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GUIDELINES FOR THE TREATMENT OF INSOMNIA IN ADULTS

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ABBREVIATIONS

AASM	American Academy of Sleep Medicine
ACP	American College of Physicians
ADHD	attention-deficit hyperactivity disorder
AEs	adverse events
AGS	American Geriatrics Society
AIS	Athens Insomnia Scale
APA	American Psychiatric Association
ATS	American Thoracic Society
BAP	British Association for Psychopharmacology
BBT-I	brief behavioral therapy for insomnia
BTIs	brief therapies for insomnia
CADTH	Canadian Agency for Drugs and Technologies in Health
CBT-I	cognitive-behavioral therapy for insomnia
CIH	complementary and integrative health
CL	ConsumerLab.com
DED	diazepam equivalent dose
DoD	Department of Defense
DSHEA	Dietary Supplement Health and Education Act
DSM-5	Diagnostic and Statistical Manual of the American Psychiatric Association, Fifth Edition
DUR	Drug Utilization Review
ESRS	European Sleep Research Society
FDA	Food and Drug Administration
GMPs	Good Manufacturing Practices
ICD-11	International Classification of Disease, Eleven Edition
ICER	Institute for Clinical and Economic Review
ICSD-3	International Classification of Sleep Disorders, Third Edition
ISI	Insomnia Severity Index
MeSH	Medical Subject Headings
N24SWD	non-24 hour sleep wake disorder
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NREM	non-rapid eye movement
OSA	obstructive sleep apnea
OTC	over-the-counter
PA	prior authorization
PDL	Preferred Drug List
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index
QoL	quality of life
RCT	randomized controlled trial
REM	rapid eye movement
SCN	suprachiasmatic nucleus
SMS	Smith-Magenis Syndrome

SR	systematic review
SRS	Sleep Research Society
TST	total sleep time
USP	United States Pharmacopeia
VA	Department of Veterans Affairs
WSS	World Sleep Society

1.0 INTRODUCTION

Inadequate amounts of sleep (< 7 hours per night) have been associated with adverse health consequences.¹ Insomnia is a common sleep disorder among adults in the United States (US). According to *International Classification of Sleep Disorders, Third Edition* (ICSD-3), insomnia is defined as trouble initiating and/or maintaining sleep, or premature awakening that results in symptoms during wakefulness (eg, decreased energy, fatigue, problems with attention or cognition, mood fluctuations, irritability).²⁻⁵ Approximately 30–50% of the general population is affected with occasional short-term insomnia, whereas at least 5–10% of the general population has chronic insomnia (defined as symptoms persisting for ≥ 3 months, and occur ≥ 3 times a week).^{3,4} The prevalence of chronic insomnia is significantly higher in individuals who are affected by medical and/or psychiatric conditions, female sex, or older in age.^{3,6} Insomnia may occur as an independent condition, or comorbid with other diseases (eg, anxiety, sleep apnea).^{4,7}

Insomnia poses a significant economic burden due to the higher utilization of health care visits, productivity loss, and insomnia-related errors/accidents.³ Annually, insomnia results in more than 5.5 million outpatient visits.⁶ In the US, annual insomnia-related costs contribute to approximately \$30–\$107 billion.⁷

The initial management of insomnia typically involves resolving contributing factors (eg, poor sleep habits) and treating comorbidities that may interfere with sleep quality.^{3,8} While cognitive behavioral therapy for insomnia (CBT-I) is often preferred first-line, some patients may require CBT-I in combination with pharmacotherapy for a quicker response.⁸ Adults with chronic insomnia use a wide variety of pharmacologic agents with differing pharmacokinetic and pharmacodynamic properties.⁹ The pharmacologic agents with a U.S. Food and Drug Administration (FDA)-approved indication for the treatment of insomnia belong to numerous drug classes including z-drugs (zaleplon, eszopiclone, zolpidem), benzodiazepines (eg, triazolam, estazolam), tricyclic antidepressant/histamine receptor antagonist (ie, doxepin), orexin receptor antagonists (eg, suvorexant, lemborexant), and melatonin receptor agonists (ie, ramelteon).⁷⁻⁹

This report will first review guidelines for the management of chronic insomnia in *adults* (≥ 18 years of age), including nonpharmacologic and pharmacologic therapies. Second, this report will review in detail the efficacy and safety of melatonin, based on information from systematic reviews (SRs) for the treatment of insomnia. This report does not address other sleep disorders (eg, parasomnias, restless leg syndrome, non-24 hour sleep wake disorder [N24SWD], obstructive sleep apnea [OSA]).

