adults (≥65 years), disabled patients, severe liver dysfunction, or concomitant use with potent CYP3A4 inhibitors (max dose): 2 mg PO once daily Take immediately prior to bedtime, with ≥7–8 hours of sleep prior to planned wake-up time. Avoid taking with or right after a high-fat meal.
Zaleplon **Sonata**[21] (1999) Oral Capsule: 5 mg, 10 mg **Class IV CS**	Indicated for insomnia, short-term. Reduced sleep onset in clinical studies (duration of clinical studies: ≤30 days) Dosing: • Adults: Start at 10 mg PO once daily; for underweight individuals, 5 mg PO daily should be considered. Dose may be increased to 20 mg PO daily if lower dose is ineffective • Max dose: 20 mg PO once daily • Adults (≥65 years), disabled patients, mild to moderate liver impairment: Start at 5 mg PO once daily; doses greater than 10 mg are not recommended. Avoid use in those with severe liver impairment Take immediately prior to bedtime, or after going to bed with difficulty falling asleep. Avoid taking with or right after a high-fat meal.

Zolpidem tartrate
 	
Ambien[14] (1999)
Film-Coated Oral Tablet: 5 mg, 10 mg
Class IV CS
	Indicated for insomnia characterized as trouble initiating sleep, short-term (duration of clinical studies: 4–5 weeks)
	Dosing:
	• Adults: Dose may be titrated up to 10 mg PO once daily if the lower dose is ineffective, but may increase the likelihood of next-day impairment
	  ○ Women: Initiate at 5 mg PO once daily due to the lower clearance of the drug
	  ○ Men: Initiate at 5 or 10 mg PO once daily

Abbreviations: CR, controlled-release; CS, controlled substance; CYP, cytochrome; N24SWD, Non-24 hour sleep-wake disorder; PO, by mouth; SMS, Smith-Magenis Syndrome

Table 2. FDA-Approved Sedative Hypnotics (Non-benzodiazepines, Non-barbituarates)[1,45]

Generic Name **Brand** (approval year) and Preparation **Controlled substance class**	**Labeled Indication & Dosing Recommendations**
	• Max dose: 10 mg PO once daily • Adults (≥65 years), disabled patients, mild to moderate liver impairment: 5 mg PO once daily is the recommended dose (regardless of sex). Avoid use in those with severe liver impairment Take immediately prior to bedtime, with ≥7–8 hours of sleep prior to planned wake-up time. Do not administer more than once during a single night. Avoid taking with or right after a high-fat meal.

Zolpidem tartrate
 	
Ambien CR[15] (2005)
Oral Extended-Release Tablet:
6.25 mg, 12.5 mg
Class IV CS
	Indicated for sleep maintenance and/or sleep onset insomnia, short-term (duration of clinical studies: ≤24 weeks)
	Dosing:
	• Adults: Dose may be titrated up to 12.5 mg PO once daily if the lower dose is ineffective, but may increase the likelihood of next-day impairment
	  ○ Women: Initiate at 6.25 mg PO once daily due to the lower clearance of the drug
	  ○ Men: Initiate at 6.25 or 12.5 mg PO once daily
	• Max dose: 12.5 mg PO once daily
	• Adults (≥65 years), disabled patients, mild to moderate liver impairment: 6.25 mg PO once daily is the recommended dose (regardless of sex). Avoid use in those with severe liver impairment
	Take immediately prior to bedtime, with ≥7–8 hours of sleep prior to planned wake-up time. Avoid taking with or right after a high-fat meal.

Zolpidem tartrate
 	
Edluar[16] (2009)
Sublingual Tablet:
5 mg, 10 mg
Class IV CS
	Indicated for insomnia characterized as trouble initiating sleep, short-term (duration of clinical studies: 4–5 weeks)
	Dosing:
	• Adults: Dose may be titrated up to 10 mg PO once daily if the lower dose is ineffective, but may increase the likelihood of next-day impairment
	  ○ Women: Initiate at 5 mg PO once daily due to the lower clearance of the drug
	  ○ Men: Initiate at 5 or 10 mg PO once daily
	• Max dose: 10 mg PO once daily
	• Adults (≥65 years), disabled patients, liver impairment: 5 mg PO once daily is the recommended dose (regardless of sex)
	Take immediately prior to bedtime, with ≥7–8 hours of sleep prior to planned wake-up time. Sublingual tablet(s) should be placed under the tongue and allowed to fully dissolve. The tablet(s) should not be swallowed, or taken with water. Avoid taking with or right after a high-fat meal.

Abbreviations: CR, controlled-release; CS, controlled substance; CYP, cytochrome; N24SWD, Non-24 hour sleep-wake disorder; PO, by mouth; SMS, Smith-Magenis Syndrome

Table 2. FDA-Approved Sedative Hypnotics (Non-benzodiazepines, Non-barbituarates)[1,45]

Generic Name **Brand** (approval year) and Preparation **Controlled substance class**	**Labeled Indication & Dosing Recommendations**

Zolpidem tartrate
 	
Intermezzo[17] (2011)
Sublingual Tablet:
1.75 mg, 3.5 mg
Class IV CS
	Indicated for as-needed use for insomnia characterized as trouble falling back asleep after awakening in the night when there is ≥4 hours of sleep prior to planned wake-up time
	Dosing:
	• Adults:
	  ○ Women (recommended and max dose): 1.75 mg PO once daily as needed
	  ○ Men (recommended and max dose): 3.5 mg PO once daily as needed
	• Adults (≥65 years), liver impairment: 1.75 PO once daily at night as needed is the recommended dose (regardless of sex)
	Take when there is ≥4 hours of sleep prior to planned wake-up time to help with returning to sleep after awakening in the night. Sublingual tablet(s) should be placed under the tongue and allowed to fully dissolve. The tablet(s) should not be swallowed, or taken with water. Avoid taking with or right after a high-fat meal.

Zolpidem tartrate
 	
Zolpimist[18] (2008)
5 mg/actuation Oral Spray; supplied as: 30 sprays/4.5 mL or 60 sprays/7.7 mL
Class IV CS
	Indicated for insomnia characterized as trouble initiating sleep, short-term (duration of clinical studies: 4–5 weeks)
	Dosing:
	• Adults: Dose may be titrated up to 2 sprays (10 mg) PO once per night if the lower dose is ineffective, but may increase the likelihood of next-day impairment
	  ○ Women: Initiate at 1 spray (5 mg) PO once daily due to the lower clearance of the drug
	  ○ Men: Initiate at 1 or 2 sprays (5 or 10 mg) PO once daily
	• Max dose: 2 sprays (10 mg) PO once daily
	• Adults (≥65 years), disabled patients, liver impairment: 1 spray (5 mg) PO once daily is the recommended dose (regardless of sex)
	Take immediately prior to bedtime, with ≥7–8 hours of sleep prior to planned wake-up time. Use during the middle of the night is not recommended. Avoid taking with or right after a high-fat meal.

H_1-Antihistamine Antidepressant	
Doxepin **Silenor**[22] (1969)	Indicated for sleep maintenance insomnia (duration of clinical studies: ≤3 months) Dosing: • Adults: 3 to 6 mg PO once daily is the recommended dose • Max dose: 6 mg PO once daily

Abbreviations: CR, controlled-release; CS, controlled substance; CYP, cytochrome; N24SWD, Non-24 hour sleep-wake disorder; PO, by mouth; SMS, Smith-Magenis Syndrome

Table 2. FDA-Approved Sedative Hypnotics (Non-benzodiazepines, Non-barbituarates)[1,45]

Generic Name **Brand** (approval year) and Preparation **Controlled substance class**	**Labeled Indication & Dosing Recommendations**
Immediate-Release Oral Tablet: 3 mg, 6 mg	• Adults (≥65 years): Initiate at 3 mg PO once daily; dose may be titrated up to 6 mg PO once daily if the lower dose is ineffective Take within 30 minutes prior to bedtime. To minimize the chance of next-day impairment, avoid taking within 3 hours of eating food.
Orexin Receptor Antagonists	
Suvorexant **Belsomra**[19] (2014) Film-Coated Oral Tablet: 5 mg, 10 mg, 15 mg, 20 mg **Class IV CS**	Indicated for sleep maintenance and/or sleep onset insomnia Dosing: • Adults (including those ≥65 years of age): Initiate at 10 mg PO once daily; dose may be titrated up to 20 mg PO once daily if the lower dose is ineffective, but well-tolerated. • Max dose: 20 mg PO once daily • Moderate CYP3A inhibitors: Initiate at 5 mg PO once daily; dose should not exceed 10 mg PO once daily. Avoid use with strong CYP3A inhibitors • Women and obese patients: Drug exposure is increased; consider the risk before increasing the dose, particularly in obese women Take within 30 minutes prior to bedtime, with ≥7 hours of sleep prior to planned wake-up time. Do not administer more than once during a single night. Avoid taking with or immediately after a meal.
Lemborexant **Dayvigo**[11] (2019) Film-Coated Oral Tablet: 5 mg, 10 mg **Class IV CS**	Indicated for sleep maintenance and/or sleep onset insomnia Dosing: • Adults (including those ≥65 years of age): Initiate at 5 mg PO once daily; dose may be titrated up to 10 mg PO once daily if the lower dose is ineffective, but well-tolerated. • Max dose: 10 mg PO once daily • Moderate liver impairment (initiation and max dose): 5 mg PO once daily. Avoid use in those with severe liver impairment, and individuals taking strong or moderate CYP3A inhibitors and/or inducers Take immediately prior to bedtime, with ≥7 hours of sleep prior to planned wake-up time. Do not administer more than once during a single night. Avoid taking with or immediately after a meal.
Daridorexant	Indicated for sleep maintenance and/or sleep onset insomnia

Abbreviations: CR, controlled-release; CS, controlled substance; CYP, cytochrome; N24SWD, Non-24 hour sleep-wake disorder; PO, by mouth; SMS, Smith-Magenis Syndrome

Table 2. FDA-Approved Sedative Hypnotics (Non-benzodiazepines, Non-barbituarates)[1,45]

Generic Name **Brand** (approval year) and Preparation **Controlled substance class**	**Labeled Indication & Dosing Recommendations**
Quviviq[12] (2022) Film-Coated Oral Tablet: 25 mg, 50 mg **Class IV CS**	Dosing: • Adults (including those ≥65 years of age): Initiate at 25 or 50 mg PO once daily • Max dose: 50 mg PO once daily • Moderate liver impairment, moderate CYP3A4 inhibitors (max dose): 25 mg PO once daily. Avoid use in those with severe liver impairment, and individuals taking strong CYP3A4 inhibitors, and/or moderate or strong CYP3A4 inducers Take within 30 minutes prior to bedtime , with ≥7 hours of sleep prior to planned wake-up time. Do not administer more than once during a single night. Avoid taking with or immediately after a meal.
Melatonin Receptor Agonists	
Ramelteon **Rozerem**[23] (2005) Film-Coated Oral Tablet: 8 mg	Indicated for sleep onset insomnia (duration of clinical studies: ≤6 months) Dosing: • Adults (including those ≥65 years of age): 8 mg PO once daily • Max dose: 8 mg PO once daily • Avoid use in individuals with severe liver impairment, and use *cautiously* in those with moderate liver impairment. Furthermore, combination use should be avoided with fluvoxamine, and *cautiously* used in individuals taking other CYP1A2 inhibitors Take within 30 minutes prior to bedtime; avoid taking with or immediately after a high-fat meal.
Tasimelteon **Hetlioz**[13] (2014) Oral Capsule: 20 mg Oral Suspension [**Hetlioz LQ**]: 4 mg/mL; supplied in 48 mL or 158 mL bottles	Capsules are indicated for: • N24SWD in adults • Nighttime sleep disturbances in SMS for individuals ≥16 years of age Oral suspension is indicated *only* for nighttime sleep disturbances in SMS for children aged 3–15 years Dosing: • Capsules: 20 mg PO once daily • Oral suspension: The recommended dose varies by body weight (≤28 kg is 0.7 mg/kg; >28 kg is 20 mg) Avoid using either formulation with strong CYP1A2 inhibitors (eg, fluvoxamine) and/or strong CYP3A4 inhibitors (eg, rifampin) Both formulations: Take one hour prior to bed without food, administration should occur around the same time each day.

Abbreviations: CR, controlled-release; CS, controlled substance; CYP, cytochrome; N24SWD, Non-24 hour sleep-wake disorder; PO, by mouth; SMS, Smith-Magenis Syndrome

2.0 METHODS

2.1 Systematic Literature Search

Search strategies, comprising of keyword phrases and controlled vocabulary (eg, Medical Subject Headings [MeSH] terms, Emtree terms), were updated from our 2019 P&T report on nBH agents[1] for systematic reviews (SRs) of randomized controlled trials (RCTs) in 3 bibliographic databases (Ovid MEDLINE, Epistemonikos, and Embase). Databases were searched from January 2019 to June 24th, July 1st, and July 7th of 2022, respectively. Refer to **Appendix A** for the complete search strategies. To identify SRs of RCTs in Ovid MEDLINE, a McMaster University filter[46] and a combination of independently derived filters were used. An independently derived SR filter was used in Embase and the website-imbedded filter for publication type was used in Epistemonikos. To supplement the SR searches, Ovid MEDLINE and Embase were also searched for RCTs from January 2019 to July 11th and July 14th of 2022, respectively. Publication filters for RCTs from the Cochrane Collaboration Handbook were used in Ovid-Medline and Embase.[47] For Embase searches, conference abstracts were excluded and the language was restricted to English.

Product prescribing information (ie, package inserts) was searched on drug sponsor websites, DailyMed (https://dailymed.nlm.nih.gov/dailymed/), and/or the Drugs@FDA website (https://www.accessdata.fda.gov/scripts/cder/daf/).

Our previous 2019 P&T report on this drug class was also referred to for relevant guidelines and head-to-head comparison information.[1]

We also screened reference lists of related SRs and other relevant websites for additional information:

- For recent guidelines published in 2016 and onward addressing the treatment of insomnia, N24SWD, and SMS, we searched the following organizational websites: American Academy of Sleep Medicine (AASM), American College of Physicians (ACP), Veterans Affairs/Department of Defense (VA/DoD), British Association for Psychopharmacology (BAP), European Sleep Research Society (ESRS), ECRI Guidelines Trust, Parents and Researchers Interested in Smith-Magenis Syndrome (PRISMS), Institute for Clinical and Economic Review (ICER), and the National Institute for Health and Care Excellence (NICE)
- Evidence-based drug information databases: UpToDate and Lexicomp

Guidelines were excluded if they met one or more of the following criteria:

1. Published within countries other than the US or Europe
2. Only addresses other sleep disorders (eg, circadian rhythm disorders, nightmare disorder, parasomnias, narcolepsy)
3. Only addresses the deprescribing of pharmacotherapies used to treat insomnia

2.2 Screening

To assess eligibility for inclusion, publication titles and abstracts were screened independently by two reviewers. Conflicts were resolved by consensus between reviewers. For citations that received 2 votes for inclusion, the full text was retrieved. Upon reviewing the full text, the final determination for

inclusion was made by the lead author. Only one reviewer screened potential references identified from article bibliographies, and organizational websites for inclusion. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart (**Figure 1**) for the literature screening process is provided in **Appendix B**.

2.3 Inclusion and Exclusion Criteria

Systematic review meta-analyses (SRMAs) of RCTs, and/or individual RCTs that included direct head-to-head efficacy comparisons among the agents listed in **Table 2,** for their respective approved indications were included. For studies including patients without a diagnosed FDA-approved indication for these agents, we extracted comparative safety-related outcomes only. Excluded references met one or more of the following criteria:

1. Review articles that did not use a SR methodology
2. RCTs with a placebo comparison only or included an active comparator other than the agents of interest
3. RCTs that included a placebo and active comparator, but did not report a statistical comparison between active agents of interest and did not provide confidence intervals for the placebo comparisons of each active arm
4. Network meta-analyses (NMAs) with only indirect comparisons
5. Observational studies, pharmacokinetic studies, or post-hoc exploratory or subgroup analyses studies

3.0 DISEASE OVERVIEW

3.1 Insomnia

The International Classification of Sleep Disorders, Third Edition (ICSD-3) defines insomnia as trouble initiating or maintaining sleep that results in symptoms while awake, and occurs despite a suitable sleep environment and adequate opportunity to sleep.[2,3] Insomnia is characteristically distinct from other sleep disorders (eg, circadian rhythm sleep-wake disorders, parasomnias, narcolepsy, sleep-related breathing disorders).[3] Usually, acute insomnia (symptom duration of <3 months) is caused by a discernible stressor (eg, divorce, work-related stress, employment status), and resolves once the stressor subsides.[30] Chronic insomnia is symptoms that persist for ≥3 times per week for at least 3 months.[2,4] The persistence of insomnia symptoms may be attributed to anxiety related to sleep, poor sleep habits, and potential issues in physiologic sleep-regulating processes.[31] Precipitating factors also include pain-inflicting diseases (eg, arthritis, cancer), or comorbid psychiatric disorders (eg, depression, anxiety).[31]

Occasional acute insomnia affects an estimated 30−50% of the population, whereas the prevalence of insomnia as a chronic condition is approximately ≥5−10% of the population.[2] Chronic insomnia can drastically impact a patient's health-related quality of life and socio-occupational function.[2] Chronic insomnia has been associated with the development of hypertension, cardiovascular disease, type 2 diabetes, and depression.[2,31,48] Symptoms of insomnia include fatigue, irritability, mood fluctuations, and difficulties with attention or cognition that may result in negative consequences (eg, work-related

absence, higher chance of errors/accidents, routine medical visits),[2,4,49] contributing to a significant economic burden with costs estimated to exceed $100 billion annually in the US.[31]

Although, insomnia frequently occurs with other somatic or psychiatric disorders such as chronic pain, anxiety, or sleep apnea,[4,30,50] treatment of such disorders may not always resolve co-occurring insomnia. To recognize insomnia as an independent condition that warrants treatment, the ICSD-3 updated the nosology of insomnia, merging former definitions of primary and secondary (ie, comorbid) insomnia into the classification of chronic insomnia disorder.[3,4,50,51]

Diagnosis of chronic insomnia is purely by clinical evaluation and does not require laboratory assessments, although certain tests (eg, thyroid function tests, blood glucose) may be used when other comorbidities are suspected.[52] Clinical evaluation includes consideration of the patient's sleep patterns, mental health, and medical history.[28,30] Objective measures of sleep (eg, polysomnography [PSG]) often underrepresent subjective reports of sleep difficulty expressed by patients suffering with chronic insomnia.[28] Thus, PSG is not routinely recommended for diagnosis of chronic insomnia,[4,52] but may be indicated when certain comorbid sleep disorders are suspected (eg, sleep-related movement disorders, sleep apnea) or in the case of treatment-resistant insomnia.[53] **Table 3** outlines the ICSD-3 criteria for diagnosing chronic insomnia based on the patient's symptomatology.