2.0 METHODS

2.1 Literature Search for Clinical Practice Guidelines

Search strategies, consisting of keyword phrases and controlled vocabulary, were used for Ovid Medline, including a guideline filter derived from the Canadian Agency for Drugs and Technologies in Health (CADTH),¹⁰ and Epistemonikos to identify relevant clinical practice guidelines for the treatment of insomnia in *adults* (see **Appendix A** for the search strategies). These databases were searched from January 2016 to April 2022. The following additional databases and organizational websites were also searched for guidelines pertaining to the management of adult insomnia (searched in April 2022):

1. American Academy of Sleep Medicine (AASM), Department of Veterans Affairs (VA)/Department of Defense (DoD), American College of Physicians (ACP), European Sleep Research Society (ESRS), British Association for Psychopharmacology (BAP), National Institute for Health and Care Excellence (NICE)
2. UpToDate (<https://www.uptodate.com>)
3. ECRI Guidelines Trust (<https://guidelines.ecri.org/>)

We also searched Choosing Wisely (<https://www.choosingwisely.org/clinician-lists/>), an evidence-based medicine website for clinicians, for position statements for insomnia in adults using the key words “insomnia” or “sleep.”

We excluded guidelines meeting one or more of the following criteria:

1. Published prior to 2016
2. Published by organizations located outside of the US or Europe
3. Only address other specific sleep disorders (eg, parasomnias, circadian rhythm disorders, nightmare disorder, restless legs syndrome, narcolepsy, PTSD-related insomnia)
4. Only address deprescribing of pharmacologic agents (eg, benzodiazepines, antipsychotics) used for the treatment of insomnia

The Institute for Clinical and Economic Review (ICER) website (<https://icer.org/>) was searched for relevant reviews about the treatment of insomnia in adults. Product prescribing information was searched on DailyMed (<https://dailymed.nlm.nih.gov/dailymed/>), the Drugs@FDA website (<https://www.accessdata.fda.gov/scripts/cder/daf/>), and/or the drug sponsors’ websites.

2.2 Literature Search for Systematic Reviews of Melatonin

A literature search for recent (2018 to April 2022) SRs of randomized controlled trials (RCTs) evaluating the efficacy and/or safety of melatonin for the treatment of insomnia in adults was conducted in Epistemonikos using free-text terms (see **Appendix A**).

2.3 Literature Search Results

2.3.1 Chronic Insomnia Guidelines

The following 6 guidelines for treating chronic insomnia were included, listed in order of most recent publication year:

- 2021 American Academy of Sleep Medicine (AASM) guideline on behavioral and psychological treatments for adults with chronic insomnia¹¹
- 2019 Department of Veterans Affairs (VA)/Department of Defense (DoD) guideline for the management of chronic insomnia and obstructive sleep apnea²
- 2019 British Association for Psychopharmacology (BAP) an updated consensus statement for the treatment of insomnia, parasomnias, and circadian rhythm disorders¹²
- 2017 AASM guideline on pharmacologic treatment for adults with chronic insomnia³
- 2017 European Sleep Research Society (ESRS) guideline on the diagnosis and treatment of insomnia¹³

- 2016 American College of Physicians (ACP) guideline on the management of chronic insomnia in adults⁷

2.3.2 Melatonin Systematic Reviews

The following 6 SRs were identified, listed in order of most recent publication year:

- Effect of melatonin on sleep quality and insomnia in patients with cancer (**Jafari-Koulaee et al 2021**)¹⁴
- Efficacy and safety of over-the-counter medications used in older people for the treatment of primary insomnia (**Almond et al 2021**)¹⁵
- Melatonin and melatonin agonists as treatments for benzodiazepines and hypnotics withdrawal in patients with primary insomnia (**Moreira-Fumero et al 2020**)¹⁶
- Adverse events associated with melatonin for the treatment of primary or secondary sleep disorders (**Besag et al 2019**)¹⁷
- An umbrella review for the efficacy of melatonin and melatonin agonists in insomnia (**Low et al 2019**)¹⁸
- Treatment options for insomnia in schizophrenia (**Oliveira et al 2018**)¹⁹

3.0 BACKGROUND ON THE IMPORTANCE OF SLEEP

Sleep plays a fundamental role in an individual's health and overall quality of life (QoL).^{1,20-22} Sleep impacts neural development, learning, and memory; cellular functions for toxin disposal; and physiologic regulation of the cardiovascular and metabolic systems.^{20,22} Thus, it is vital for individuals to acquire good-quality and an adequate duration of sleep on a regular basis.¹