Table 3. ICSD-3 Clinical Diagnostic Criteria for Chronic Insomnia[4]

Patient must have at least one symptom from each category below (related to sleep and while awake) occurring 3 times a week or more for at least 3 months to be diagnosed with chronic insomnia • **Symptoms related to sleep:** trouble initiating or maintaining sleep, awakening earlier than desired, reluctant to maintain a suitable sleep schedule, require the involvement of the parent or caregiver in order to sleep • **Symptoms that occur while awake:** tiredness/fatigue, cognition or attention problems, behavioral concerns, reduced family, social, or academic performance, irritability/alterations in mood, diminished motivation or energy, accident/error prone, dissatisfied with the quality/quantity of sleep or express sleep-related concerns

Abbreviations: ICSD-3, International Classification of Sleep Disorders, Third Edition

The goal of treating insomnia is to improve the quality and quantity of sleep, functionality while awake, and alleviate any insomnia-related psychological or physical distress.[5,54]

3.2 Non-24 Hour Sleep-Wake Disorder (N24SWD)

N24SWD occurs when an individual is unable to maintain entrainment between their endogenous circadian clock and the 24-hour environment, often due the inability to perceive light, a key entrainment cue.[6-8] Thus, N24SWD often occurs in blind individuals (up to 63% of cases) that have alternations in their photoreceptive capabilities, but the disorder has been reported among individuals with sight.[6-8] Complete blindness occurs gradually, and may be due to congenital defects, trauma-induced, or certain conditions such as glaucoma, diabetic retinopathy, and retinitis pigmentosa.[55] According to the ICSD-3, N24SWD is categorized under Circadian Rhythm Sleep-Wake Disorders (CRSWD),[3] and requires fulfilling the following criteria to be diagnosed[7,8]:

- A history of alternating periods of a sleep disturbance (ie, insomnia, excessive tiredness) and being asymptomatic
- Symptoms persisting for ≥3 months

- An observable gradual pattern of shifting sleep-wake times for ≥14 days (preferably a longer duration for those that are blind) using actigraphy and/or daily sleep journals
- Sleep disturbance is not likely attributed to another condition or pharmacologic agent

3.3 Smith-Magenis Syndrome (SMS)

SMS is a rare, genetic neurodevelopmental disorder that results from chromosome 17p11.2 microdeletion (90% of cases) or mutations in the *RAI1* gene (10% of cases).[9,10,56] The estimated global prevalence is 1 in 25,000 people, but the actual prevalence may be closer to 1 in 15,000 due to underdiagnosis.[9,10] SMS is often characterized by developmental and intellectual disabilities, behavioral issues (eg, self-harm, hostility, attention-seeking, temper tantrums) and dysmorphic physical characteristics that become more distinct with age (eg, midface hypoplasia, brachycephaly).[9,10,56] Furthermore, behavioral issues may coincide with insufficient sleep due to the frequent nighttime awakenings, premature awakenings, and excessive tiredness promoting inappropriate napping during daytime hours (sleep attacks).[10,56] An estimated 65−100% of individuals affected with SMS experience sleep disturbances,[56] potentially due to the inversion of endogenous melatonin production, along with other unknown factors contributing to altered sleep architecture associated with the disorder.[9,10] Sleep disturbances are often identified in early childhood (even during infancy), and continue to persist into adulthood.[10,32] The clinical suspicion of SMS is often determined by characteristic presentation, but is confirmed with genetic testing (eg, chromosome microarray analysis).[9,10,56]

4.0 CLINICAL PRACTICE GUIDELINE RECOMMENDATIONS

4.1 Insomnia

Guidelines published within the past 5 years regarding pharmacotherapy for chronic insomnia in adults include the 2017 guideline by the American Academy of Sleep Medicine (AASM), the 2016 guideline by the American College of Physicians (ACP), the 2019 guideline by the Veterans Affairs/Department of Defense (VA/DoD), the 2019 guideline by the British Association for Psychopharmacology (BAP), and the 2017 guideline by the European Sleep Research Society (ESRS).[2,5,28,30,31] These guidelines predate regulatory approval of the newer ORAs, lemborexant and daridorexant, so these agents are not included in guideline recommendations.[2,5,28,30,31] The 2017 AASM guideline does not generally recommend one medication over another, but rather provides recommendations according to the particular insomnia subtype (onset or maintenance).[2] ACP (2016) does not provide drug-specific recommendations, but instead provides an overview of the benefits and harms of pharmacotherapies, and clinical considerations.[5] Additionally, AASM published a 2021 guideline addressing only behavioral and psychological interventions for the treatment of chronic insomnia.[29]

For adults with chronic insomnia, cognitive behavioral therapy for insomnia (CBT-I) is recommended as the primary first-line treatment.[5,28-31] After a trial of CBT-I, or in the case of insufficient response or inability to participate in CBT-I due to accessibility or other barriers (eg, affordability), short-term pharmacotherapy is recommended.[2,5,28,30,31] However, AASM (2017) recognizes that some patients may not benefit from CBT-I and recommends hypnotic pharmacotherapy either alone or in combination with CBT-I.[2]

When deciding to initiate pharmacotherapy for insomnia, numerous factors are considered including the patient's sleep patterns, psychiatric and medical history, sleep-related symptoms, substance-use disorders, treatment accessibility, potential sleep-hindering pharmacotherapies, contraindications, and patient preferences.[2,28] Drug-specific factors that are considered when selecting a pharmacologic agent include pharmacokinetic characteristics (eg, duration of action), risk of adverse effects, effectiveness, and the patient's response to prior treatments.[2,31] The therapeutic indication of the selected pharmacologic agent should correspond to the symptoms expressed by the patient (ie, sleep maintenance or sleep onset).

The 2017 AASM guideline provides recommendations according to the insomnia subtype (ie, sleep maintenance or sleep onset), which in some cases differs from the FDA-approved indication. For example, suvorexant is FDA-approved for sleep maintenance and/or sleep onset, but the 2017 AASM guideline recommends this medication only for sleep maintenance because sleep onset significantly improved with only the highest dose (20 mg) compared to placebo in clinical trials.[2] In addition, the product labeling for zolpidem IR does not include the treatment of sleep maintenance; however, AASM (2017) recommends zolpidem IR for sleep maintenance (primarily based on studies using zolpidem 10 mg).[2] **Table 4** shows the 2017 AASM guideline-recommended nBH agents compared to the FDA-approved indication, along with certain sleep parameter outcomes as reported in the 2017 AASM guideline.[2]

Table 4. Pharmacologic Indication According to Insomnia Subtype, FDA vs AASM[1,45]

Pharmacologic Agent	Sleep Onset	Sleep Maintenance	Trouble falling back asleep after nighttime awakening	Sleep parameter outcomes (vs placebo)[2]
Eszopiclone	FDA AASM (WR)			**Sleep onset:** reduced by 14 min on average (95% CI 3 to 24) **TST:** 28 to 57 min longer on average (95% CI 18 to 76) **WASO:** 10 to 14 min mean reduction (95% CI 2 to 18) **Sleep quality:** moderate-to-large improvement
Zaleplon	FDA AASM (WR)			**Sleep onset:** reduced by 10 min on average (95% CI 0 to 19) **Sleep quality:** no improvement
Zolpidem	FDA approved for Ambien, Zolpimist, Edluar FDA approved for Ambien CR AASM (WR)		FDA approved for Intermezzo	**Sleep onset:** reduced by 5 to 12 min on average (95% CI 0 to 19) **TST:** 29 min longer on average (95% CI 11 to 47 min) **WASO:** 25 min mean reduction (95% CI 18 to 33) **Sleep quality:** moderate improvement
Doxepin		FDA		

Table 4. Pharmacologic Indication According to Insomnia Subtype, FDA vs AASM[1,45]

Pharmacologic Agent	Sleep Onset	Sleep Maintenance	Trouble falling back asleep after nighttime awakening	Sleep parameter outcomes (vs placebo)[2]
		AASM (WR)		**TST:** 26 to 32 min longer on average (95% CI 18 to 40) **WASO:** 22 to 23 min mean reduction (95% CI 14 to 30) **Sleep quality:** small-to-moderate improvement
Suvorexant	FDA			**TST:** 10 min longer on average (95% CI 2 to 19) **WASO:** 16 to 28 min mean reduction (95% CI 7 to 43) **Sleep quality:** NR
		AASM (WR)		
Ramelteon	FDA			**Sleep onset:** reduced by 9 min on average (95% CI 6 to 12) **Sleep quality:** no improvement
	AASM (WR)			

Abbreviations: AASM, recommended by American Academy of Sleep Medicine; CI, confidence interval; FDA, approved by the Food and Drug Administration; NR, not reported; TST, total sleep time; vs, versus; WASO, wake-after-sleep onset; WR, weak recommendation strength in support of the treatment

Most clinical guidelines that provide guidance on agent selection recommend ramelteon, low-dose doxepin, the z-drugs (ie, zolpidem, zaleplon, and eszopiclone), and suvorexant for the treatment of chronic insomnia in adults.[2,5,28,30,31] Across reviewed US guidelines, the strength of recommendations in favor of using these agents tends to be *weak*, signifying that the treatment approaches may not be applicable to all patients due to a lack of certainty about their appropriateness.[2,28] In such cases, treatment selection should be guided by physician clinical judgement in the context of patient preferences and values.[2,28] Nonetheless, this should not be interpreted as a lack of evidence for drug efficacy in the management of insomnia-related symptoms; nor does it imply that the recommendations are irrelevant to patient care.[2,28]

US guidelines weakly recommend against the use of over-the-counter dietary supplements (eg, melatonin, valerian) and sleep aids (ie, diphenhydramine) due to insufficient evidence demonstrating a definitive benefit and/or concerns regarding safety.[2,28] Regarding the off-label use of other prescription agents, US guidelines tend to weakly recommend against the antidepressant, trazodone and sedating antipsychotics (eg, quetiapine, ziprasidone) for the treatment of chronic insomnia.[2,28] However, "…a recommendation *against use*, particularly when associated with low quality evidence, is not equivalent to a demonstration of ineffectiveness. Rather, it is often an indication that the available evidence is simply insufficient and fails to provide convincing support in favor [of the treatment].." (page 343).[2] Therefore, agents with a weak recommendation against use should not be construed to mean they should never be used, but rather, should be employed based on consideration of patient-specific factors.[57] European guidelines recommend antidepressants, primarily those with sedating effects (eg, doxepin) strictly for the short-term management of insomnia,[30] or in the presence of comorbid

depression.[31] **Table 5** includes pharmacologic guideline recommendations *only* for sedative hypnotics of interest for the treatment of chronic insomnia. Please refer **Table 1** in **Appendix C** for a complete summary of nonpharmacologic and pharmacologic guideline recommendations for the treatment of chronic insomnia and other sleep disorders (eg, N24SWD).

Table 5. Summary of Clinical Practice Guideline Recommendations For the Agents of Interest

Guideline (Sponsoring Organization; Year)	Recommendations[a]
UNITED STATES GUIDELINES	
Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and OSA **(VA/DoD; 2019)[28]**	• Low-dose doxepin (ie, 3 or 6 mg) or a z-drug (eg, eszopiclone, zaleplon, zolpidem) for patients requiring the short-term use of pharmacotherapy is suggested (**Weak for**) • Ramelteon and suvorexant have insufficient evidence to recommend either for or against use (**Neither for or against**)
Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults **(AASM; 2017)[2]**	<u>Sleep Maintenance Insomnia</u> The following nBH agents are recommended vs no treatment • Low-dose doxepin (3 or 6 mg) (**Weak; LOE: low**) • Suvorexant (10, 15/20, or 20 mg) (**Weak; LOE: low**) • Eszopiclone (2 or 3 mg) (**Weak; LOE: very low**) • Zolpidem (10 mg) (**Weak; LOE: very low**) <u>Sleep Onset Insomnia</u> The following nBH agents are recommended vs no treatment • Zaleplon (10 mg) (**Weak; LOE: low**) • Ramelteon (8 mg) (**Weak; LOE: very low**) • Eszopiclone (2 or 3 mg) (**Weak; LOE: very low**) • Zolpidem (10 mg) (**Weak; LOE: very low**)
Management of Chronic Insomnia Disorder in Adults **(ACP; 2016)[5]**	For patients with an inadequate response to CBT-I alone, a shared decision-making approach regarding the affordability and benefits/harms of using pharmacologic agents is recommended when deciding to initiate pharmacotherapy (**Weak**; **LOE: low**)
EUROPEAN GUIDELINES	
An Updated Consensus Statement on Evidence-based Treatment of Insomnia, Parasomnias, and Circadian Rhythm Disorders **(BAP; 2019)[31]**	• Low-dose doxepin is recommend as effective for insomnia (**Strength A**) • If GABA-A hypnotics are used in older adults, a shorter half-life agent is preferred to minimize adverse effects (**Strength A**) • In pregnant people suffering from intractable insomnia, zolpidem or zopiclone is recommended when short-term pharmacotherapy is indicted, taking into account the risks/benefits (**Strength D**)

European Guideline for the Diagnosis and Treatment of Insomnia **(ESRS; 2017)[30]**	• For the short-term treatment of insomnia (≤4 weeks), benzodiazepines and z-drugs are effective (**Strength - ; LOE: high**)
	  ○ Z-drugs are as efficacious as benzodiazepines (**Strength - ; LOE: moderate**)
	  ▪ Shorter half-life z-drugs and benzodiazepines may induce less next-morning sedation (**Strength - ; LOE: moderate**)

Table 5. Summary of Clinical Practice Guideline Recommendations For the Agents of Interest

Guideline (Sponsoring Organization; Year)	Recommendations[a]
	• For the short-term treatment of insomnia, sedating antidepressants (eg, doxepin) are effective, but contraindications should be considered (**Strength - ; LOE: moderate**) • Usually ongoing therapy with benzodiazepines, z-drugs, or sedating antidepressants are not recommended due to the risk of adverse effects and lack of available evidence. Reducing daily administration to intermittent dosing is recommended, if applicable (**Strong; LOE: low**)

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; DoD, Department of Defense; ESRS, European Sleep Research Society; LOE, level of evidence; nBH, non-benzodiazepine, non-barbiturate hypnotic; OSA, obstructive sleep apnea; VA, Department of Veterans Affairs; vs, versus

[a] See Appendix C for complete recommendations, and information about the interpretation of the recommendation strength and the level of evidence (LOE)

4.2 Non-24 Hour Sleep-Wake Disorder (N24SWD)

Pharmacologic agents utilized for the treatment of N24SWD include over-the-counter melatonin and tasimelteon.[8] Tasimelteon is the only FDA-approved agent for the treatment of N24SWD.[8,24,25]

Although tasimelteon was FDA-approved in 2014 for N24SWD, the 2019 BAP and 2015 AASM guidelines that address N24SWD do not include recommendations for or against its use.[7,13,31] Both guidelines recommend melatonin for non-sighted adults with N24SWD.[7,31] While both guidelines mention that tasimelteon has shown entrainment benefit compared to placebo in non-sighted individuals with N24SWD (20% vs 3%, respectively),[7,31] authors of the 2015 AASM guideline remark that the effect is lower than the 67% entrainment rate obtained for melatonin by a meta-analysis with placebo as the comparator.[7] However, the authors acknowledge uncertainty regarding the apparent difference in efficacy between tasimelteon and melatonin as indicated by indirectly comparing their effects, noting that the lower entrainment rate may have been due to a shorter treatment duration with tasimelteon.[7] In support of this rationale, increased entrainment rates have been reported with longer treatment durations of tasimelteon.[7]

In addition to melatonin for the treatment of N24SWD, the 2019 BAP guideline also recommends other interventions such as scheduled light exposure for people with sight and behavioral approaches.[31] According to the 2019 BAP guideline, patients with circadian rhythm disorders, including N24SWD should be treated in specialized sleep clinics due to the additional attention required for therapeutic timing.[31]

4.3 Smith-Magenis Syndrome (SMS)

Following the initial approval of tasimelteon in 2014 for N24SWD, the product was approved in 2020 for the treatment of sleep disturbances in SMS.[26] The management of SMS is targeted at underlying conditions that manifest during the course of the disorder (eg, epilepsy, behavior issues, sleep disturbances, psychiatric disorders).[9,32] Yet, evidence for the treatment modalities often used for SMS-related conditions tend to be limited, as there are few, if any, clinical trials in patients with SMS.[32] Thus,

clinicians must often depend on best practices and medication trials tailored to the presenting issue (eg, obesity, constipation, growth hormone deficiency, cardiac abnormalities).[32] Before the approval of tasimelteon, guideline-directed management of sleep disturbances in SMS focused on behavioral and environmental modification, and the use of melatonin either alone or in combination with acebutolol.[32]

The 2018 guideline by the Parents and Researchers Interested in Smith-Magenis Syndrome (PRISMS) was the only identified guideline that addresses the management of individuals with SMS.[32] Its publication predated the recent approval of tasimelteon for use in patients with SMS, thus does not comment on its use.[32] Of note, the PRISMS guideline does not provide graded recommendations, but rather provides statements to inform clinicians on the diagnosis, treatment of manifesting conditions, and ongoing surveillance in patients with SMS.[32] For the management of sleep, the guideline encourages the use of nonpharmacologic interventions such as establishing a consistent sleep routine, and ensuring a suitable sleep environment (eg, quiet and dark, use of rhythmic sound), including "SMS-proofing" the bedroom by using an enclosed bed to limit the potential for self-harm.[32] In terms of pharmacologic management, PRISMS notes that over-the-counter low-dose melatonin taken at bedtime has anecdotal evidence of sleep improvement without reports of serious adverse effects.[32] A 4–6 week trial of melatonin may be considered for individuals complaining of sleep disturbances.[32] Additionally, in open label trials, the concomitant use of acebutolol, a β1-adrengergic antagonist (acts by blocking endogenous signaling of melatonin)[56] administered as 10 mg/kg in the morning with evening administrations of melatonin was found to restore plasma concentrations of melatonin, and improve sleep duration, tiredness, and behavior.[9,32] Before initiating a medication trial, the clinician should take into account the patient's baseline sleep pattern and medical condition(s).[32]

5.0 PHARMACOLOGY

The agents reviewed in this report modulate physiologic mechanisms involved in sleep. Their mechanisms of action are outlined in **Table 6**.

Table 6. Mechanism of Action of FDA-Approved Hypnotics (Non-benzodiazepines, Non-barbiturates)

Active Ingredient (Brands)	Proposed Pharmacology
Z-drugs	
Eszopiclone (Lunesta)[20]	Uncertain, but is thought to bind to domains of GABA-receptor complexes located near or allosterically coupled to benzodiazepine receptors
Zaleplon (Sonata)[21]	Binds to GABA-benzodiazepine receptor complexes to modulate the chloride channel, which is hypothesized to be attributed to the pharmacologic effects. Also selectively binds to the omega-1 receptor located in the brain on the alpha-1 subunit of the GABA-A receptor
Zolpidem tartrate (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist)[14-18]	Binds to the alpha-1 subunit of the GABA-A receptor (positive modulator), resulting in inhibition of neuronal excitation due to the chloride channel opening more frequently
H_1-Antihistamine Antidepressant	
Doxepin (Silenor)[22]	Uncertain, but the sedative effects appear to be mediated through the antagonism of the histamine H_1 receptor
Orexin Receptor Antagonists	
Suvorexant (Belsomra)[19]	Antagonizes the orexin receptors (OX1R and OX2R) by blocking the binding of orexin A and orexin B (wake-stimulating neuropeptides)
Lemborexant (Dayvigo)[11]	
Daridorexant (Quviviq)[12]	
Melatonin Receptor Agonists	
Ramelteon (Rozerem)[23]	Antagonizes melatonin receptors, with a high affinity for the MT_1 and MT_2 receptors. Compared to the parent compound, the active metabolite (M-II) has about $1/10^{th}$ and $1/5^{th}$ the binding affinity for MT_1 and MT_2, respectively
Tasimelteon (Hetlioz; Hetlioz LQ)[13]	Uncertain, but acts as an agonist at melatonin receptors, MT_1 and MT_2. Expresses a higher binding affinity to the MT_2 receptor than the MT_1 receptor. Compared to the parent compound, the major active metabolites have $<1/10^{th}$ the binding affinity for the MT_1 and MT_2 receptors

Abbreviations: CR, controlled-release; FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid

The z-drugs (ie, eszopiclone, zaleplon, and zolpidem) bind to the gamma-aminobutyric acid-A (GABA-A) receptor, with zaleplon and zolpidem preferentially binding to the alpha-1 subunit, which has been attributed to the sedating effects of these medications.[1,51] The alpha 2 and 3 subunits located on the GABA-A receptor are thought to be involved in producing effects on anxiety and depression.[51] By modulating the GABA-A receptor, neuronal excitation is inhibited due to the chloride channel opening

more frequently.[14] Dissimilar from zaleplon and zolpidem, eszopiclone has a high binding affinity for alpha 2 and 3, in addition to alpha 1 GABA-A receptor subunits, indicating that eszopiclone may produce anxiolytic effects along with sedating effects.[51]

Depending on the formulation of zolpidem, the peak plasma concentrations differ.[14-18] For the oral spray (Zolpimist), peak plasma concentrations are acquired approximately 1 hour after ingestion,[18] whereas it is slightly longer (between 1–2 hours) for IR (Ambien), controlled-release (Ambien CR), and the sublingual tablet, Edluar.[14-16] For the sublingual tablet, Intermezzo, peak plasma concentrations are reached within 35–75 minutes after it completely dissolves.[17] The other z-drugs, eszopiclone and zaleplon take a similar time as the zolpidem oral spray (~ 1 hour) to reach peak plasma concentrations after ingestion.[20,21] The absorption of these agents is delayed if the medication is taken with or immediately after a high-fat meal, causing the effectiveness of the medication to be reduced.[14-18,20,21]

Zaleplon has a quick onset and short duration of action (T_{max} and half-life of approximately 1 hour)[21], attributing to the distinctive use in patients who have difficulty falling asleep after going to bed, in addition to prophylactic use.[21] Zaleplon is also used (but not FDA-approved) for middle-of-the-night awakening as long as 5 hours remain before anticipated wake-up time.[58] Intermezzo is the only other z-drug that can be used for awakening in the middle-of-the-night, which it is uniquely indicated to treat.[17]

The controlled-release formulation of zolpidem (Ambien CR) was formulated as a bilayer tablet with one layer releasing part of the dose upon absorption and the other layer gradually releasing the remaining dose over several hours to create a sustained effect to improve sleep maintenance during the night.[15] The elimination half-life of the controlled-release product was targeted to be similar to the IR product to minimize the risk of next-day impairment[59]; thus, the half-lives of both products are similar to each other.[14,15] In terms of comparing the IR formulation to the controlled-release, the package insert contains a pharmacokinetic graph of zolpidem (10 mg IR and 12.5 mg controlled-release) mean plasma concentration-time profiles from healthy males after a single administration of either dose/formulation of zolpidem.[15] The controlled-release formulation demonstrated a slight increase in plasma concentrations starting at 2 hours and continuing to 8 hours after administration, compared to the IR formulation[15]; however, it is unclear whether this observation translates into clinically meaningful differences between the immediate-and controlled-release formulations. Nonetheless, the controlled-release formulation is approved for sleep maintenance, however, the IR formulation is not.[14,15]

With respect to certain pharmacokinetic parameters (eg, C_{max}, AUC), Edluar and Zolpimist are bioequivalent to zolpidem IR (Ambien).[16,18] Both products are absorbed quickly and have a short elimination half-life[16,18]; thus, they are indicated for sleep onset insomnia.[16,18] FDA approval for these products was primarily based on established bioequivalency to the zolpidem IR product, Ambien, as well as providing more convenient administration options for some patients.[60,61] Likewise, the FDA-approval of Intermezzo sublingual tablets depended on the established safety profile of Ambien.[62] As previously mentioned, Intermezzo is used for returning to sleep upon awakening in the middle of the night, which is a distinct indication from any of the other nBH agents.[17]

Low-dose doxepin (Silenor), an H_1-antihistamine antidepressant, is approved for sleep maintenance insomnia due to the longer onset of action.[22] Although the exact mechanism of doxepin remains uncertain, the sedating effects may be mediated via histamine H_1 receptor antagonism.[22]

Ramelteon is a melatonin receptor agonist at the MT_1 and MT_2 receptors, involved in regulating the circadian rhythm in the sleep-wake cycle.[23] Ramelteon has a quick absorption, favoring its use for sleep onset insomnia.[23] Tasimelteon, also a melatonin agonist, FDA-approved for N24SWD and sleep disturbances in SMS, has a higher affinity for the MT_2 than MT_1 receptor.[13]

The ORAs (ie, suvorexant, lemborexant, and daridorexant) inhibit the orexin neuropeptide signaling pathway that contributes to wakefulness.[11,12,19] ORAs suppress the wake drive by binding to OX1R and OX2R receptors to prevent wake-stimulating neuropeptides (orexin A and orexin B) from binding to these receptors.[11,12,19] ORAs are approved for sleep maintenance and/or sleep onset insomnia as they have a rapid onset of action and long elimination half-life.[11,12,19] However, the onset of effect may be delayed when taken with or after a high-fat meal.[11,12,19]

Table 7 summarizes information about the pharmacokinetic parameters of these agents. The metabolism of the agents listed in table 7 involve cytochrome (CYP) enzymes[11-23]; thus, package inserts for most of these agents caution about their use in combination with strong CYP inhibitors or inducers.[14-18,20-23] More stern warnings for concomitant agents that affect CYP metabolism apply to the ORAs and tasimelteon[11-13,19]: suvorexant, lemborexant, and daridorexant should be avoided with strong CYP3A inhibitors; lemborexant should be avoided with moderate CYP3A inhibitors; lemborexant and daridorexant should be avoided with strong or moderate CYP3A inducers; and tasimelteon should be avoided with strong CYP1A2 inhibitors and CYP3A4 inducers.[11-13,19] Please refer to Section 8.4 of this report for additional information on drug-drug interactions.

Table 7. Pharmacokinetic Parameters

Generic Name (Brand Name)	T_{max}	Half-life (hrs)	Metabolism	Excretion
Z-drugs				
Eszopiclone[20] **(Lunesta)**	1 hr; delayed by ~1 hr when taken with a high-fat meal	6	Hepatic oxidation and demethylation via CYP3A4 (major) and CYP2E1	75% excreted in the urine as metabolites, <10% as parent substance
Zaleplon[21] **(Sonata)**	1 hr; delayed by ~2 hrs when taken with a high-fat meal	1	Aldehyde oxidase (mainly) and CPY3A4 to all inactive metabolites	70% excreted in the urine as metabolites, <1% unchanged ~17% in feces, mainly as metabolites
Zolpidem tartrate[14] **(Ambien)** *IR tablet*	1.6 hrs; delayed by ~60% (2.2 hours) when taken with a high-fat meal	~2.5 (depends on the dosage)	Hepatic; primarily via CYP3A4, CYP2C9, CYP1A2	Primarily as metabolites excreted into the urine
Zolpidem tartrate[15] **(Ambien CR)** *CR tablet*	1.5 hrs; delayed by ~2 hrs when taken with or after a high-fat meal	2.8		
Zolpidem tartrate[16] **(Edluar)** *Sublingual tablet*	~1.4 hrs (82 min); delayed by 28% (105 min) when taken after a high-fat meal	~2.7 (depends on the dosage)		
Zolpidem tartrate[17] **(Intermezzo)** *Sublingual tablet*	35 to 75 min; delayed by ~2 hrs when taken with food	2.5		
Zolpidem tartrate[18] **(Zolpimist)** *Oral spray*	~1 hour; delayed by 225% (2.6 hours) when taken with or after a high-fat meal	~3 (depends on the dosage)		

Abbreviations: CR, controlled-release; CYP; cytochrome; IR, immediate-release

Table 7. Pharmacokinetic Parameters

Generic Name (Brand Name)	T_{max}	Half-life (hrs)	Metabolism	Excretion
H_1-Antihistamine Antidepressant				
Doxepin[22] **(Silenor)**	3.5 hrs; delayed by ~3 hrs when taken with a high-fat meal	15.3	Hepatic oxidation and demethylation via CYP2C19 and CYP2D6 (major), CYP2C9, and CYP1A2	Primarily as metabolites excreted into the urine; <3% as the parent compound or nordoxepin
Orexin Receptor Antagonists				
Suvorexant[19] **(Belsomra)**	2 hrs (range 30 min to 6 hrs); delayed by ~1.5 hrs when taken with a high-fat meal	12	Hepatic; CYP3A (major) and CYP2C19. Hydroxyl-suvorexant (inactive metabolite)	Primarily excreted in the feces (66%), with 23% in the urine
Lemborexant[11] **(DayVigo)**	1 to 3 hrs; delayed by 2 hrs when taken after a high-fat meal	~18 (depends on the dosage)	Hepatic; CYP3A4 (major) and CYP3A5	Primarily excreted in the feces (~57%), with ~29% in the urine. <1% as excreted as unchanged
Daridorexant[12] **(Quviviq)**	1 to 2 hrs; delayed by 1.3 hrs when taken with a high-fat meal	8	Hepatic; CYP3A4 (major). <3% by other CYP enzymes	Primarily excreted in the feces (~57%), with ~28% in the urine, mainly as metabolites. Small amounts of the parent compound were identified in the urine and feces
Melatonin Receptor Agonists				
Ramelteon[23] **(Rozerem)**	0.75 hrs (range 0.5 to 1.5 hrs); delayed by 45 min when taken with a high-fat meal	1 to 2.6	Hepatic; glucuronidation and oxidation via CYP1A2 (major), CYP2C, and CYP3A4	Primarily excreted in the urine (84%) as metabolites, with ~4% in the feces. <0.1% as the parent compound in the urine and feces
Tasimelteon[13] **(Hetlioz, Hetlioz LQ)**	Capsule: 0.5 to 3 hrs; Suspension: 15 to 30 min Delayed by ~1.75 hrs when taken with a high-fat meal	1.3 ± 0.4	Hepatic; oxidation and oxidative dealkylation via CYP1A2 and CYP3A4, phenolic glucuronidation Metabolites: 13-fold or less activity than tasimelteon	Primarily excreted in the urine (85%) as metabolites, with 4% in the feces. <1% as the parent compound in the urine

Abbreviations: CR, controlled-release; CYP; cytochrome; IR, immediate-release

6.0 DIRECT-COMPARATIVE EVIDENCE FOR SEDATIVE HYPNOTICS

Literature searches from 2019 to 2022 for SRs of RCTs and individual RCTs yielded a total of 481 unique records, of which 10 records (comprising of 8 head-to-head RCTs) met inclusion criteria for the qualitative synthesis. One RCT (SUNRISE 1) was represented among 3 of the 10 included records.[33-35] **Figure 1** in **Appendix B** displays the PRISMA flow diagram for the publication screening process.

Head-to-head comparative evidence among patients with insomnia identified since our previous P&T report[1] includes the newer ORA, lemborexant compared to low-dose extended-release (ER) zolpidem in older adults[33-35]; suvorexant versus eszopiclone in patients (16–89 years of age) with major depressive disorder (MDD) and benzodiazepine-resistant insomnia [36]; and zaleplon or eszopiclone compared to immediate-release (IR) zolpidem in older adults or the general adult population.[37,38] Common primary efficacy endpoints of these RCTs included total sleep time (TST), sleep efficiency, latency to persistent sleep (LPS), and wake-after-sleep onset (WASO).[35-38] Sleep outcomes were reported either objectively by PSG and/or subjectively (eg, sleep journals, questionnaires).[2] No direct head-to-head comparative RCTs were identified for tasimelteon, doxepin, daridorexant, or ramelteon versus any other agent of interest for their approved indications.

There were also 4 head-to-head studies in patients *without* insomnia from which we extracted safety comparisons; these studies include ORAs versus ramelteon and/or zolpidem for outcomes such as cognitive function and abuse potential (*refer to Section 6.5 for details*).[63-66]

6.1 Zaleplon vs Zolpidem IR Tablet

Our previous 2019 P&T report[1] included two systematic review meta-analyses (SRMAs): a 2015 Agency for Healthcare Research and Quality (AHRQ) SRMA of 169 RCTs and a 2016 ACP SRMA of 35 RCTs.[39,40] These SRMAs included data from 2 RCTs (Elie et al and Fry et al) that evaluated zaleplon compared to placebo, but also included a zolpidem arm.[67,68] Authors of the AHRQ SR acknowledged that their assessment of comparative effectiveness between zaleplon and zolpidem was limited because head-to-head statistical comparisons were not provided by the 2 RCTs.[39,67,68] However, based on this meta-analysis, a similar reduction in sleep onset resulted with zaleplon 10 mg compared to zolpidem IR 10 mg.[39] A significant difference in sleep latency resulted in favor of zolpidem 10 mg (high-end dosage) only when compared to the low-end dosage of zaleplon 5 mg (approximately 14 minute improvement, 95% CI -25.1 to -2.3).[39] No significant differences resulted between zolpidem 10 mg and all dosages of zaleplon (5, 10, or 20 mg) with respect to subjective sleep quality, number of patients reporting ≥1 adverse event, overall withdrawals, and adverse event-related withdrawals.[39,40] There was insufficient data to evaluate the comparative effectiveness between zaleplon and zolpidem for sleep efficiency and TST.[39]

Our recent literature search also identified an additional RCT (**Ancoli-Israel et al, 1999**) comparing zaleplon and zolpidem[38] that was not included in either of the aforementioned meta-analyses.[39,40] This RCT was a double-blind, placebo-controlled, study comparing 2 weeks of treatment with either zaleplon (5 or 10 mg) or zolpidem IR (5 mg) in older adults with insomnia (≥65 years of age, n=549).[38] Zaleplon 10 mg, but not the 5 mg dose, statistically improved subjective sleep latency compared to zolpidem 5 mg at weeks 1 and 2 of treatment.[38] However, subjective TST significantly improved with zolpidem 5 mg compared to zaleplon 5 mg.[38] In terms of safety, the incidence of somnolence was numerically higher

with zolpidem IR 5 mg versus zaleplon 5 mg (10% vs 4%, respectively); the incidence of somnolence with zaleplon 10 mg was not reported.[38]

6.2 Lemborexant vs Zolpidem ER Tablet

SUNRISE 1 is the only identified head-to-head RCT for lemborexant versus zolpidem in patients (older adults only) with insomnia.[35] Results from this trial were reported among 3 publications: (1) the main publication including the primary and key secondary outcomes[35]; (2) a report on the prespecified exploratory analysis for sleep architecture-related outcomes[34]; and (3) a report of the results in terms of number needed to treat (NNT) and number needed to harm (NNH).[33] Details about these publications are reviewed in the following sections.

6.2.1 SUNRISE 1 Trial

SUNRISE 1 is a phase 3 RCT that evaluated the efficacy and safety of lemborexant (5 and 10 mg), taken at bedtime for 30 days, compared to zolpidem ER 6.25 mg, and placebo in older adults (women ≥55 years of age; men ≥65 years of age) diagnosed with insomnia (NCT02783729, n=1006).[35] The primary endpoint was the change from baseline to day 30 in objective LPS (log-transformed) for lemborexant versus placebo.[35] Objective LPS was measured using pairwise PSG, for example, averaging nights 1 and 2 LPS PSG measures and comparing those to the average of nights 29 and 30 to determine the change from baseline.[35] Secondary endpoints included measures of sleep efficiency, WASO, including WASO during the second half of the night, patient-reported outcomes on sleep maintenance and onset, and comparisons versus zolpidem ER.[35]

Both dosages of lemborexant (5 and 10 mg) produced significantly greater reductions in objective LPS at nights 1 and 2 compared to zolpidem ER 6.25 mg.[35] Furthermore, the significant difference between active arms was maintained to the end of the treatment period (nights 29 and 30).[35] Both doses of lemborexant were significantly better than zolpidem ER at the beginning (nights 1, 2) and end (nights 29 and 30) of the treatment period for secondary endpoints regarding improvements in objective sleep efficiency and WASO, including WASO during the second half of the night.[35] Subjective sleep onset latency was significantly reduced for both lemborexant treatment groups versus zolpidem ER during the first 7 nights and at day 30.[35] However, lemborexant performed similar to zolpidem for subjective sleep efficiency.[35] Regarding the change in subjective WASO, no significant differences were observed for both doses of lemborexant (5 and 10 mg) compared to zolpidem ER 6.25 mg for the first 7 nights[35]; however, at the end of the treatment period (day 30), zolpidem ER 6.25 mg demonstrated a significant reduction versus lemborexant 5 mg only (not 10 mg).[35]

In terms of safety, the overall incidence of treatment-emergent adverse events (TEAEs) was numerically higher for zolpidem ER (35.4%) compared to either dose of lemborexant (5 mg, 27.8%; 10 mg, 30.65%).[35] Numerically, more somnolence occurred in the lemborexant-treated patients compared to zolpidem-treated patients (7.1% lemborexant 10 mg, 4.1% lemborexant 5 mg, 1.5% zolpidem ER).[35] Although considered to be mild in severity, 4 participants receiving lemborexant (1 in the 5 mg arm and 3 in the 10 mg arm) reported an incident of sleep paralysis.[35] No deaths occurred and no potential withdrawal symptoms were noted in any of the treatment groups.[35]

Table 8 outlines efficacy results for the primary and secondary endpoints and pertinent safety information from the SUNRISE 1 trial.