To maintain optimal health, the recommended amount of sleep for adults (aged 18–60) is ≥ 7 hours per night according to the American Academy of Sleep Medicine (AASM) and the Sleep Research Society (SRS).^{1,21} Likewise, the National Sleep Foundation consensus report recommends 7–9 hours of sleep per night for adults 18–64 years of age, and 7–8 hours of sleep per night for older adults (≥ 65 years of age).²³ Obtaining < 7 hours per night is associated with adverse health consequences such as weight gain, diabetes, hypertension, cardiovascular disease, and depression.¹ Additionally, individuals may have impaired immunity, reduced performance, and increased risk of errors/accidents.¹ It remains unclear if excessive sleeping (> 9 hours per night) is associated with adverse health consequences.¹

Another vital component of sleep-quality is the consistency of the sleep-wake schedule.⁴ Similar to sleep deficiency, a fluctuating bedtime and awakening time may cause daytime sleepiness, impairment in concentration and memory, and insomnia.⁴

4.0 INSOMNIA OVERVIEW

The ICSD-3 differentiates insomnia from other sleep disorders (eg, narcolepsy, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders)²⁴ and defines it as trouble initiating and/or maintaining sleep, or premature awakening that results in symptoms during wakefulness (eg, decreased energy, fatigue, problems with attention, irritability) (see **Table 1**).²⁻⁴ To be diagnosed with insomnia, wakefulness should occur despite the intention to sleep, a suitable sleep environment, and an

adequate opportunity to sleep.^{3,4} **Table 1** outlines the symptoms that are required to meet a diagnosis of insomnia according to the ICSD-3 criteria.

Table 1. ICSD-3 Symptom Criteria for Clinical Insomnia

	Sleep	During Wakefulness
Symptoms^a	• Trouble initiating sleep • Trouble maintaining sleep • Premature awakening • Resistance to adhering to an appropriate sleep schedule • Trouble sleeping without parent/caregiver intervention	• Attention, concentration, or memory issues • Diminished family, social, vocational, or academic performance • Mood fluctuations or irritability • Tiredness/ fatigue • Behavioral issues • Lack of motivation/energy/initiative • Accident or error prone • Dissatisfaction or concerns regarding sleep

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

^a Must experience one or more of the symptoms listed in each category (sleep and wakefulness) for a diagnosis⁴

Typically, short-term insomnia (symptoms that persist < 3 months) manifests due to a recognizable stressor, such as work-related stress or personal conflicts (eg, loss of a job or loved one, divorce, argument), and subsides when the stressor is eliminated.¹³ Chronic insomnia is defined as symptoms that persist for ≥ 3 months and occur ≥ 3 times a week.^{3,4} Factors that contribute to the persistence of insomnia include sleep-related anxiety, maladaptive coping strategies, poor sleep habits, and dysregulated physiologic sleep mechanisms.^{12,13} Precipitating factors also include comorbid psychiatric conditions such as depression and anxiety, or pain-inflicting illnesses such as cancer or arthritis.¹²

The ICSD-3 no longer includes primary and secondary (ie, comorbid) insomnia subclassifications.^{4,24,25} Other diagnostic classification systems, the *Diagnostic and Statistical Manual of the American Psychiatric Association, Fifth Edition* (DSM-5) and the *International Classification of Disease, Eleven Edition* (ICD-11) made similar modifications by eliminating the distinction between primary and secondary insomnia.²⁵ The 2005 National Institute of Health (NIH) State of the Science Conference Statement proposed an alternative term for secondary insomnia, “comorbid insomnia”, to refer to insomnia that coincides with another psychiatric/medical condition due to concern that using “secondary insomnia” would promote a delay in treatment.²⁶ These modifications recognize insomnia as an independent disorder,²⁵ although it may be comorbid with other conditions such as anxiety, chronic pain, or other sleep disorders (eg, sleep apnea).⁴ The DSM-5 further suggests that it allows comorbid conditions (medical and psychiatric) and *insomnia* to be addressed and treated appropriately to prevent negative patient outcomes.²⁷

4.1 Diagnostic Assessment of Chronic Insomnia

Generally, the diagnosis of chronic insomnia is based on clinical evaluation that includes a sleep history and evaluation of present sleep-wake performance, as well as a medical, substance, and psychiatric history to identify any potential precipitating comorbid conditions.^{2,13,28} No laboratory tests are required, though select tests may be indicated based on clinical suspicion of other comorbidities.²⁹