Table 8. Summary of the Efficacy and Safety Information from the SUNRISE 1 Trial

RCT Design (author, year, trial name)	Population	Intervention	Efficacy Results (mean; SD)	Safety Results
Multicenter, randomized, double-blind, parallel-group, active-comparator, placebo-controlled, phase 3 study (Rosenberg, 2019, **SUNRISE 1**)[35]	Older adults (women ≥55 years of age; men ≥65 years of age) diagnosed with insomnia per DSM-5 criteria, with sleep maintenance issues[a]	LEM 5 mg po nightly (N=266) vs LEM 10 mg po nightly (N=269) vs ZOL ER 6.25 mg po nightly (N=263) vs PBO po nightly (N=208) Duration: 30 days	**Primary endpoint:** Baseline change in LPS: Objective LPS was measured using pairwise PSG, for example, averaging night 1 and 2 LPS PSG measures and comparing those to the average of night 29 and 30 to determine the change from baseline. First 2 nights of the treatment period (nights 1 and 2): • **LEM 5 mg vs ZOL ER 6.25 mg:** 28.3 (24.4) min vs 31.9 (23.7) min. LSGM ratio= 0.87 (95% CI 0.78 to 0.98); p=0.02 • **LEM 10 mg vs ZOL ER 6.25 mg:** 25.1 (16.7) min vs 31.9 (23.7) min. LSGM ratio= 0.82 (95% CI 0.73 to 0.92); p<0.001 Last 2 nights of the treatment period (nights 29 and 30): • **LEM 5 mg vs ZOL ER 6.25 mg:** 25.8 (24.3) min. vs 37.1 (28.4) min. LSGM ratio= 0.63 (95% CI 0.56 to 0.72); p<0.001 • **LEM 10 mg vs ZOL ER 6.25 mg:** 22.8 (17.5) min vs 37.1 (28.4) min. LSGM ratio= 0.59 (95% CI 0.52 to 0.68); p<0.001 **Key secondary endpoints:** Baseline change in sleep efficiency: First 2 nights of the treatment period (nights 1 and 2): • **LEM 5 mg vs ZOL ER 6.25 mg:** 82.0% (8.4) vs 79.9% (8.5). LSM difference= 2.1 (95% CI 0.8 to 3.3); p=0.001 • **LEM 10 mg vs ZOL ER 6.25 mg:** 84.3% (7.6) vs 79.9% (8.5). LSM difference= 4.6 (3.4 to 5.9); p<0.001 Last 2 nights of the treatment period (nights 29 and 30): • **LEM 5 mg vs ZOL ER 6.25 mg:** 81.3% (8.8) vs 77.2% (10.2). LSM difference= 3.9 (95% CI 2.5 to 5.3); p<0.001 • **LEM 10 mg vs ZOL ER 6.25 mg:** 82.0% (8.8) vs 77.2% (10.2). LSM difference= 4.9 (3.5 to 6.3); p<0.001	Most frequently reported TEAEs (≥2% in any active treatment group) • Headache LEM 5 mg (6.4%) vs LEM 10 mg (4.9%) vs ZOL ER (5.3%) vs PBO (6.2%) • Somnolence LEM 5 mg (4.1%) vs LEM 10 mg (7.1%) vs ZOL ER (1.5%) vs PBO (1.9%) • UTI LEM 5 mg (1.1%) vs LEM 10 mg (3.4%) vs ZOL ER (0.8%) vs PBO (1.0%) • Nasopharyngitis LEM 5 mg (2.6%) vs LEM 10 mg (0.4%) vs ZOL ER (0.4%) vs PBO (1.4%) • URTI LEM 5 mg (2.3%) vs LEM 10 mg (0.4%) vs ZOL ER (0.8%) vs PBO (1.9%) • Dizziness

Abbreviations: AEs, adverse events; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER, extended-release; LEM, lemborexant; LPS, latency to persistent sleep; LSGM, least squares geometric means; LSM, least squares mean; PBO, placebo; PO, by mouth; PSG, polysomnography; SAE, serious adverse events; SD, standard deviation; TEAEs, treatment-emergent adverse events; URTI, upper respiratory tract infection; vs, versus; WASO, wake-after-sleep onset; ZOL, zolpidem

Table 8. Summary of the Efficacy and Safety Information from the SUNRISE 1 Trial

RCT Design (author, year, trial name)	Population	Intervention	Efficacy Results (mean; SD)	Safety Results
			WASO: First 2 nights of the treatment period (nights 1 and 2): • **LEM 5 mg vs ZOL ER 6.25 mg:** 63.5 (31.5) min vs 69.9 (33.5) min. LSM difference= –6.2 (95% CI –11.2 to –1.2); p=0.02 • **LEM 10 mg vs ZOL ER 6.25 mg:** 55.2 (30.5) min vs 69.9 (33.5) min. LSM difference= –15.0 (95% CI –20.0 to –10.1); p<0.001 Last 2 nights of the treatment period (nights 29 and 30): • **LEM 5 mg vs ZOL ER 6.25 mg:** 69.1 (34.5) min vs 77.7 (39.9) min. LSM difference= –7.7 (95% CI –13.4 to –2.1); p=0.007 • **LEM 10 mg vs ZOL ER 6.25 mg:** 68.6 (35.2) min vs 77.7 (39.9) min. LSM difference= –9.1 (95% CI –14.8 to –3.5); p=0.002 WASO in Second Half of the Night: First 2 nights of the treatment period (nights 1 and 2): • **LEM 5 mg vs ZOL ER 6.25 mg:** 46.3 (25.6) min vs 53.3 (27.7) min. LSM difference= –6.5 (95% CI –10.6 to –2.4); p=0.002 • **LEM 10 mg vs ZOL ER 6.25 mg:** 39.8 (23.7) min vs 53.3 (27.7) min. LSM difference= –13.1 (95% CI –17.2 to –9.0); p<0.001 Last 2 nights of the treatment period (nights 29 and 30): • **LEM 5 mg vs ZOL ER 6.25 mg:** 49.1 (28.2) min vs 56.7 (31.1) min. LSM difference= –6.7 (95% CI –11.2 to –2.2); p=0.004 • **LEM 10 mg vs ZOL ER 6.25 mg:** 48.2 (27.8) min vs 56.7 (31.1) min. LSM difference= –8.0 (95% CI –12.5 to –3.5); p<0.001	LEM 5 mg (1.1%) vs LEM 10 mg (0.7%) vs ZOL ER (3.0%) vs PBO (1.9%) Discontinued Treatment due to AEs: LEM 5 mg (0.8%) vs LEM 10 mg (1.1%) vs ZOL ER (2.7%) vs PBO (1.0%) SAEs: LEM 5 mg (0.8%) vs LEM 10 mg (0%) vs ZOL ER (1.5%) vs PBO (0%)

[a] *Required to have a subjective wake-after-sleep onset of ≥1 hour at minimum 3 nights per week in the prior 4 weeks, typical time spent in bed (7 to 9 hours), Insomnia Severity Index score of ≥13, and evidence of insomnia characterized by sleep maintenance issues. Participants could have problems with sleep onset, but this was not mandatory for enrollment.*[35]

Abbreviations: AEs, adverse events; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER, extended-release; LEM, lemborexant; LPS, latency to persistent sleep; LSGM, least squares geometric means; LSM, least squares mean; PBO, placebo; PO, by mouth; PSG, polysomnography; SAE, serious adverse events; SD, standard deviation; TEAEs, treatment-emergent adverse events; URTI, upper respiratory tract infection; vs, versus; WASO, wake-after-sleep onset; ZOL, zolpidem

6.2.1.1 Other publications that included data from the SUNRISE 1 trial

A study by **Moline et al** evaluated a prespecified exploratory analysis for sleep architecture-related outcomes.[34] The sleep architecture parameters included change from baseline in TST and certain sleep stages (N1, N2, N3, total NREM, R*),[69] as measured by PSG at nights 1 and 2, and nights 29 and 30.[34]

Lemborexant 5 and 10 mg significantly improved TST and the duration in N1 sleep stage versus zolpidem ER 6.25 mg at the beginning (nights 1 and 2) and at the end of the treatment period (nights 29 and 30).[34] Regarding the duration within the N2 sleep stage, only lemborexant 5 mg had a significant difference compared to zolpidem ER at nights 1 and 2; no other significant differences between either dose of lemborexant or zolpidem ER were noted for this outcome.[34] Although the treatment difference for the duration within the N3 sleep stage on nights 1 and 2 was not significant for lemborexant 5 mg, and was significantly lower for lemborexant 10 mg compared to zolpidem ER, the difference between lemborexant 5 mg and zolpidem ER was significant by the end of the treatment period (night 30).[34] Lemborexant 5 and 10 mg did not show a significant difference for the total number of minutes for all NREM sleep stages combined during nights 1 and 2 compared to zolpidem ER; however, the difference was significant at the end of the treatment period (nights 29 and 30).[34] Compared to ER zolpidem, both doses of lemborexant significantly increased the duration of stage R sleep and reduced the latency to this sleep stage at both time points (nights 1 and 2; and nights 29 and 30).[34]

Citrome et al assessed the benefit-risk profile of lemborexant compared to zolpidem ER from SUNRISE 1 data, in terms of NNT and NNH.[33] For subjective sleep onset latency (defined as ≥15% improvement in mean, alternative definition) at week 4, both doses of lemborexant (5 and 10 mg) resulted in <10 NNT values compared to zolpidem ER 6.25 mg, which is considered a desirable value by the study authors.[33] Although authors note that directly comparing lemborexant to zolpidem ER for PSG-related outcomes (LPS and WASO) was not part of the original statistical plan, the results favored lemborexant (5 and 10 mg) with NNT values of <10 at day 30 compared to zolpidem ER.[33] For somnolence, an NNH of 39 was calculated for lemborexant 5 mg compared to 6.25 mg of zolpidem ER (non-significant), whereas, an NNH of 18 ($p<0.05$) was found for the higher dose (10 mg) of lemborexant versus zolpidem ER.[33]

6.3 Suvorexant vs Eszopiclone

A 4-week, open-label randomized trial by **Shigetsura et al** evaluated the benefit of switching from benzodiazepines to either suvorexant or eszopiclone for benzodiazepine-treatment resistant insomnia in individuals (aged 16–89 years) with major depressive disorder (MDD) (n=18).[36] Patients who failed a benzodiazepine for sleep after a trial of at least 2 weeks were randomized to eszopiclone (2 or 3 mg) or suvorexant (15 or 20 mg), taken nightly immediately prior to bedtime.[36] Participants over the age of 65 were randomized to receive lower doses of eszopiclone or suvorexant, whereas, younger participants received higher doses.[36] The primary endpoint was the change in insomnia severity from baseline at week 2 and week 4 based on the Japanese version of the Insomnia Severity Index (ISI-J)[70].[36] Secondary endpoints were changes from baseline in Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J)[71], the Beck Depression Inventory-II (BDI-II)[72], and the Generalized Anxiety Disorder 7 (GAD-7)[73].[36] The

* Sleep occurs in 2 phases: non-rapid eye movement (NREM) and rapid eye movement (REM), with NREM consisting of N1, N2, and N3 stages. The progression of sleep occurs in the following order, with each stage representing increasingly deeper sleep: wake, N1, N2, N3, and REM.

Digit Symbol Substitution Test (DSST)[74] and Digit Span Test (DST)[75] were used to assess effects on cognitive function and next-day impairment at week 4.[36] Suvorexant and eszopiclone performed similarly to each other on all primary and secondary endpoints, with no significant differences indicated at week 2 or week 4.[36]

Regarding drug-specific adverse events, unpleasant taste was reported only in eszopiclone-treated patients, with no reports occurring in suvorexant-treated patients (4 vs 0, respectively).[36]

6.4 Eszopiclone vs Zolpidem IR Tablet

A randomized, crossover study (**Erman et al**) evaluated the efficacy and safety of eszopiclone compared to zolpidem IR for the treatment of insomnia in adults (21–64 years of age, n=65).[37] Patients were randomized to a treatment sequence consisting of eszopiclone (1 mg, 2 mg, 2.5 mg, 3 mg), zolpidem 10 mg, and placebo.[37] Doses were taken nightly for 2 consecutive nights, followed by a mandatory washout period of 3–7 days before crossing over to the next treatment.[37] The primary endpoint was LPS, measured by PSG.[37] Key secondary endpoints were WASO and sleep efficiency.[37]

Compared to eszopiclone 1 mg, zolpidem 10 mg significantly reduced LPS and improved sleep efficiency.[37] Yet, the higher doses of eszopiclone (2−3 mg) performed similarly to zolpidem 10 mg for improving LPS and sleep efficiency, suggesting a dose-response relationship.[37] Non-significant differences were observed between all tested doses of eszopiclone and zolpidem 10 mg for WASO.[37]

Rates of unpleasant taste were reported more frequently in eszopiclone-treated patients, whereas rates of dizziness and hallucinations were numerically higher in patients treated with zolpidem IR.[37] Overall, CNS-related adverse events occurred more frequently in zolpidem-treated patients (23.4%) compared to eszopiclone (6.2–12.5%, depending on the dose).[37]

6.5 Other Head-to-Head Trials with Orexin Receptor Antagonists in Adults *Without* Insomnia

In populations *without* insomnia, we identified the following head-to-head individual RCTs:

- A small RCT evaluated lemborexant 5 and 10 mg compared to zolpidem ER (6.25 mg) regarding their effects on cognitive performance, postural stability, and auditory awakening threshold in healthy older adults[64]
- Two small RCTs evaluated the abuse potential of the newer ORAs, lemborexant or daridorexant compared to supratherapeutic doses of suvorexant and zolpidem IR among healthy adult, recreational sedative drug users[63,66]
- A small RCT assessed the residual effects of low-dose suvorexant, ramelteon, and zolpidem IR in healthy older adults[65]

The following subsections provide details regarding the safety comparisons for these studies.

6.5.1 Safety Effects of Lemborexant vs Zolpidem ER Tablet in Healthy Older Adults

A crossover RCT by **Murphy et al** evaluated lemborexant (5 and 10 mg) compared to zolpidem ER (6.25 mg) regarding their effects on cognitive performance, postural stability, and auditory awakening threshold (AAT) in *healthy* older adults (women ≥55 years of age; men ≥65 years of age, n=63).[64] Participants were randomized (1:1:1:1) to 1 of 4-period, single-dose crossover sequences containing lemborexant (5 mg, 10 mg), zolpidem ER 6.25 mg, and placebo, each taken at bedtime.[64] Treatment phases were followed by a 14-day washout period, with the final treatment phase followed by a 14-day follow-up period prior to the end of the study.[64]

Change in mean postural stability in the middle of the night (4 hours after the dose) from baseline, the primary endpoint, was significantly better with lemborexant 5 and 10 mg compared to zolpidem ER 6.25 mg after being awakened in the middle of the night.[64] Lemborexant 5 and 10 mg performed similarly to zolpidem ER for postural stability upon awakening in the morning.[64] In terms of auditory arousal, neither dose of lemborexant or zolpidem prevented participants from being awakened by the auditory stimulus in the middle of the night.[64] The AAT (decibels) required to awaken participants was similar between the treatment groups.[64] In terms of cognitive performance upon awakening in the middle of the night, zolpidem ER demonstrated significantly greater impairment compared to both doses of lemborexant for speed of memory recall; whereas, zolpidem ER was significantly worse compared to only lemborexant 5 mg (not 10 mg) for continuity of attention and quality of memory.[64] However, the higher dose of lemborexant (10 mg) produced significantly more impairment on power of attention compared to zolpidem ER.[64] Upon awakening in the morning, no evidence of residual effects on cognitive impairment was observed with either dose of lemborexant or zolpidem ER.[64]

6.5.2 Abuse Potential of Orexin Receptor Antagonists vs Zolpidem

Two randomized, single-dose, 6-way crossover studies (**Landry et al** and **Ufer et al**) were conducted to evaluate the abuse potential of the newer ORAs, lemborexant or daridorexant, compared to suvorexant or zolpidem IR.[63,66] Both studies were conducted in *healthy* adult (18–55 years of age), recreational sedative drug users.[63,66] Each trial included a mandatory washout period (at least 3 or 14 days depending on the trial) between treatments.[63,66] The primary endpoint in both trials was the peak effect (E_{max}) on the visual analog scale (VAS) for "at this moment" drug-liking.[63,66] Secondary endpoints included overall drug-liking VAS score, high VAS score, take-drug again VAS score, bad effects VAS score, good-drug effects VAS score, stoned VAS score, and any effects VAS score.[63,66] Sedative-related endpoints were alertness/drowsiness VAS score, Observer's Assessment of Alertness/Sedation (OAA/S) scale,[76] and Addiction Research Center Inventory for the Pentobarbital-chlorpromazine-alcohol Group (ARCI PCAG).[63,66,77,78] Additional details are provided below for each trial.

6.5.2.1 Lemborexant vs Suvorexant vs Zolpidem IR Tablet in Recreational Sedative Drug Users

Landry et al evaluated the abuse potential of lemborexant compared to zolpidem IR or suvorexant in non-dependent, recreational sedative drug users (n=32).[63] Participants were randomly assigned to a treatment sequence consisting of placebo, lemborexant (10 mg, 20 mg, 30 mg), zolpidem IR 30 mg, and suvorexant 40 mg.[63]

For the primary endpoint and key secondary endpoints, no significant differences were observed for either dose of lemborexant compared to suvorexant 40 mg and zolpidem 30 mg.[63] Regarding other endpoints, lemborexant (10 mg, 20 mg, 30 mg) had a significantly greater impact (E_{max}) on stoned VAS scores, bad effects VAS scores, and any effects VAS scores compared to suvorexant 40 mg.[63] Compared to zolpidem 30 mg, lemborexant 30 mg had a greater impact on any effects VAS scores, whereas lemborexant 10 mg had a lesser impact on bad-effects VAS scores.[63] Based on the alertness/drowsiness VAS scores, all doses of lemborexant produced significantly greater sedative effects compared to zolpidem 30 mg, but when measured as the OAA/S composite and sum scores, the sedative effects of lemborexant (each dose) was significantly lower compared to zolpidem 30 mg.[63] However, the OAA/S composite and sum scores, ARCI PCAG, and alertness/drowsiness VAS scores indicated that the higher doses of lemborexant (20 and 30 mg) had significantly greater sedative effects compared to suvorexant 40 mg.[63]

The most frequently reported TEAEs (>3 participants in any active treatment arm) were somnolence, sleep paralysis, dizziness, muscular weakness, double vision, headache, nausea, and vomiting.[63] Somnolence and dizziness were the 2 TEAEs that were considered to be associated with the potential for drug abuse.[63] Sleep paralysis was reported in participants that received an ORA (lemborexant and suvorexant). Three participants experienced recurrent episodes of sleep paralysis: 1 participant with lemborexant 10 mg and suvorexant 40 mg; 1 participant with each dose of lemborexant (10-, 20-, and 30 mg); and 1 participant with lemborexant 10 and 20 mg.[63] One participant experienced severe cataplexy and somnolence after taking zolpidem, but no other severe TEAEs were reported in any of the treatment groups.[63]

6.5.2.2 Daridorexant vs Suvorexant vs Zolpidem IR Tablet in Recreational Sedative Drug Users

Ufer et al evaluated the abuse potential of daridorexant compared to supratherapeutic doses of zolpidem and suvorexant in *healthy* adult, recreational sedative drug users (n=63).[66] Participants were randomly assigned to a treatment sequence consisting of placebo, daridorexant (50 mg, 100 mg, 150 mg), zolpidem IR 30 mg, and suvorexant 150 mg.[66] An additional secondary endpoint included in this trial not previously mentioned above was the measure of perceptual/psychedelic effects based on the Bowdle VAS score.[66]

Regarding the drug-liking VAS E_{max} (primary endpoint), and some secondary endpoints (good effects VAS scores, high VAS scores, overall drug-liking VAS scores, alertness/drowsiness VAS scores), only the lowest dose of daridorexant (50 mg) had significantly less effect compared to zolpidem IR 30 mg and suvorexant 150 mg, while take-drug again VAS scores was significantly less only for daridorexant 50 mg compared to suvorexant 150 mg.[66] At supratherapeutic doses of daridorexant (100 and 150 mg), differences versus zolpidem 30 mg or suvorexant 150 mg were non-significant for these aforementioned endpoints, except for high VAS scores which was significantly less with daridorexant 100 mg compared to zolpidem 30 mg.[66] With respect to alternations of perception (measured via Bowdle VAS score), daridorexant (at all doses) produced a significantly less effect compared to zolpidem 30 mg; whereas, when compared to suvorexant 150 mg, only daridorexant 50 and 100 mg showed significantly less effects.[66] Any-effects VAS scores were significantly lower for daridorexant 50 mg compared to zolpidem 30 mg and suvorexant 150 mg, and for daridorexant 100 mg versus suvorexant 150 mg.[66]

The most commonly reported adverse event across all active comparator treatment groups was somnolence, showing a dose-dependent relationship for daridorexant (44.8%, 59.4%, and 80.6%; 50 mg, 100 mg, and 150 mg, respectively) compared to 53.6% for zolpidem and 68.7% for suvorexant.[66] Daridorexant-treated patients numerically reported euphoric mood less often (3–5.8%, depending on the dose) compared to patients receiving zolpidem (20.3%) and suvorexant (9%).[66] Consistent with other trials (Landry et al),[63] hallucinations were reported more frequently for zolpidem (5.8%) compared to the ORAs (0% for daridorexant and 1.5% for suvorexant).[66] Conversely, sleep paralysis was reported more often for daridorexant (3–10.1%, depending on the dose) and suvorexant (13.4%) compared to zolpidem (1.4%).[66] Only one participant discontinued treatment due to an adverse effect (paresthesia) after receiving zolpidem IR 30 mg.[66]

6.5.3 Suvorexant vs Ramelteon vs Zolpidem IR Tablet

Uemura et al conducted a double-blind, randomized, crossover study to evaluate the residual effects of a single-time low-dose administration of suvorexant, ramelteon, or zolpidem in *healthy* older adults (60–75 years of age, n=14).[65] Participants were randomized to a treatment sequence consisting of placebo, suvorexant 10 mg, zolpidem IR 5 mg, and ramelteon 4 mg, administered as a single-dose at bedtime, with a 6-day washout period between each treatment.[65] Participants slept from 23:00 to 6:00 with an interruption between 4:00 to 4:30 to allow for evaluations, before participants were instructed to go back to sleep for the second sleep period (4:30 to 6:00).[65] Objective measures for cognitive and physical function (eg, body sway test) were obtained during the night of administration and the next day.[65]

Only the body sway test (eyes closed), which is reflective of standing balance, showed a significant difference between treatment groups, whereas all other objective assessments showed no significant treatment differences (eg, timed up and go test, functional reach test, short-term memory test).[65] For the body sway test (closed eyes), zolpidem IR 5 mg was associated with significantly less movement compared to suvorexant 10 mg and ramelteon 4 mg.[65]

7.0 SPECIAL POPULATIONS

7.1 Pediatric

Insomnia is considered a common condition among children, with between 15–25% of children and adolescents experiencing trouble initiating or maintaining sleep.[79] Insomnia often occurs with other conditions such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), epilepsy, and cerebral palsy.[31,80]

The safety and effectiveness of the nBH agents, except for tasimelteon, has not been proven in clinical trials for pediatric use.[11-23] The use of tasimelteon capsules for the treatment of sleep disturbances in SMS is not indicated for pediatric patients younger than 16 years of age[13]; whereas the oral suspension has been safely established in children as young as 3 years of age.[13]

Although other hypnotics are not indicated for use in the pediatric population, package inserts for zolpidem products[14-18] mention an 8-week controlled trial in pediatric patients (6–17 years of age) with insomnia related to ADHD. Compared to placebo, an oral solution of zolpidem administered at 0.25 mg/kg nightly at bedtime failed to improve sleep latency. The most common TEAEs (>5%) that occurred

in zolpidem-treated patients compared to patients that received placebo were dizziness, headache, and hallucinations.[14,15,18] Similar results were observed for eszopiclone at 1-, 2-, or 3 mg doses in a 12-week controlled trial in pediatric patients (6–17 years of age) with insomnia related to ADHD.[20] Compared to placebo, eszopiclone (1-, 2-, and 3 mg) failed to significantly reduce LPS, as measured by PSG after 12 weeks of therapy.[20] The most common TEAEs that occurred in eszopiclone-treated patients compared to patients that received placebo were dysgeusia, dizziness, hallucinations, and suicidal ideation.[20]

In terms of guideline recommendations for the management of sleep in children, the 2019 BAP guideline recommends behavioral interventions prior to other treatment modalities for children with disturbed sleep.[31] In terms of medications, BAP suggests melatonin may be used in children with ASD or ADHD not being treated with a simulant to alleviate sleep difficulties.[31]

7.2 Pregnancy

In general, there is a paucity of data to guide the use of these agents during pregnancy.

The 2019 BAP guideline contains general recommendations for the management of sleep-related problems during pregnancy, including insomnia.[31] Similar to the general population, good sleep hygiene and lifestyle modification are recommended prior to pharmacological treatments.[31] In addition, special consideration of pregnancy-related complaints should be managed appropriately (eg, pillow support, reducing fluids).[31] Although limited evidence exists to support CBT-I in pregnancy, BAP (2019) recommends that this invention may be reasonable in this patient population.[31] For patients with intractable insomnia who require pharmacologic management, zolpidem or zopiclone are recommended for short-term use, due to the lower risk of fetal/maternal harm relative to other sedative hypnotics.[31]

7.3 Older Adults

Older adults (≥65 years of age) are usually more sensitive to adverse effects of sedative hypnotics[14-18,20-22]; thus, doxepin in this patient population has a lower initial dose compared to younger adults,[22] and eszopiclone, zolpidem, and zaleplon have reduced maximum doses.[14-18,20,21] Compared to younger adults, exposure to tasimelteon has been found to be increased approximately twofold in older adults, resulting in a potential greater risk of adverse events.[13]

The 2019 American Geriatrics Society (AGS) Beers Criteria recommends that older adults avoid eszopiclone, zaleplon, and zolpidem due to their similar adverse effect profile to benzodiazepines when used in older adults (eg, falls, fractures, delirium), especially in older adults with delirium or history of fractures or falls.[81] Suvorexant, low-dose doxepin, tasimelteon, and ramelteon are not included on the list of potentially inappropriate medications for older adults in the Beers Criteria.[81] This document predates the FDA-approval of daridorexant and lemborexant; thus, these agents are not mentioned.[81]

7.4 Other Special Populations

Suvorexant exposure is increased in women and obese patients[19]; thus, the risk of adverse effects should be considered before increasing the dose in these subpopulations, particularly in obese women.[19] Although starting at a lower dose (5 mg rather than 10 mg) is not explicitly recommended in the product labeling, this may be considered for women and obese patients.[19]

Also due to the reduced drug clearance in women, zolpidem-containing products are recommended to be started at lower doses for women relative to men.[14-18] Product labeling does allow for dose increases up to the maximum recommended dose based on treatment response, to ensure appropriate management of the condition while minimizing potential harms.[14-18]

The efficacy of tasimelteon may be reduced in smokers, due to CYP1A2 induction based on lower drug exposure observed in smokers compared to non-smokers.[13]

Table 9 provides additional details from the product labeling for the use of these agents in pregnancy, renal/hepatic impairment, and older adults.

Table 9. Recommendations for Use in Special Populations According to Product Labeling

Active Ingredient (Brands)	Pregnancy	Breastfeeding	Older Adults (>65 years)	Renal or Hepatic Impairment
Z-drugs				
Eszopiclone[20] **(Lunesta)**	• Insufficient human data • At approximately 200 times the MRHD, toxicities occurred in animal offspring	• Unknown if secreted in human milk • No human data • Potential toxicity is suggested[82] • Consider risks vs benefits	• Increased total exposure and elimination • Dose should be restricted to 2 mg nightly	• Severe hepatic impairment: restricted to 2 mg nightly • No dose adjustments for mild/moderate hepatic impairment • No dose adjustments for renal impairment
Zaleplon[21] **(Sonata)**	• No human data • Animal studies suggest potential fetal harm • Consider risks vs benefits	• Small amounts secreted in human milk (highest concentrations achieved ~1 hr after maternal administration) • Unknown fetal effects • Not recommended	• Since older adults may be more sensitive to adverse effects, start at 5 mg • Dosages above 10 mg are not recommended	• Mild or moderate hepatic impairment: restricted to 5 mg nightly • Severe hepatic impairment: avoid • Severe renal impairment: avoid due to limited data • No dose adjustment for mild or moderate renal impairment
Zolpidem tartrate[14-18] **(Ambien; Ambien CR; Edluar; Intermezzo; Zolpimist)**	• Neonates exposed to the drug later in the third trimester may experience respiratory depression and sedation • No definitive association has been established for major birth defects • Consider risks vs benefits	• Secreted in human milk • Nursing infant may experience adverse effects (eg, CNS depression, excessive sedation)	Since older adults may be more sensitive to adverse effects, the initial dose is lower relative to younger adults: • 5 mg for Ambien, Edluar, and Zolpimist • 6.25 for Ambien CR • 1.75 mg for Intermezzo	• Mild or moderate hepatic impairment: lower doses are recommended (5 mg for Ambien, Edluar, and Zolpimist; 6.25 mg for Ambien CR; 1.25 mg for Intermezzo) • Severe hepatic impairment: avoid Ambien and Ambien CR • No dose adjustment for renal impairment

Abbreviations: CNS, central nervous system; CR, controlled-release; MRHD, maximum recommended human dose; NAS, neonatal abstinence syndrome; vs, versus

Table 9. Recommendations for Use in Special Populations According to Product Labeling

Active Ingredient (Brands)	Pregnancy	Breastfeeding	Older Adults (>65 years)	Renal or Hepatic Impairment
H_1-Antihistamine Antidepressant				
Doxepin[22] **(Silenor)**	• Animal studies imply potential fetal harm • Use in the third trimester may increase the risk of poor adaptation in the newborn • Human data imply low risk, but NAS may occur when used near term[83]	• Secreted in human milk • Nursing infant may experience adverse effects (eg, poor suckling, hypotonia, respiratory depression, excessive sedation) • Not recommended	• Start at the lower dose (3 mg) due to increased sensitivity in this population relative to younger adults • Evaluate side effects before increasing the dose to 6 mg	• Hepatic impairment: start at 3 mg • Renal impairment: Not been studied, but not anticipated to affect drug concentrations
Orexin Receptor Antagonists				
Suvorexant[19] **(Belsomra)**	• Insufficient human data • Animal data implies a low risk for fetal harm[84]	• Unknown if secreted in human milk, but likely since it is present in animal milk • No human data • Monitor for excessive sedation in drug-exposed newborns • Consider risks vs benefits	• No clinically relevant differences were observed between older and younger adults • Older adults are at higher risk of falls due to sedation effects	• Severe hepatic impairment: avoid • No dose adjustment for mild/moderate hepatic impairment • No dose adjustment for renal impairment
Lemborexant[11] **(Dayvigo)**	• No human data • Animal studies imply potential fetal harm	• Unknown if secreted in human milk, but likely since it is present in animal milk • No human data • Monitor for excessive sedation in drug-exposed newborns • Consider risks vs benefits	• Increased risk of somnolence with higher doses (10 mg) in older adults compared to younger adults • Use caution when increasing the dose above 5 mg	• Moderate hepatic impairment: do not exceed 5 mg • Severe hepatic impairment: avoid; not been studied in this population • No dose adjustment for mild hepatic impairment; may have increased risk of somnolence • No dose adjustment for renal impairment

Abbreviations: CNS, central nervous system; CR, controlled-release; MRHD, maximum recommended human dose; NAS, neonatal abstinence syndrome; vs, versus

Table 9. Recommendations for Use in Special Populations According to Product Labeling

Active Ingredient (Brands)	Pregnancy	Breastfeeding	Older Adults (>65 years)	Renal or Hepatic Impairment
Daridorexant[12] (Quviviq)	• No human data • No fetal or maternal toxicities occurred in animal studies	• Unknown if secreted in human milk, but likely since it is present in animal milk • No human data • Monitor for excessive sedation in drug-exposed newborns • Consider risks vs benefits	• No dose adjustment is recommended • Incidence of fatigue and somnolence increased with age • Older adults are at higher risk of falls due to sedation effects	• Moderate hepatic impairment: do not exceed 25 mg • Severe hepatic impairment: avoid; not been studied in this population • No dose adjustment for mild hepatic impairment • No dose adjustment for renal impairment
Melatonin Receptor Agonists				
Ramelteon[23] (Rozerem)	• No drug-associated risks of fetal or maternal outcomes have been identified from post-marketing reports • Animal studies imply potential fetal harm	• Unknown if secreted in human milk, but likely since it is present in animal milk • No human data • Somnolence may occur in drug-exposed neonates • Consider risks vs benefits	• No clinically relevant differences were observed between older and younger adults	• Mild/moderate hepatic impairment: use caution due to increased drug exposure • Severe hepatic impairment: avoid • No dose adjustment for renal impairment
Tasimelteon[13] (Hetlioz; Hetlioz LQ)	• Insufficient human data • Animal studies imply potential fetal harm	• Unknown if secreted in human milk • No human data • Consider risks vs benefits	• Drug exposure is increased by approximately twofold in older adults relative to younger adults	• Severe hepatic impairment: avoid; not been studied in this population • No dose adjustment for mild/moderate hepatic impairment • No dose adjustment for renal impairment

Abbreviations: CNS, central nervous system; CR, controlled-release; MRHD, maximum recommended human dose; NAS, neonatal abstinence syndrome; vs, versus

8.0 SAFETY

8.1 Adverse Events

The commonly reported adverse events (AEs) as reported in the prescribing information are summarized below. Details are provided about the AE profile in children for products that are approved for use in the this patient population (ie, tasimelteon).

Generally, due to older adults (≥65 years of age) having an increased risk of experiencing sedative side effects, certain agents are initiated at lower dosages relative to the younger population (refer to **Table 2** for the FDA-recommended dosages).[14-18,20-22]

Z-drugs:

- Zolpidem
  - Ambien
    - Short-term (<10 nights; AE ≥1%; significant difference from placebo): drowsiness, dizziness, diarrhea[14]
    - Long-term (25–35 nights; AE ≥3%; significant difference from placebo): dizziness, drugged feelings[14]
  - Ambien CR (AE >10% in either older adults or adults): next-day somnolence, headache, dizziness[15]
  - Intermezzo (AE >1% in adults): nausea, fatigue, headache[17]
  - Edluar
    - Short-term (<10 nights; AE ≥1%; significant difference from placebo): drowsiness, dizziness, diarrhea[16]
    - Long-term (28–35 nights; AE ≥3%; significant difference from placebo): dizziness, drugged feelings[16]
  - Zolpimist
    - Short-term (<10 nights; AE ≥1%; significant difference from placebo): drowsiness, dizziness, diarrhea[18]
    - Long-term (28–35 nights; AE ≥3%; significant difference from placebo): dizziness, drugged feelings[18]
- Eszopiclone (AE ≥2%): unpleasant taste, somnolence, headache, dizziness, respiratory infection, rash, dry mouth, anxiety, hallucinations, and viral infections[20]
- Zaleplon (AE ≥5%; at least twice the incidence of the placebo group): abdominal pain[21]

Orexin receptor antagonists:

- Suvorexant (AE ≥5%; at least twice the incidence of the placebo group): somnolence[19]
- Lemborexant (AE ≥5%; at least twice the incidence of the placebo group): somnolence[11]
- Daridorexant (AE ≥5%; equal to or greater than the incidence in the placebo group): fatigue, headache, somnolence[12]

Melatonin receptor agonists:

- Ramelteon (AE ≥3%; greater incidence than in the placebo group): somnolence, nausea, dizziness, fatigue, and exacerbated insomnia[23]
- Tasimelteon (AE >5%; at least twice the incidence of the placebo group): increased alanine aminotransferase, headache, nightmares or unusual dreams, urinary tract infection, upper respiratory infection
    - Similar side effect profile in pediatrics (3–15 years of age) for the treatment of nighttime sleep disturbances in SMS, and patients aged ≥16 years for the treatment of N24SWD receiving the oral suspension and capsule formulations, respectively[13]

H_1 Antihistamine Antidepressant:

- Doxepin (AE ≥2%; greater incidence than in the placebo group): nausea, somnolence/sedation, upper respiratory tract infection[22]

8.2 Contraindications

Eszopiclone, zolpidem, zaleplon, ramelteon, and doxepin should not be used in patients with a previous history of a hypersensitivity reaction, including angioedema.[14-18,20-23] In addition, the z-drugs (ie, zolpidem, zaleplon, and eszopiclone) are contraindicated in patients with a history of complex sleep behaviors[14-18,20,21]; ramelteon should not be used with fluvoxamine (strong CYP1A2 inhibitor),[23] and doxepin should not be used in patients who currently or previously received monoamine oxidase inhibitors (MAOIs) within the past 14 days.[22] Labeling for the ORAs states that these agents are contraindicated in patients with narcolepsy.[11,12,19]

Tasimelteon is the only agent that does not contain any labeled contraindications.[13]

8.3 Warnings and Precautions

Label warnings and precautions for the z-drugs, doxepin, ramelteon, and ORAs include the following:[11,12,14-23]

- Recommendation to re-evaluate for potential co-morbid conditions if insomnia fails to remit after 7–10 days on pharmacotherapy
- Recommendation to evaluate for worsening depression or suicidal ideation
- Elevated risk of next-day impairment, especially when used in combination with CNS depressants (eg, opioids, alcohol, benzodiazepines)
- Elevated risk of complex sleep behaviors (eg, sleep-driving, sleep walking)

While the development of complex sleep behaviors is included as a label warning for most of the reviewed agents,[11,12,14-23] only the z-drugs have it listed as a **black box warning**.[14-18,20,21] Complex sleep behaviors may occur at recommended dosages with or without combination use of CNS depressants after an initial or any subsequent administration.[14-18,20,21] Patients generally do not remember experiencing these events, which may result in serious, and potentially fatal injuries to the patient or others.[14-18,20,21] The agent should be discontinued immediately in patients that experience a complex sleep behavior.[11,12,14,19,20]

Other warnings and precautions only apply to certain drugs or drug classes (refer to **Table 10**). The z-drugs, doxepin, and ramelteon include a warning for the potential development of behavioral changes (eg, decreased inhibition, depersonalization, agitation, hallucinations) and abnormal thinking.[14-18,20-23] Any new behavioral or mental changes that occur during treatment should be evaluated immediately.[11,14,19]

ORAs contain a unique warning for the potential risk of sleep paralysis (unable to speak or move during sleep-wake changes for up to several minutes), hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms (night or daytime episodes of brief, periodic leg weakness).[11,12,19] Ramelteon carries a unique warning for the potential risk of altered reproductive hormone concentrations.[23] Lower testosterone and higher prolactin levels have been associated with ramelteon, but effects of chronic (including intermittent) use on the reproductive axis in pediatric and adolescent individuals remains unknown.[23]

The z-drugs (ie, eszopiclone, zolpidem, and zaleplon) also carry warnings for withdrawal symptoms, which may occur upon drug discontinuation or rapid dose reductions.[14-18,20,21] The risk of dependence and abuse may be increased in patients who have a history of substance abuse (drug or alcohol); thus, it is recommend that these agents be used extremely carefully in patients who have a current or prior history of substance abuse.[14,20,21] Doxepin, ramelteon, tasimelteon, and the ORAs do not carry warnings for withdrawal effects, and do not appear to induce physical dependence; however, of these, the ORAs are known to have abuse potential.[11-13,19,22,23]

Due to the potential for respiratory depression, ORAs and z-drugs carry warnings to consider the potential effects on the respiratory drive in patients with compromised respiratory function caused by an associated disorder (eg, chronic obstructive pulmonary disease [COPD], obstructive sleep apnea [OSA]).[11,12,14-21] In addition, ramelteon, and generally doxepin, are not recommended in patients with severe OSA due to not being studied in this patient population.[22,23]

Tasimelteon carries a warning only for the risk of somnolence following administration.[13] Labeling recommends that patients should minimize activity after taking tasimelteon due to the potential for impaired functionality for activities that require alertness.[13]

Table 10 provides additional information on labeled warnings and precautions based on package inserts (ie, product labeling).