Sleep diaries, symptom checklists, and validated self-administered sleep questionnaires (eg, Pittsburgh Sleep Quality Index)³⁰ may be used to aid in determining symptom severity and response to treatment.^{4,28,29} The Department of Veterans Affairs/Department of Defense (VA/DoD) (2019) suggests the Insomnia Severity Index (ISI)³¹ or Athens Insomnia Scale (AIS)³² should be used to assess insomnia symptoms.² Actigraphy may be used to help rule out other sleep disorders, particularly circadian sleep-wake rhythm disorders, or to objectively evaluate sleep parameters (eg, sleep-wake cycles, sleep duration, sleep efficiency).^{13,29} Polysomnography (PSG; sleep study) is not routinely recommended for the diagnosis of chronic insomnia alone, including for occupational workers that experience chronic fatigue.^{4,28,29,33} However, a PSG may be indicated when clinical suspicion for a comorbid sleep disorder (eg, sleep apnea, sleep-related movement disorders, narcolepsy) exists, or in cases of treatment-resistant insomnia.^{13,28,29} There is generally insufficient evidence to support or disprove the use of additional diagnostic testing in adults with chronic insomnia that are unresponsive to psychological and/or pharmacological interventions.²

5.0 TREATMENT OF CHRONIC INSOMNIA IN ADULTS

The goals of insomnia management are to improve sleep, mitigate psychological or physical distress/dysfunction that result from the disorder,⁷ and improve function.¹² Nonpharmacologic interventions, primarily cognitive-behavioral therapy for insomnia (CBT-I), pharmacologic interventions, or a combination of both modalities are often used to treat chronic insomnia in adults.^{7,8} Pharmacologic agents often produce a quicker response in symptom resolution compared to nonpharmacologic therapies, but the effects can fade after cessation of the agent.^{8,34}

5.1 Nonpharmacologic Interventions

Psychological therapies for the treatment of insomnia include sleep restriction, stimulus control, education on sleep hygiene, and CBT-I.¹¹ CBT-I is a multicomponent approach that includes behavioral therapies (eg, sleep restriction, stimulus control), cognitive therapies, and education (ie, sleep hygiene) to modify maladaptive, conditioned behaviors and thoughts (eg, anxious) that contribute to inadequate sleep.^{6,8,35} Additional information on specific behavioral nonpharmacologic therapies are provided below:

- **Sleep restriction therapy** is meant to enhance sleep efficiency by restricting time in bed such that time spent in bed is matched to the sleep duration as close as possible.^{11,35} The purpose is to prevent extended periods of time in bed that result in nighttime wakefulness.³⁵ The amount of time in bed is adjusted based on sleep efficiency thresholds (eg, >90%, 85–90%, <85%) until an adequate sleep duration and overall satisfactory quality of sleep is achieved.^{11,35}
- **Stimulus control** includes re-associating the bed or bedroom with sleep and setting a consistent wake-time.¹¹ According to the AASM 2021 behavioral and psychological guideline, some methods of achieving stimulus control include the following:¹¹
 - Going to bed only when tired; leaving the bed when unable to fall asleep; only using the bed or bedroom for sleep and sex (no reading or watching TV in bed); having a consistent wake time every morning; and minimizing naps during the day¹¹

- **Sleep hygiene** consists of comprehensive recommendations about lifestyle and environmental factors to improve sleep quality.¹¹ It may also include education on typical sleep patterns and physiological changes in sleep over time.¹¹ Some examples of sleep hygiene include the following:³⁵
 - Establishing a regular schedule for going to bed and waking up
 - Avoiding daytime naps, particularly naps that exceed an hour and/or that occur later in the afternoon/evening
 - Restricting caffeine use after lunchtime
 - Restricting alcohol use close to bedtime (alcohol is initially sedating, but causes wakefulness as it is metabolized and alters physiologic sleep architecture)
 - Avoiding nicotine use around bedtime due to its stimulant effects
 - Performing physical exercise 4–6 hours prior to going to bed, which can promote sleep onset (though exercising closer to bedtime [ie, within 2 hours] is not recommended)
 - Keeping the sleep environment quiet and dark to avoid unnecessary noise and light exposure