Table 10. Contraindications, Warnings, and Precautions According to Product Labeling[1,11-23]

Contraindications
• Hypersensitivity to active substance or any excipient, including history of angioedema (ZOL; ESZ; RAM; DOX; ZAL) • History of complex sleep behaviors (ZOL; ESZ; ZAL) • Narcolepsy (LEM; DAR; SUV) • Use with fluvoxamine (strong CYP1A2 inhibitor; RAM) • Currently taking or previously took MAIOs within the past 14 days (DOX) • Severe urinary retention or untreated narrow angle glaucoma (DOX)
Warnings and Precautions
Applies to agents indicated for the treatment of insomnia: (ESZ, ZAL, ZOL, DOX, RAM, SUV, DAR, LEM) • Re-evaluate for potential co-morbid conditions if insomnia fails to remit after 7–10 days on pharmacotherapy • Worsening depression or suicidal ideation may occur, especially in patients with comorbid depression • Next-day impairment (eg, inability to drive or operate heavy machinery) can occur; thus, avoid activities that require alertness or concentration. The risk of daytime impairment is increased when co-administered with other CNS depressants (eg, opioids, alcohol, benzodiazepines) • The development of complex sleep behaviors (eg, sleep-driving) should be evaluated immediately **Applies to certain medications:** • Behavioral changes (eg, agitation, depersonalization, hallucinations) and abnormal thinking that occurs with pharmacotherapy should be evaluated immediately (ESZ, ZAL, ZOL, DOX, RAM) • Do not rechallenge patients that experience anaphylactic reactions, including angioedema (RAM, ESZ, ZOL, ZAL) • Due to increased drug sensitivity in older adults, initiate and/or use lower maintenance dosages (ESZ, ZAL, ZOL, DOX) • Respiratory effects should be considered in patients with compromised respiratory function (DAR, LEM, SUV, ESZ, ZAL, ZOL) • In patients with severe OSA, use should be avoided (RAM) or generally not recommended (DOX) • Withdrawal symptoms can occur with sudden discontinuation or dramatic dose reductions (ZOL, ESZ, ZAL) • In patients with altered hemodynamic or metabolic responses or hepatic impairment, caution should be used (ESZ, ZAL, ZOL); avoid in patients with severe hepatic impairment (ZOL) • May cause reproductive hormone changes (reduced testosterone; increased prolactin; RAM) • May cause sleep paralysis, cataplexy-like symptoms, or hypnagogic/hypnopompic hallucinations (DAR, LEM, SUV) • May cause somnolence; patients should minimize activity after administration due to the potential for impaired functionality for activities that require alertness (TAS) • Dose may need to be reduced when used in combination with sedating antihistamines or CNS depressants due to the potential for additive sedative effects (DOX)

Abbreviations: DAR, daridorexant; DOX, doxepin; ESZ, eszopiclone; LEM, lemborexant; MAOIs, monoamine oxidase inhibitors; OSA, obstructive sleep apnea; RAM, ramelteon; SUV, suvorexant; TAS, tasimelteon; ZAL, zaleplon; ZOL, zolpidem

8.4 Drug-drug Interactions

Drug-drug interactions (DDIs) are a potential concern for these agents.[11-23] Avoiding the use of sedating hypnotics (eg, z-drugs, doxepin, ramelteon) with CNS depressants, including alcohol, is recommended due to the additive sedating effects.[14-18,22]

The z-drugs and ORAs are extensively metabolized by CYP3A4:

- The coadministration of *strong* CYP3A4 inhibitors (eg, ketoconazole) and/or inducers (eg, rifampin) is not recommended[14-18,20,21]
- Additionally, lemborexant is not recommended to be used with moderate CYP3A inhibitors (eg, verapamil, fluconazole) and/or inducers (eg, modafinil, efavirenz).[11] A maximum dose reduction (5 mg) is recommended for lemborexant when taken with weak CYP3A inhibitors (eg, ranitidine)[11]
- While moderate CYP3A4 *inducers* are not recommended to be used with daridorexant, the maximum dose is reduced to 25 mg when used with moderate CYP3A4 *inhibitors*[12]
- For suvorexant, a lower initial dose (5 mg) is recommended when used with moderate CYP3A inhibitors, with a potential maximum dose up to 10 mg based on treatment response[19]

The melatonin receptor agonists (tasimelteon and ramelteon) are extensively metabolized by CYP1A2 and CYP3A4:

- The coadministration of strong CYP1A2 inhibitors (eg, fluvoxamine) is not recommended due to the potential increase in drug exposure (contraindication for ramelteon)[13,23]
- The combination use of tasimelteon with strong CYP3A4 inducers should be avoided[13]
- While the labeling for ramelteon notes decreased drug exposure with strong CYP inducers (eg, rifampin), labeling does not explicitly recommend that combination use should be avoided[23]

Table 11 provides a summary of potential DDIs based on product labeling.

Table 11. Drug-Drug Interaction Information According to Product Labeling

Drug Interactions
• Zolpidem (all products): Imipramine, chlorpromazine, CNS depressants (eg, alcohol, opioids), ketoconazole (strong CYP3A inhibitor), CYP3A4 inducers (eg, rifampin) • Eszopiclone: Rifampicin, ketoconazole, CNS depressants • Zaleplon: Imipramine, CNS depressants, ketoconazole, CYP3A4 inducers • Doxepin: Cimetidine, MAOIs, CNS depressants, including alcohol and sedating antihistamines, tolazamide • Ramelteon: Donepezil, doxepin, ketoconazole, alcohol, fluconazole (strong CYP2C9 inhibitor), rifampin • Tasimelteon: Strong CYP3A4 inducers, strong CYP1A2 inhibitors • Suvorexant: Digoxin, strong CYP3A inducers, CYP3A inhibitors • Lemborexant: Strong or moderate CYP3A inducers and/or inhibitors, weak CYP3A inhibitors • Daridorexant: Strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers, moderate CYP3A4 inhibitors

Abbreviations: CYP, cytochrome P450; MAOIs, monoamine oxidase inhibitors;

REFERENCES

1. Gonzales V, Frydrych V, Martinez Alonso E, et al. Utah Medicaid Pharmacy and Therapeutics Committee Drug Class Review Report. Hypnotics (Non-benzodiazepines, non-barbiturates). Report finalized May 2019; presented June 2019. Accessed July 6, 2022. Available at: https://medicaid.utah.gov/pharmacy/pt-committee/

2. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. 2017;13(2):307-349.

3. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest*. 2014;146(5):1387-1394.

4. Perez MN, Salas RME. Insomnia. *Continuum (Minneap Minn)*. 2020;26(4):1003-1015.

5. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med*. 2016;165(2):125-33.

6. Abbott SM. Non-24-hour Sleep-Wake Rhythm Disorder. *Neurol Clin*. 2019;37(3):545-552.

7. Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). An Update for 2015: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. 2015;11(10):1199-236.

8. UpToDate.com. Non-24-hour sleep-wake rhythm disorder [by SM Abbott]. [Online database.] Waltham, MA: Wolters Kluwer. Last updated April 13, 2022. Accessed July 7, 2022. Available at: https://www.uptodate.com/contents/non-24-hour-sleep-wake-rhythm-disorder.

9. Smith ACM, Boyd KE, Brennan C, et al. Smith-Magenis Syndrome. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. *GeneReviews(®)*. University of Washington, Seattle Copyright © 1993-2022, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.

10. Kaplan KA, Elsea SH, Potocki L. Management of Sleep Disturbances Associated with Smith-Magenis Syndrome. *CNS Drugs*. 2020;34(7):723-730.

11. Eisai Inc. Dayvigo (lemborexant) tablets, for oral use [Package insert]. Revised March 2022. Woodcliff Lake, NJ: Eisai Inc.

12. Idorsia Pharmaceuticals US Inc. Quviviq (daridorexant) tablets, for oral use [Package insert]. Revised April 2022. Radnor, PA: Idorsia Pharmaceuticals US Inc.

13. Vanda Pharmaceuticals Inc. Hetlioz (tasimelteon) capsules and suspension, for oral use [Package Insert]. Revised December 2020. Washington, D.C.: Vanda Pharmaceuticals Inc.

14. Sanofi-aventis US LLC. Ambien (zolpidem tartrate) tablets, for oral use [Package Insert]. Revised February 2022. Bridgewater, NJ: Sanofi-aventis US LLC.

15. Sanofi-aventis US LLC. Ambien CR (zolpidem tartrate) extended-release tablets, for oral use [Package insert]. Revised February 2022. Bridgewater, NJ: Sanofi-aventis US LLC.

16. Meda Pharmaceuticals Inc. Edluar (zolpidem tartrate) sublingual tablets, for oral use [Package Insert]. Revised August 2019. Somerset, NJ: Meda Pharmaceuticals Inc.

17. Purdue Pharma L.P. Intermezzo (zolpidem tartrate) sublingual tablets, for oral use [Package insert]. Revised August 2019. Stamford, CT: Purdue Pharma L.P.

18. Aytu BioScience Inc. Zolpimist (zolpidem tartrate) spray, for oral use [Package insert]. Revised August 2019. Englewood, CO: Aytu BioScience Inc.

19. Merck & Co. Inc. Belsomra (suvorexant) tablets, for oral use [Package insert]. Revised March 2021. Whitehouse Station, NJ: Merck & Co. Inc.

20. Sunovion Pharmaceuticals Inc. Lunesta (eszopiclone) tablets, for oral use [Package insert]. Revised August 2019. Marlborough, MA: Sunovion Pharmaceuticals Inc.

21. Pfizer Inc. Sonata (zaleplon) capsules, for oral use [Package insert]. Revised December 2019. New York, NY: Pfizer Inc.

22. Currax Pharmaceuticals LLC. Silenor (doxepin) tablets, for oral use [Package insert]. Revised October 2020. Morristown, NJ: Currax Pharmaceuticals LLC.

23. Takeda Pharmaceuticals America Inc. Rozerem (ramelteon) tablets, for oral use [Package insert]. Revised November 2021. Lexington, MA: Takeda Pharmaceuticals America Inc.

24. Neubauer DN. Tasimelteon for the treatment of non-24-hour sleep-wake disorder. *Drugs Today (Barc)*. 2015;51(1):29-35.

25. Hetlioz.com. Welcome to Hetlioz (tasimelteon). [Online website]. Accessed July 15, 2022. Available at: https://hetlioz.com.

26. Center for Drug Evaluation and Research. Multi-discipline review (application number 214517Orig1s000): Tasimelteon (Hetlioz). US Food and Drug Administration. 2020. Accessed July 15, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214517Orig1s000MultidisciplineR.pdf.

27. PRNewswire.com. FDA approves Hetlioz (tasimelteon) for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome. [Online website]. Accessed July 5, 2022. Available at: https://www.prnewswire.com/news-releases/fda-approves-hetlioz-tasimelteon-for-the-treatment-of-nighttime-sleep-disturbances-in-smith-magenis-syndrome-301183162.html.

28. Chowdhuri S, Ulmer C, Mysliwiec V, Spevak C, et al. VA/DoD Clinicial Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea [Guidelines]. Department of Veterans Affairs/Department of Defense. Last updated 2019. Accessed July 5, 2022. Available at: https://www.healthquality.va.gov/guidelines/CD/insomnia/VADoDSleepCPGFinal508.pdf.

29. Edinger JD, Arnedt JT, Bertisch SM, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. Feb 1 2021;17(2):255-262. doi:10.5664/jcsm.8986

30. Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res*. 2017;26(6):675-700.

31. Wilson S, Anderson K, Baldwin D, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update. *J Psychopharmacol*. 2019;33(8):923-947.

32. Smith ACM, Boyd KE, Brennan C, Charles J, et al. PRISMS Medical Management Guidelines for an Individual Diagnosed with SMS [Guidelines]. Parents and Researchers Interested In Smith-Magenis Syndrome. Last updated 2018. Accessed July 15, 2022. Available at: https://www.prisms.org/wp-content/uploads/pdf/mmg/PRISMS_Medical_Management_Guidelines2018.pdf.

33. Citrome L, Juday T, Frech F, Atkins N, Jr. Lemborexant for the Treatment of Insomnia: Direct and Indirect Comparisons With Other Hypnotics Using Number Needed to Treat, Number Needed to Harm, and Likelihood to Be Helped or Harmed. *J Clin Psychiatry*. 2021;82

34. Moline M, Zammit G, Cheng JY, Perdomo C, Kumar D, Mayleben D. Comparison of the effect of lemborexant with placebo and zolpidem tartrate extended release on sleep architecture in older adults with insomnia disorder. *J Clin Sleep Med*. 2021;17(6):1167-1174.

35. Rosenberg R, Murphy P, Zammit G, et al. Comparison of Lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial. *JAMA Netw Open*. 2019;2(12):e1918254.

36. Shigetsura Y, Imai S, Endo H, et al. Assessment of Suvorexant and Eszopiclone as Alternatives to Benzodiazepines for Treating Insomnia in Patients With Major Depressive Disorder. *Clin Neuropharmacol*. 2022;45(3):52-60.

37. Erman MK, Zammit G, Rubens R, et al. A polysomnographic placebo-controlled evaluation of the efficacy and safety of eszopiclone relative to placebo and zolpidem in the treatment of primary insomnia. *J Clin Sleep Med*. Jun 15 2008;4(3):229-34.

38. Ancoli-Israel S, Walsh JK, Mangano RM, Fujimori M. Zaleplon, A Novel Nonbenzodiazepine Hypnotic, Effectively Treats Insomnia in Elderly Patients Without Causing Rebound Effects. *Prim Care Companion J Clin Psychiatry*. 1999;1(4):114-120.

39. Brasure M, MacDonald R, Fuchs E. *Comparative Effectiveness Reviews, No. 159: Management of Insomnia Disorder*. Vol 2015 Dec. Rockville, MD: Agency for Healthcare Research and Quality US; 2015.

40. Wilt TJ, MacDonald R, Brasure M, et al. Pharmacologic Treatment of Insomnia Disorder: An Evidence Report for a Clinical Practice Guideline by the American College of Physicians. *Ann Intern Med*. 2016;165(2):103-12.

41. Roerig Division of Pfizer Inc. Sinequan (doxepin HCl) capsules and concentrate, for oral use [Package insert]. Revised June 2014. New York, NY: Roerig Division of Pfizer Inc.

42. UpToDate.com. Overview of the treatment of insomnia in adults [by JW Winkelman]. [Online database.] Waltham, MA: Wolters Kluwer. Last updated April 27, 2022. Accessed July 5, 2022. Available at: https://www.uptodate.com/contents/overview-of-the-treatment-of-insomnia-in-adults.

43. UpToDate.com. Risk factors, comorbidities, and consequences of insomnia in adults [by MH Bonnet and DL Arand]. [Online database.] Waltham, MA: Wolters Kluwer. Last updated April 15, 2022. Accessed July 5, 2022. Available at: https://www.uptodate.com/contents/risk-factorscomorbidities-and-consequences-of-insomnia-in-adults.

44. Utah Department of Health & Human Services. *Utah Medicaid Preferred Drug List & Pharmacy Coverage Resources.* Utah Department of Health & Human Services; 2022. Last Updated August 1, 2022. Accessed August 8, 2022. Available at: https://medicaid.utah.gov/pharmacy/preferred-drug-list/

45. Luloh M, Gonzales V, Heath L, et al. Utah Medicaid Drug Utilization Review Report. Guidelines for the treatment of insomnia in adults. Report finalized June 2022; presented July 2022. Accessed July 6, 2022. Available at: https://medicaid.utah.gov/pharmacy/drug-utilization-review-board/.

46. McMaster Univiersity Health Information Research Unit. Search filters for Medline in Ovid syntax and the PubMed translation. Last modified February 2016. Accessed July 6, 2022. Available at: https://hiru.mcmaster.ca/hiru/hiru_hedges_medline_strategies.aspx.

47. Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins J, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

48. Wang L, Pan Y, Ye C, et al. A network meta-analysis of the long- and short-term efficacy of sleep medicines in adults and older adults. *Neurosci Biobehav Rev*. 2021;131:489-496.

49. McElroy H, O'Leary B, Adena M, Campbell R, Monfared AAT, Meier G. Comparative efficacy of lemborexant and other insomnia treatments: a network meta-analysis. *J Manag Care Spec Pharm*. 2021;27(9):1296-1308.

50. Riemann D, Benz F, Dressle RJ, et al. Insomnia disorder: State of the science and challenges for the future. *J Sleep Res*. 2022;

51. Rösner S, Englbrecht C, Wehrle R, Hajak G, Soyka M. Eszopiclone for insomnia. *Cochrane Database Syst Rev*. 2018;10(10):Cd010703.

52. UpToDate.com. Evaluation and diagnosis of insomnia in adults [by MH Bonnet and DL Arand]. [Online database.] Waltham, MA: Wolters Kluwer. Last updated June 2021. Accessed July 7, 2022. Available at: https://www.uptodate.com/contents/evaluation-and-diagnosis-of-insomniain-adults.

53. ChoosingWisely.org. Don't perform polysomnography in chronic insomnia patients unless there is concern for a comorbid sleep disorder [American Academy of Sleep Medicine]. [Online database.] Philadelphia, PA: ABIM Foundation. Last updated December 21, 2021. Accessed July 7, 2022. Available at: https://www.choosingwisely.org/clinician-lists/american-academy-sleepmedicine-polysomnography-for-chronic-insomnia/.

54. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4(5):487-504.

55. Non-24.com. Loss of light perception. [Online website]. Accessed July 7, 2022. Available at: https://www.non-24.com/loss-of-light-perception.

56. De Leersnyder H. Smith-Magenis syndrome. *Handb Clin Neurol*. 2013;111:295-6.

57. Sateia MJ, Sherrill WC, Jr., Winter-Rosenberg C, Heald JL. Payer Perspective of the American Academy of Sleep Medicine Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia. *J Clin Sleep Med*. Feb 15 2017;13(2):155-157. doi:10.5664/jcsm.6428

58. Walsh JK, Pollak CP, Scharf MB, Schweitzer PK, Vogel GW. Lack of residual sedation following middle-of-the-night zaleplon administration in sleep maintenance insomnia. *Clin Neuropharmacol*. 2000;23(1):17-21.

59. Center for Drug Evaluation and Research. Medical Review(s), Application Number 21-774: Ambien CR (Zolpidem Tartrate). US Food and Drug Administration. 2005. Accessed July 18, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021774s000_AmbienTOC.cfm.

60. Center for Drug Evaluation and Research. Summary Review, Application Number 21-997: Edluar (Zolpidem Tartrate) Subligual Tablets. US Food and Drug Administration. 2009. Accessed July 18, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021997s000TOC.cfm.

61. Center for Drug Evaluation and Research. Summary Review, Application Number 22-196: Zolpimist (Zolpidem Tartrate) Oral Spray. US Food and Drug Administration. 2008. Accessed July 18, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022196s000TOC.cfm

62. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s), Application Number 022328Orig1s000: Intermezzo (Zolpidem Tartrate). US Food and Drug Administration. 2011. Accessed July 18, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022328Orig1s000TOC.cfm.

63. Landry I, Hall N, Aluri J, et al. Abuse Potential of Lemborexant, a Dual Orexin Receptor Antagonist, Compared With Zolpidem and Suvorexant in Recreational Sedative Users. *J Clin Psychopharmacol*. 2022;42(4):365-373.

64. Murphy P, Kumar D, Zammit G, Rosenberg R, Moline M. Safety of lemborexant versus placebo and zolpidem: effects on auditory awakening threshold, postural stability, and cognitive performance in healthy older participants in the middle of the night and upon morning awakening. *J Clin Sleep Med*. 2020;16(5):765-773.

65. Uemura SI, Imanishi A, Terui Y, et al. Residual effects of low dose of suvorexant, zolpidem, and ramelteon in healthy elderly subjects: A randomized double-blind study. *Neuropsychopharmacol Rep*. 2022;

66. Ufer M, Kelsh D, Schoedel KA, Dingemanse J. Abuse potential assessment of the new dual orexin receptor antagonist daridorexant in recreational sedative drug users as compared to suvorexant and zolpidem. *Sleep*. 2022;45(3)

67. Elie R, Rüther E, Farr I, Emilien G, Salinas E. Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. Zaleplon Clinical Study Group. *J Clin Psychiatry*. 1999;60(8):536-44.

68. Fry J, Scharf M, Mangano R, Fujimori M. Zaleplon improves sleep without producing rebound effects in outpatients with insomnia. Zaleplon Clinical Study Group. *Int Clin Psychopharmacol*. 2000;15(3):141-52.

69. Patel AK, Reddy V, Araujo JF. Physiology, Sleep Stages. *StatPearls*. StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

70. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*. 2001;2(4):297-307.

71. Doi Y, Minowa M, Uchiyama M, et al. Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. *Psychiatry Res*. 2000;97(2-3):165-72.

72. Kojima M, Furukawa TA, Takahashi H, Kawai M, Nagaya T, Tokudome S. Cross-cultural validation of the Beck Depression Inventory-II in Japan. *Psychiatry Res*. 2002;110(3):291-9.

73. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-7.

74. Chen X, Hu N, Wang Y, Gao X. Validation of a brain-computer interface version of the digit symbol substitution test in healthy subjects. *Comput Biol Med*. 2020;120:103729.

75. Leung JL, Lee GT, Lam YH, Chan RC, Wu JY. The use of the Digit Span Test in screening for cognitive impairment in acute medical inpatients. *Int Psychogeriatr*. 2011;23(10):1569-74.

76. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol*. Aug 1990;10(4):244-51.

77. Hill HE, Haertzen CA, Wolbach AB, Jr., Miner EJ. The Addiction Research Center Inventory: Standardization of scales which evaluate subjective effects of morphine, amphetamine, pentobarbital, alcohol, LSD-25, pyrahexyl, and chlorpromazine. *Psychopharmacologia*. May 15 1963;4:167-83. doi:10.1007/bf02584089

78. Haertzen CA. Addiction Research Center Inventory (ARCI): development of a general drug estimation scale. *J Nerv Ment Dis*. 1965;141(3):300-7.

79. Practice Point: Melatonin for the management of sleep disorders in children and adolescents. Canadian Paediatric Society. (posted June 2012, updated 2018, reaffirmed August 2021). https://cps.ca/en/documents/position/melatonin-sleep-disorders-children-adolescents. Published 2018. Accessed August 1, 2022.

80. UpToDate.com. Medical disorders resulting in problem sleeplessness in children [by SH Sheldon]. [Online database.] Waltham, MA: Wolters Kluwer. Last updated April 8, 2022. Accessed August 1, 2022. Available at: https://www.uptodate.com/contents/medical-disorders-resulting-in-problem-sleeplessness-in-children.

81. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019;67(4):674-694.

82. Lexi.com. Eszopiclone (Briggs Drugs in Pregnancy and Lactation): Breast-feeding Summary. [Online database.] Hudson, OH: Lexicomp. Last updated May 23, 2022. Accessed August 4, 2022. Available at: http://online.lexi.com.

83. Lexi.com. Doxepin (Briggs Drugs in Pregnancy and Lactation): Pregnancy Summary. [Online database.] Hudson, OH: Lexicomp. Last updated May 23, 2022. Accessed August 4, 2022. Available at: http://online.lexi.com.

84. Lexi.com. Suvorexant (Briggs Drugs in Pregnancy and Lactation): Pregnancy Summary. [Online database.] Hudson, OH: Lexicomp. Last updated May 23, 2022. Accessed August 4, 2022. Available at: http://online.lexi.com. .

85. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. Doi: 10.1136/bmj.n71.

86. Qaseem A, Snow V, Owens DK, Shekelle P. The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. *Ann Intern Med*. 2010;153(3):194-9.

APPENDIX A – LITERATURE SEARCH STRATEGIES

Ovid Medline Literature Search Strategies

Appendix A, Table 1. Ovid Medline Literature Search Strategy for Systematic Reviews

Database(s): Ovid MEDLINEI and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to June 23, 2022>

Date of search: June 24, 2022

#	Searches	Results
1	exp Sleep Wake Disorders/ or exp "Sleep Initiation and Maintenance Disorders"/ or exp Sleep Stages/de or exp Sleep Latency/de	106703
2	insomnia*.ti,ab,kf,kw.	26620
3	(sleep adj2 (maintenance or latency or onset or initiat* or disorder*)).ti,ab,kf,kw.	38791
4	1 or 2 or 3	130761
5	(tricyclic antidepressant* or TCA or sedative* or hypnotic* or (orexin adj3 (antagonist* or inhibit*)) or nonbenzodiazepine* or non-benzodiazepin* or Z-drug).ti,ab,kf,kw.	58355
6	exp "Hypnotics and Sedatives"/ or antidepressive agents/ or antidepressive agents, tricyclic/ or Orexin Receptor Antagonists/ or sleep aids, pharmaceutical/	182226
7	Doxepin/ or Eszopiclone/ or Zolpidem/ or Ramelteon/ or Suvorexant/ or Lemborexant/ or Tasimelteon/ or Zaleplon/	2647
8	(doxepin or eszopiclone or zolpidem or ramelteon or suvorexant or lemborexant or daridorexant or tasimelteon or zaleplon).ti,ab,kf,kw.	4708
9	5 or 6 or 7 or 8	219165
10	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw	461543
11	(MEDLINE or Embase or PubMed or systematic review).tw. or meta analysis.pt.	431436
12	10 or 11	538357
13	4 and 9 and 12	449
14	Limit 13 to yr="2019 – Current"	**127**

Appendix A, Table 2. Ovid Medline Literature Search Strategy for Randomized Controlled Trials

Database(s): Ovid MEDLINEI and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to June 23, 2022>

Date of search: July 11, 2022

#	Searches	Results
1	exp Sleep Wake Disorders/ or exp "Sleep Initiation and Maintenance Disorders"/ or exp Sleep Stages/de or exp Sleep Latency/de	106896
2	insomnia*.ti,ab,kf,kw.	26723

Appendix A, Table 2. Ovid Medline Literature Search Strategy for Randomized Controlled Trials

Database(s): Ovid MEDLINEI and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to June 23, 2022>

Date of search: July 11, 2022

#	Searches	Results
3	(sleep adj2 (maintenance or latency or onset or initiat* or disorder*)).ti,ab,kf,kw.	38952
4	1 or 2 or 3	131099
5	Doxepin/ or Eszopiclone/ or Zolpidem/ or Ramelteon/ or Suvorexant/ or Lemborexant/ or Tasimelteon/ or Zaleplon/	2651
6	(doxepin or eszopiclone or zolpidem or ramelteon or suvorexant or lemborexant or daridorexant or tasimelteon or zaleplon).ti,ab,kf,kw.	4717
7	5 or 6	5198
8	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1341429
9	4 and 7 and 8	629
10	Limit 9 to yr=”2019 – Current”	**111**

Embase Literature Search Strategies

Appendix A, Table 3. Embase Literature Search Strategy for Systematic Reviews

Date of search: July 7, 2022

#	Searches	Results
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 lemborexant:ti,ab,kw OR daridorexant:ti,ab,kw OR tasimelteon:ti,ab,kw OR zaleplon:ti,ab,kw	7053
2	‘doxepin’/de OR ‘eszopiclone’/de OR ‘zolpidem’/de OR ‘zolpidem tartrate’/de OR ‘ramelteon’/de OR ‘suvorexant’/de OR ‘lemborexant’/de OR ‘daridorexant’/de OR ‘tasimelteon’/de OR ‘zaleplon’/de	21617
3	‘hypnotic sedative agent’/mj OR ‘hypnotic agent’/mj OR ‘benzodiazepine receptor stimulating agent’/mj OR ‘antidepressant agent’/mj OR ‘tricyclic antidepressant agent’/mj OR ‘orexin receptor antagonist’/mj	53594
4	‘hypnotic sedative agent’/exp/dd_cm OR ‘hypnotic agent’/exp/dd_cm OR ‘benzodiazepine receptor stimulating agent’/exp/dd_cm OR ‘antidepressant agent’/exp/dd_cm OR ‘tricyclic antidepressant agent’/exp/dd_cm OR ‘orexin receptor antagonist’/exp/dd_cm	47776
5	antidepressant*:ti,ab,kw OR TCA:ti,ab,kw OR sedative*:ti,ab,kw OR hypnotic*:ti,ab,kw OR (orexin NEAR/3 (antagonist* or inhibit*)):ti,ab,kw OR nonbenzodiazepin*:ti,ab,kw OR ‘non benzodiazepin*’:ti,ab,kw OR ‘z drug’:ti,ab,kw	168972
6	#1 OR #2 OR #3 OR #4 OR #5	236247

Appendix A, Table 3. Embase Literature Search Strategy for Systematic Reviews

Date of search: July 7, 2022

#	Searches	Results
7	'insomnia'/exp/dm_dt OR 'sleep parameters'/exp/dm_dt OR 'circadian rhythm sleep disorder'/exp/dm_dt	9244
8	insomnia*:ti,ab,kw	45068
9	(sleep NEAR/2 (maintenance OR latency OR onset OR initiat* OR disorder*)):ti,ab,kw	65162
10	#7 OR #8 OR #9	102570
11	(cochrane*:jt OR 'systematic review*':jt OR 'meta analysis'/mj OR 'systematic review'/exp OR ((systematic NEAR/3 review):ti,ab,kw) OR 'meta analys*':ti,ab,kw OR metaanalys*:ti,ab,kw OR search*:ti,ab OR pubmed:ab OR embase:ab OR medline:ab OR cochrane:ab OR ((overview NEAR/4 (review OR reviews)):ti)) NOT ('conference abstract'/it OR 'conference review'/it) AND [English]/lim	793568
12	#6 AND #10 AND #11	780
13	#12 AND (**2019**:py OR **2020**:py OR **2021**:py OR **2022**:py)	**205**

Appendix A, Table 4. Embase Literature Search Strategy for Randomized Controlled Trials

Date of search: July 14, 2022

#	Searches	Results
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 lemborexant:ti,ab,kw OR daridorexant:ti,ab,kw OR tasimelteon:ti,ab,kw OR zaleplon:ti,ab,kw	7084
2	'doxepin'/de OR 'eszopiclone'/de OR 'zolpidem'/de OR 'zolpidem tartrate'/de OR 'ramelteon'/de OR 'suvorexant'/de OR 'lemborexant'/de OR 'daridorexant'/de OR 'tasimelteon'/de OR 'zaleplon'/de	21654
3	#1 OR #2	22235
4	'insomnia'/exp/dm_dt OR 'sleep parameters'/exp/dm_dt OR 'circadian rhythm sleep disorder'/exp/dm_dt	9251
5	insomnia*:ti,ab,kw	45366
6	(sleep NEAR/2 (maintenance OR latency OR onset OR initiat* OR disorder*)):ti,ab,kw	65627
7	#4 OR #5 OR #6	103237
8	('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 ((doubl* 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) NOT ('conference abstract'/it OR 'conference review'/it) AND [English]/lim	2216789
9	#3 AND #7 AND #8	1411
10	#9 AND (**2019**:py OR **2020**:py OR **2021**:py OR **2022**:py)	**219**

Epistemonikos Literature Search Strategy

Appendix A, Table 5. Epistemonikos Literature Search Strategy for Systematic Reviews

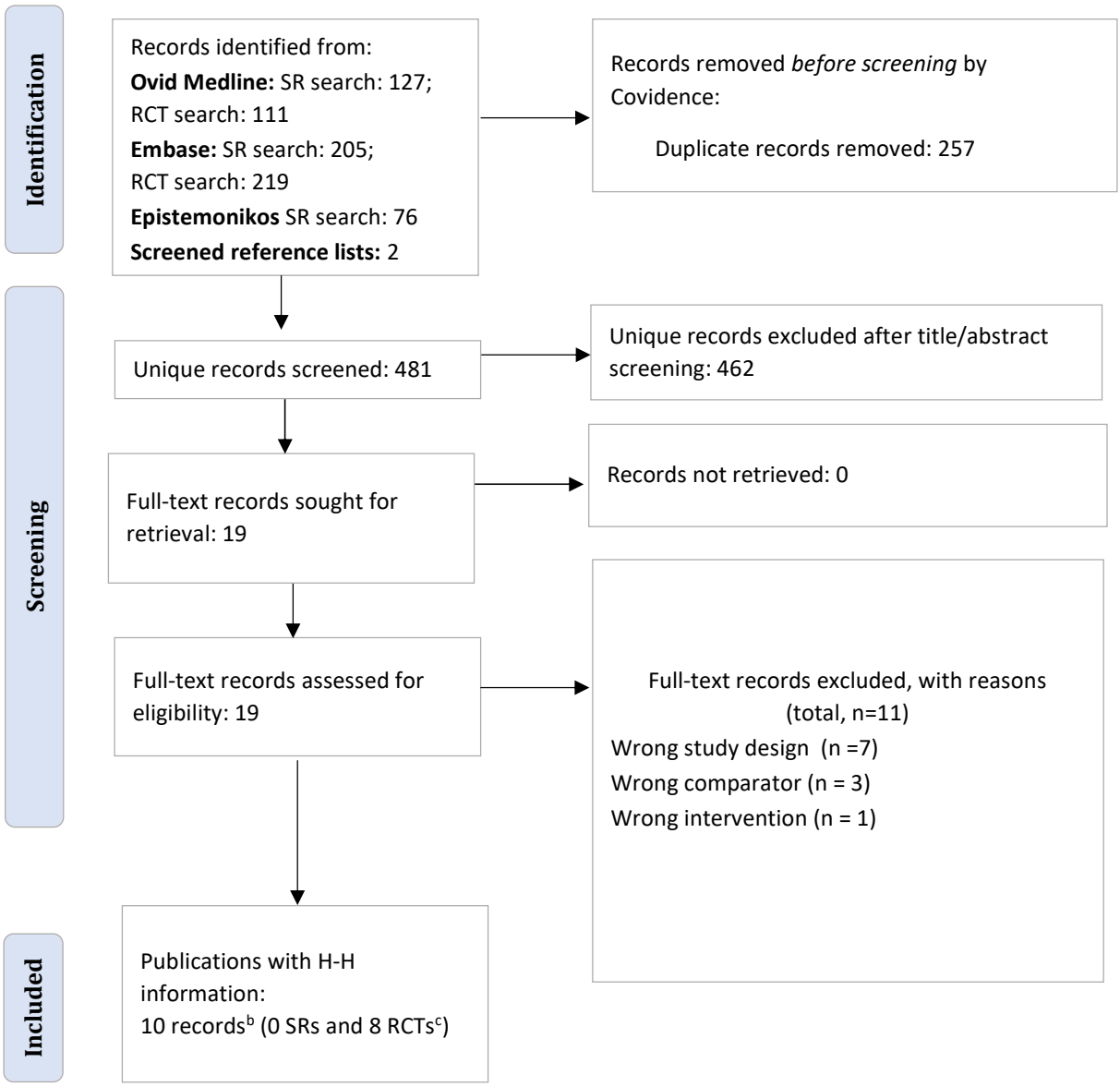
Date of search: July 1, 2022

#	Searches	Results
1	(sleep maintenance) OR (sleep latency) OR (sleep onset) OR (sleep initiat*) OR (sleep disorder*) OR insomnia*	13083
2	**AND** doxepin OR eszopiclone OR zolpidem OR ramelteon OR suvorexant OR lemborexant OR daridorexant OR tasimelteon OR zaleplon OR antidepressant* OR sedative* OR hypnotic* OR (orexin receptor antagonist*) OR (orexin receptor inhibit*) OR 52enzodiazepine52ne* OR non 52enzodiazepine* OR z drug	1150
Filter publication year	From 2019 to 2022	235
Filter publication type	Systematic Review	**76**

APPENDIX B – SCREENING OF STUDIES

The following diagram shows the flow of our screening process for the results from our literature searches, including the number of unique records excluded at each phase. Notably, head-to-head information from our previous 2019 P&T report[1] was included in this report (2 SRMAs),[39,40] but it is not depicted in the diagram below.