More generally cognitive approaches include relaxation training (eg, mindfulness, meditation) and prevention of sleep-related anxious thoughts.^{8,11} CBT-I is typically conducted by trained clinicians or mental health experts in-person over 4–8 sessions, individually or in group settings.^{7,8,11} The accessibility of CBT-I is potentially challenging due to the limited number of trained mental health physicians that may be available to provide the therapy in some geographic areas, or based on insurance coverage restrictions.^{20,35} According to the American Thoracic Society (ATS), lack of access to CBT-I results in premature treatment with sedative medications, which offer short-term benefits, but may have adverse effects in the long-term.²⁰ Some accessibility barriers to CBT-I may be overcome by the increasing reliance on remote outpatient approaches (eg, telemedicine-based delivery using computer or phone technology).^{12,20,35}

5.2 Pharmacologic Interventions

The pharmacologic agents with a U.S. Food and Drug Administration (FDA)-approved indication for the treatment of insomnia belong to numerous drug classes, have varying pharmacodynamic and pharmacokinetic properties (*refer to **Appendix B***),⁹ and include the following:⁷⁻⁹

- z-drugs (zaleplon, eszopiclone, zolpidem)
- benzodiazepines (eg, triazolam, estazolam)
- tricyclic antidepressant/histamine receptor antagonist (ie, doxepin)
- orexin receptor antagonists (eg, suvorexant, lemborexant)
- melatonin receptor agonists (ie, ramelteon)

FDA-approved insomnia indications are further categorized into insomnia subtypes (ie, sleep onset or sleep maintenance); the approved indication may differ between formulations (eg, extended-release tablet vs. sublingual tablet). The recommended dose for some agents varies by sex and/or age. For example, zolpidem tartrate-containing products (eg, Ambien, Edluar) require a lower starting dose for women compared to men due to the reduced clearance in women.³⁶⁻⁴¹ The orexin receptor antagonist, suvorexant, has a warning for increased drug exposure in women necessitating additional consideration when adjusting the dose.⁴² Although no explicit dose recommendations are provided for women in the suvorexant prescribing information, a variety of dosages are available allowing prescribers to dose-adjust using their clinical judgement.⁴² For older adults, the benzodiazepines, z-drugs, and doxepin have

reduced maximum doses and/or lowered initial doses due to an increased susceptibility to sedative effects.^{37-41,43-50} **Table 2** summarizes the prescribing information for FDA-approved agents in insomnia, including the available formulations, labeled indications, and recommended dosing.

Other agents, particularly the majority of hypnotics except doxepin and ramelteon which are non-controlled substances,³⁷⁻⁵² have a known increased risk of physical dependence, tolerance, and abuse, and thus are classified as Schedule IV controlled substances.³⁴ Because insomnia may be a symptom of psychiatric or medical conditions, individuals who are unresponsive to prescription pharmacotherapy after 7–10 days of treatment should contact their health care provider to be evaluated for other potential causes of insomnia.^{7,45-48} Some patients, especially those with other chronic comorbidities, may require continued treatment for insomnia due to persistent symptoms.³⁴ To determine if continued long-term therapy is necessary, periodic trials of lower doses and/or medication discontinuation may be helpful.³⁴

Other pharmacotherapies such as antipsychotics and antidepressants (eg, trazodone) are sometimes used off-label for the treatment of insomnia owing to their sedating effect.^{7,53} OTC dietary supplements (eg, melatonin, valerian) and sleep aids (eg, diphenhydramine) may be used for the treatment of insomnia.³⁴ With regards to the first category, the FDA regulates dietary supplements according to different standards than products classified as drugs under the Dietary Supplement Health and Education Act of 1994 (DSHEA).⁵⁴ Unlike prescription products, manufacturers of dietary supplements are not required to submit proven efficacy, safety, or quality standards to the FDA prior to marketing, thus, there is the potential for impurities in OTC dietary supplements.^{2,55} In 2007, the FDA implemented new Good Manufacturing Practices (GMPs) rules for dietary supplements, but a 2013 report showed the majority of manufacturers did not comply with the standards, potentially due to a higher cost associated with doing so.⁵⁶ OTC formulations may be considered of a higher quality if they pass certain laboratory tests by third party companies.⁴ Independent third party companies include the United States Pharmacopeia (USP) and ConsumerLab.com (CL), which may provide certification markings on the product (eg, USP or CL, respectively) signifying to the consumer the manufacturer's compliance for passing certain quality standards.^{57,58} These standards typically include that the product contains the label-specified ingredients and amounts, does not contain certain contaminants (eg, heavy metals such as lead and mercury, bacteria, pesticides), and that the product will dissolve under physiologic conditions within the body.^{57,58} USP also ensures that the product has been manufactured in an appropriate environment according to FDA and USP guidelines.⁵⁷ To continue displaying a seal of approval on the product (CL), the product is required to pass re-testing every 12 months.⁵⁸