Appendix B, Figure 1. PRISMA Flow Chart[a] for Publication Screening



Abbreviations: H-H, head to head; RCT, randomized controlled trial; SR, systematic review

[a] Modified from Page et al. 2021[85]

[b] Includes 3 records that represent 1 RCT

[c] Includes 2 RCTs that were identified from the reference lists of screened SRs

APPENDIX C – SUPPLEMENTARY GUIDELINE TABLES

Appendix C, Table 1. Summary of Guideline Recommendations for the Treatment of Chronic Insomnia in Adults and Other Sleep Disorders

Guideline (Sponsoring Organization; Year)	Recommendations
UNITED STATES GUIDELINES	
Behavioral and Psychological Treatment for Chronic Insomnia Disorder in Adults **(AASM; 2021)**[29]	• CBT-I in combination with another treatment approach is recommended (**Strong**) • Brief therapies as a multicomponent approach is suggested (**Conditional**) • Stimulus control, sleep restriction therapy, and the use of relaxation therapy (*as monotherapy*) is suggested (**Conditional**) • Sleep hygiene should not be used as the only treatment approach (**Conditional**)

Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and OSA **(VA/DoD; 2019)**[28]	Nonpharmacologic Recommendations:
	• Offering CBT-I is recommended (**Strong for**)
	  ○ As first-line treatment, CBT-I is suggested over pharmacologic agents (**Weak for**)
	  ○ Offering CBT-I to patients with comorbid psychiatric conditions is suggested (**Weak for**)
	• Offering BBT-I is suggested (**Weak for**)
	• "Offering auricular acupuncture with seed and pellet"[28] is suggested (**Weak for**)
	• Sleep hygiene as a *singular approach* is suggested against (**Weak against**)
	• The use of cranial electrical stimulation is suggested against (**Weak against**)
	Pharmacologic Recommendations:
	• Low-dose doxepin (ie, 3 or 6 mg) or a z-drug (eg, eszopiclone, zaleplon, zolpidem) for patients requiring the short-term use of pharmacotherapy is suggested (**Weak for**)
	• The use of antipsychotics, benzodiazepines, and trazodone are suggested against (**Weak against**)
	• Ramelteon and suvorexant have insufficient evidence to recommend either for or against use (**Neither for nor against**)
	• Melatonin, diphenhydramine, valerian, and chamomile are suggested against (**Weak against**)
	• Kava is not recommended (**Strong against**)

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; BBT-I, brief behavioral therapy for insomnia; CBT-I, cognitive behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; LOE, level of evidence; N24SWD, non-24 hour sleep-wake disorder; OSA, obstructive sleep apnea; VA, Department of Veterans Affairs; vs, versus

Appendix C, Table 1. Summary of Guideline Recommendations for the Treatment of Chronic Insomnia in Adults and Other Sleep Disorders

Guideline (Sponsoring Organization; Year)	Recommendations
Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults **(AASM; 2017)[2]**	<u>Sleep Maintenance Insomnia (vs no treatment)[a]</u> Recommended for: • Low-dose doxepin (3 or 6 mg) (**Weak; LOE: low**) • Suvorexant (10, 15/20, or 20 mg) (**Weak; LOE: low**) • Eszopiclone (2 or 3 mg) (**Weak; LOE: very low**) • Zolpidem (10 mg) (**Weak; LOE: very low**) • Temazepam (15 mg) (**Weak; LOE: moderate**) Recommended against: • Trazodone (50 mg) (**Weak; LOE: moderate**) • Tiagabine (4 mg) (**Weak; LOE: very low**) • Melatonin (2 mg) (**Weak; LOE: very low**) • Diphenhydramine (50 mg) (**Weak; LOE: low**) • Valerian (dosages vary, along with combinations) (**Weak; LOE: low**) • L-tryptophan (250 mg) (**Weak; LOE: high**) <u>Sleep Onset Insomnia (vs no treatment)[a]</u> Recommended for: • Zaleplon (10 mg) (**Weak; LOE: low**) • Zolpidem (10 mg) (**Weak; LOE: very low**) • Eszopiclone (2 or 3 mg) (**Weak; LOE: very low**) • Temazepam (15 mg) (**Weak; LOE: moderate**) • Triazolam (0.25 mg) (**Weak; LOE: high**) • Ramelteon (8 mg) (**Weak; LOE: very low**) Recommended against: • Trazodone (50 mg) (**Weak; LOE: moderate**) • Tiagabine (4 mg) (**Weak; LOE: very low**) • Melatonin (2 mg) (**Weak; LOE: very low**) • Diphenhydramine (50 mg) (**Weak; LOE: low**) • Valerian (dosages vary, along with combinations) (**Weak; LOE: low**) • L-tryptophan (250 mg) (**Weak; LOE: high**)
Management of Chronic Insomnia Disorder in Adults **(ACP; 2016)[5]**	<u>Nonpharmacologic Recommendations:</u> • As first-line treatment, all patients are recommended to receive CBT-I (**Strong**; **LOE: moderate**) <u>Pharmacologic Recommendations:</u> • For patients with an inadequate response to CBT-I alone, a shared decision-making approach regarding the affordability and benefits/harms of using pharmacologic agents is recommended when deciding to initiate pharmacotherapy (**Weak**; **LOE: low**)

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; BBT-I, brief behavioral therapy for insomnia; CBT-I, cognitive behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; LOE, level of evidence; N24SWD, non-24 hour sleep-wake disorder; OSA, obstructive sleep apnea; VA, Department of Veterans Affairs; vs, versus

Appendix C, Table 1. Summary of Guideline Recommendations for the Treatment of Chronic Insomnia in Adults and Other Sleep Disorders

Guideline (Sponsoring Organization; Year)	Recommendations
EUROPEAN GUIDELINES	

An Updated Consensus Statement on Evidence-based Treatment of Insomnia, Parasomnias, and Circadian Rhythm Disorders **(BAP; 2019)**[31 b]	<u>Nonpharmacologic Recommendations:</u>
	Insomnia:
	• Due to the reduced quality of life, physical/psychological dysfunction, and propensity to develop other conditions (eg, anxiety, depression), insomnia is recommended to be treated (**Strength A**)
	• CBT-I should be offered as first-line therapy (**ungraded statement**), including in older adults (**Strength A**)
	  ○ Multicomponent CBT-I, including stimulus control and sleep restriction are recommended as first-line therapy (**Strength A**)
	  ○ CBT-I is a reasonable approach for pregnant people based on a small open-label trial (**Strength B**)
	• Either CBT-I in-person or digitally conducted CBT-I (eg, computer or phone-based) are effective (**Strength A**)
	  ○ Digitally conducted CBT-I offers alternatives among evidence-based treatment options used in routine care (**Strength A**)
	Circadian Rhythm Disorders (including N24SWD):
	• Clinical evaluation of N24SWD and delayed sleep wake phase disorder are vital (**Strength A**)
	<u>Pharmacologic Recommendations:</u>
	Insomnia:
	• If CBT-I is unavailable, or the patient has an inadequate response or is unable to participate in CBT-I, an evidence-based pharmacologic agent should be recommended (**ungraded statement**)
	• When prescribing pharmacotherapy, prescribers should consider the efficacy, safety, and duration of action (**Strength A**)
	  ○ Other factors include prior pharmacologic response, side effects, and history of substance disorders (**Strength D**)
	• Ongoing pharmacotherapy is recommended to be used as clinically indicated (**Strength A**)
	  ○ Generally, when discontinuing a hypnotic, it is recommended to be gradually tapered down. Adjunctive therapy with CBT-I has shown to improve outcomes while tapering down the medication (**Strength A**)
	• Pharmacologic agents with an indication for depression may be considered when a psychiatric comorbidity exists, and should be utilized based on the medication-specific pharmacology (**Strength A**)
	  ○ Even with low-doses, fatal toxicity of tricyclic antidepressants warrants awareness for potential overdose (**Strength A**)
	  ○ Antipsychotics should not be used as first-line agents (**Strength D**)
	• Low-dose doxepin is recommend to be effective for insomnia (**Strength A**)

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; BBT-I, brief behavioral therapy for insomnia; CBT-I, cognitive behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; LOE, level of evidence; N24SWD, non-24 hour sleep-wake disorder; OSA, obstructive sleep apnea; VA, Department of Veterans Affairs; vs, versus

Appendix C, Table 1. Summary of Guideline Recommendations for the Treatment of Chronic Insomnia in Adults and Other Sleep Disorders

Guideline (Sponsoring Organization; Year)	Recommendations
	○ "Non-selective histamine antagonists have a limited role in psychiatric and primary care practice for the management of insomnia"[31] (**Strength D**) • In older adults (>55 years of age), extended-release melatonin is recommended first before trying other pharmacologic agents (**Strength B**) • If GABA-A hypnotics are used in older adults, a shorter half-life agent is preferred to minimize adverse effects (**Strength A**) • In pregnant people suffering from intractable insomnia, zolpidem or zopiclone is recommended when short-term pharmacotherapy is indicted, taking into account the risks/benefits (**Strength D**) **Circadian Rhythm Disorders (including N24SWD):** • Melatonin may be used for N24SWD in blind individuals, jet lag disorder, and delayed sleep wake phase disorder (**Strength B**) • Other interventions that may be used include behavioral approaches and scheduled light exposure (for people with sight) (**Strength B/C**) • Patients with circadian rhythm disorders should be treated in specialized sleep clinics due to the additional attention required for therapeutic timing (**Strength D**)
	<u>Pediatric Recommendations for Specific Sleep Disorders:</u> • In children with disturbed sleep, behavioral interventions are recommended to be used first before other types of interventions (eg, medications) (**Strength A**) • In children with autistic spectrum disorder, melatonin has shown to improve sleep (**Strength A**) • In children with attention deficit hyperactivity disorder not being managed with a stimulant, melatonin may be used to improve sleep onset (**Strength B**) <u>Sleep Disorder Recommendations for Adults with Intellectual Disabilities:</u> • The clinical evaluation should be reflective of the sleep disturbance experienced by the patient and used to identify any exacerbating factors (**Strength A**) • Approaches targeting behavioral, environmental, and educational aspects are recommend as first-line (**Strength A**) • Melatonin has been shown to be effective for improving sleep in this patient population (**Strength A**) • "Treatment should be planned within a capacity/best interests framework"[31] (**Strength D**)

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; BBT-I, brief behavioral therapy for insomnia; CBT-I, cognitive behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; LOE, level of evidence; N24SWD, non-24 hour sleep-wake disorder; OSA, obstructive sleep apnea; VA, Department of Veterans Affairs; vs, versus

Appendix C, Table 1. Summary of Guideline Recommendations for the Treatment of Chronic Insomnia in Adults and Other Sleep Disorders

Guideline (Sponsoring Organization; Year)	Recommendations

European Guideline for the Diagnosis and Treatment of Insomnia **(ESRS; 2017)[30] [c]**	<u>Nonpharmacologic Recommendations:</u>
	• For adults of any age, CBT-I is recommended as first-line therapy (**Strong; LOE: high**)
	• As adjunctive interventions, light therapy and exercise may be helpful (**Weak; LOE: low**)
	• "Acupuncture, aromatherapy, foot reflexology, homeopathy, meditative movement, moxibustion, and yoga are not recommended for the treatment of insomnia because of poor evidence"[30] (**Weak; LOE: very low**)
	<u>Pharmacologic Recommendations:</u>
	• If a patient has an inadequate response to CBT-I or is unavailable, the use of pharmacotherapy may be suggested (**ungraded recommendation**)
	• For the short-term treatment of insomnia (≤4 weeks), benzodiazepines and z-drugs are effective (**Strength - ; LOE: high**)
	  ○ Z-drugs are as efficacious as benzodiazepines (**Strength - ; LOE: moderate**)
	  ○ Shorter half-life z-drugs and benzodiazepines may have less next-morning sedation (**Strength - ; LOE: moderate**)
	• For the short-term treatment of insomnia, sedating antidepressants (eg, doxepin) are effective, taking into consideration contraindications (**Strength - ; LOE: moderate**)
	• Usually ongoing therapy with benzodiazepines, z-drugs, or sedating antidepressants are not recommended due to the adverse effects, risks, and lack of available evidence. Reducing daily administration to intermittent dosing is recommended, if applicable (**Strong; LOE: low**)
	• The use of antihistamines (**Strong; LOE: low**) and antipsychotics (**Strong; LOE: very low**) are not recommended due to insufficient evidence
	• Usually, the use of melatonin is not recommended due to low efficacy (**Weak; LOE: low**)
	• "Valerian and other phytotherapeutics are not recommended for the treatment of insomnia because of poor evidence"[30] (**Weak; LOE: low**)

[a] *Some pharmacologic agents were included in both sleep maintenance and sleep onset categories*

[b] *Not all recommendations regarding pregnancy or menopause are included (eg, use of hormone therapy, pregnancy-related complaints). Please refer to the guideline for all recommendations pertaining to these patient populations. The guideline does not provide any recommendations for parasomnias.*

[c] *Only recommendations regarding the treatment of insomnia were extracted from the guideline. Please refer to the guideline for recommendations about the diagnosis of insomnia*

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; BBT-I, brief behavioral therapy for insomnia; CBT-I, cognitive behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; LOE, level of evidence; N24SWD, non-24 hour sleep-wake disorder; OSA, obstructive sleep apnea; VA, Department of Veterans Affairs; vs, versus

Appendix C, Table 2. Guideline Strength of Recommendation and Level of Evidence Definitions

AASM; 2021[29]	
Strong Recommendation Strength	Recommended for the majority of patients
Conditional Recommendation Strength	Suggested for most patients, although appropriateness may differ based on the patient's unique clinical situation. The physician should use their clinical judgement, taking into consideration the patient's preferences and values to determine if the suggested course is appropriate.
VA/DoD; 2019[28], AASM; 2017[2a]	
Recommendation GRADE was based on the following 4 domains: (1) equipoise of risks compared to benefits, (2) quality of evidence (ie, high, moderate low, very low), (3) values and preferences of the target population, and (4) other factors such as cost. In addition, consideration of the strength and direction of the recommendation was accounted for in the GRADE framework.	
Strong Recommendation Strength	Recommend either for or against this treatment based on the high degree of certainty from the GRADE assessment
Weak Recommendation Strength	Suggested either for or against this treatment based on the lower degree of certainty from the GRADE assessment
ACP; 2016[5]	
High quality evidence	"RCTs without important limitations or overwhelming evidence from observational studies"[86]
Moderate quality evidence	"RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies"[86]
Low quality evidence	"Observational studies or case series"[86]
Strong Recommendation Strength	Either benefits distinctly outweigh the risks OR the risks distinctly outweigh the benefits
Weak Recommendation Strength	Equipoise exists between the benefits and risks
BAP; 2019[31]	
Level Ia	Evidence from meta-analysis of RCTs
Level Ib	Evidence from ≥1 RCT
Level Iia	Evidence from ≥1 non-randomized controlled study
Level IIb	Evidence from ≥1 other quasi-experimental study design
Level III	"Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies."[31]
Level IV	"Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both."[31]
Strength A	Based on level I evidence
Strength B	Based on level II or extrapolated from level I evidence
Strength C	Based on level III evidence or extrapolated from level I or II evidence
Strength D	Based on level IV evidence or extrapolated from level I, II, or III evidence

Appendix C, Table 2. Guideline Strength of Recommendation and Level of Evidence Definitions

ESRS; 2017[30]	
High quality evidence	"Further research is very unlikely to change our confidence in the estimate of effect"[30 b]
Moderate quality evidence	"Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate"[30 b]
Low quality evidence	"Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate"[30 b]
Very low quality evidence	"Any estimate of effect is uncertain"[30 b]
Strong Recommendation Strength	As determined based on author consensus from the GRADE assessment
Weak Recommendation Strength	

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; DoD, Department of Defense; ESRS, European Sleep Research Society; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RCTs, randomized controlled trials; VA, Department of Veterans Affairs

[a] *Used a GRADE framework based on the balance of the 4 domains listed, except the consideration of other factors*

[b] *Located in Table S1 on page 6 of the supplemental material for the European guideline for the diagnosis and treatment of insomnia*[30]

APPENDIX D – INCLUDED AND EXCLUDED REFERENCES

List of Included References

Randomized Controlled Trials

1. Shigetsura Y, Imai S, Endo H, et al. Assessment of Suvorexant and Eszopiclone as Alternatives to Benzodiazepines for Treating Insomnia in Patients With Major Depressive Disorder. *Clin Neuropharmacol*. 2022;45(3):52-60.
2. Landry I, Hall N, Aluri J, et al. Abuse Potential of Lemborexant, a Dual Orexin Receptor Antagonist, Compared With Zolpidem and Suvorexant in Recreational Sedative Users. *J Clin Psychopharmacol*. 2022;42(4):365-373.
3. Murphy P, Kumar D, Zammit G, Rosenberg R, Moline M. Safety of lemborexant versus placebo and zolpidem: effects on auditory awakening threshold, postural stability, and cognitive performance in healthy older participants in the middle of the night and upon morning awakening. *J Clin Sleep Med*. 2020;16(5):765-773.
4. Rosenberg R, Murphy P, Zammit G, et al. Comparison of Lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial. *JAMA Netw Open*. 2019;2(12):e1918254.
5. Uemura SI, Imanishi A, Terui Y, et al. Residual effects of low dose of suvorexant, zolpidem, and ramelteon in healthy elderly subjects: A randomized double-blind study. *Neuropsychopharmacol Rep*. 2022;
6. Ufer M, Kelsh D, Schoedel KA, Dingemanse J. Abuse potential assessment of the new dual orexin receptor antagonist daridorexant in recreational sedative drug users as compared to suvorexant and zolpidem. *Sleep*. 2022;45(3)

Randomized controlled trials identified from screened systematic reviews:

7. Ancoli-Israel S, Walsh JK, Mangano RM, Fujimori M. Zaleplon, A Novel Nonbenzodiazepine Hypnotic, Effectively Treats Insomnia in Elderly Patients Without Causing Rebound Effects. *Prim Care Companion J Clin Psychiatry*. 1999;1(4):114-120.
8. Erman MK, Zammit G, Rubens R, et al. A polysomnographic placebo-controlled evaluation of the efficacy and safety of eszopiclone relative to placebo and zolpidem in the treatment of primary insomnia. *J Clin Sleep Med*. Jun 15 2008;4(3):229-34.

Other publications that contained data from the SUNRISE 1 trial:

9. Citrome L, Juday T, Frech F, Atkins N, Jr. Lemborexant for the Treatment of Insomnia: Direct and Indirect Comparisons With Other Hypnotics Using Number Needed to Treat, Number Needed to Harm, and Likelihood to Be Helped or Harmed. *J Clin Psychiatry*. 2021;82
10. Moline M, Zammit G, Cheng JY, Perdomo C, Kumar D, Mayleben D. Comparison of the effect of lemborexant with placebo and zolpidem tartrate extended release on sleep architecture in older adults with insomnia disorder. *J Clin Sleep Med*. 2021;17(6):1167-1174.

List of Excluded References

Wrong study design

1. Waters K. Review of the Efficacy and Safety of Lemborexant, a Dual Receptor Orexin Antagonist (DORA), in the Treatment of Adults With Insomnia Disorder. *Ann Pharmacother*. 2022;56(2):213-221.
2. Sys J, Van Cleynenbreugel S, Deschodt M, Van der Linden L, Tournoy J. Efficacy and safety of non-benzodiazepine and non-Z-drug hypnotic medication for insomnia in older people: a systematic literature review. *Eur J Clin Pharmacol*. 2020;76(3):363-381.
3. Samara MT, Huhn M, Chiocchia V, et al. Efficacy, acceptability, and tolerability of all available treatments for insomnia in the elderly: a systematic review and network meta-analysis. *Acta Psychiatr Scand*. 2020;142(1):6-17.
4. Chiu HY, Lee HC, Liu JW, et al. Comparative efficacy and safety of hypnotics for insomnia in older adults: a systematic review and network meta-analysis. *Sleep*. 2021;44(5)
5. Kishi T, Nomura I, Matsuda Y, et al. Lemborexant vs suvorexant for insomnia: A systematic review and network meta-analysis. *J Psychiatr Res*. 2020;128:68-74.
6. McElroy H, O'Leary B, Adena M, Campbell R, Monfared AAT, Meier G. Comparative efficacy of lemborexant and other insomnia treatments: a network meta-analysis. *J Manag Care Spec Pharm*. 2021;27(9):1296-1308.
7. Wang L, Pan Y, Ye C, et al. A network meta-analysis of the long- and short-term efficacy of sleep medicines in adults and older adults. *Neurosci Biobehav Rev*. 2021;131:489-496.

Wrong comparator

8. Rios P, Cardoso R, Morra D, et al. Comparative effectiveness and safety of pharmacological and non-pharmacological interventions for insomnia: an overview of reviews. *Syst Rev*. 2019;8(1):281.
9. Scharner V, Hasieber L, Sönnichsen A, Mann E. Efficacy and safety of Z-substances in the management of insomnia in older adults: a systematic review for the development of recommendations to reduce potentially inappropriate prescribing. *BMC Geriatr*. 2022;22(1):87.
10. Dauvilliers Y, Zammit G, Fietze I, et al. Daridorexant, a New Dual Orexin Receptor Antagonist to Treat Insomnia Disorder. *Ann Neurol*. 2020;87(3):347-356.

Wrong intervention

11. Louzada LL, Machado FV, Nóbrega OT, Camargos EF. Zopiclone to treat insomnia in older adults: A systematic review. *Eur Neuropsychopharmacol*. 2021;50:75-92.