Table 2. FDA-Approved Pharmacologic Agents for the Treatment of Insomnia in Adults

Generic Name Brand (approval year) and Preparation Controlled substance class	Labeled Indication	Dosing Recommendation
<i>Z-drugs</i>		
Eszopiclone Lunesta ⁴³ (2004) 1 mg oral tablet 2 mg oral tablet 3 mg oral tablet Class IV CS	Indicated for the treatment of insomnia. Reduced <u>sleep latency</u> and improved <u>sleep maintenance</u> in clinical trials (study duration ≤ 6 months)	Adults: Start at 1 mg PO once daily, <u>taken immediately prior to bedtime</u> , with ≥ 7 to 8 hours prior to anticipated wake-up time. Dose may be increased to 2 mg or 3 mg PO daily if lower dose is ineffective, but may increase the risk of impairment during the next day for activities that require alertness (eg, driving). Avoid taking with or right after a high-fat meal Max dose: 3 mg PO daily Adults (≥ 65 years), disabled patients, severe liver impairment, or concomitant use with potent CYP3A4 inhibitors (<u>max dose</u>): 2 mg PO once daily before bed
Zaleplon Sonata ⁴⁴ (1999) 5 mg oral capsule 10 mg oral capsule Class IV CS	Indicated for insomnia, short-term treatment. Reduced <u>sleep onset</u> in clinical trials (study duration ≤ 30 days)	Adults: Start at 10 mg PO once daily right before bed, or if nighttime awakenings occur and it is challenging to fall back asleep. For low weight individuals, 5 mg PO daily should be considered. Dose may be increased to 20 mg PO daily if an initial trial period of the lower dose proves to be ineffective. Avoid taking with or right after a high-fat meal Max dose: 20 mg PO daily prior to bed or during the night (if trouble falling back to sleep) Adults (≥ 65 years), disabled patients, mild to moderate liver impairment: Start at 5 mg PO once daily before bed. Doses exceeding 10 mg are not recommended for use in older adults. Avoid use: Severe liver impairment
Zolpidem tartrate ^a Ambien ³⁷ (1999) 5 mg oral tablet 10 mg oral tablet Class IV CS	Indicated for sleep <u>onset insomnia</u> , short-term treatment. (study duration 4 to 5 weeks)	Adults: Taken <u>immediately prior to bedtime</u> , with ≥ 7 to 8 hours prior to anticipated wake-up time. Dose may be increased to 10 mg PO once daily if the lower dose is ineffective, but may increase the risk of impairment during the next day for activities that require alertness (eg, driving). It should not be administered more than once during a single night. Avoid taking with or right after a meal Women: Initiate at 5 mg PO once daily due to decreased clearance in women Men: Initiate at 5 or 10 mg PO once daily

Abbreviations: CR, controlled-release; CS, controlled substance; CYP, cytochrome; PO, by mouth

^a Although not included within the FDA-approved indication, zolpidem tartrate has demonstrated to reduce sleep latency for ≤ 35 days in clinical trials

Table 2. FDA-Approved Pharmacologic Agents for the Treatment of Insomnia in Adults

Generic Name Brand (approval year) and Preparation Controlled substance class	Labeled Indication	Dosing Recommendation
		Max dose: 10 mg PO daily Adults (≥ 65 years), disabled patients, mild to moderate liver impairment: Recommended dose of 5 mg PO once daily prior to bed (regardless of sex) Avoid use: Severe liver impairment
Zolpidem tartrate^a Ambien CR³⁸ (2005) 6.25 mg oral extended-release tablet 12.5 mg oral extended-release tablet Class IV CS	Indicated for <u>sleep maintenance</u> and/or <u>sleep onset</u> insomnia, short-term. (study duration ≤ 24 weeks)	Adults: Taken <u>immediately prior to bedtime</u> , with ≥ 7 to 8 hours prior to anticipated wake-up time. Dose may be increased to 12.5 mg PO daily if lower dose is ineffective, but may increase the risk of impairment during the next day for activities that require alertness (eg, driving). Avoid taking with or right after a meal Women: Initiate at 6.25 mg PO once daily due to decreased clearance in women Men: Initiate at either 6.25 or 12.5 mg PO once daily Max dose: 12.5 mg PO daily Adults (≥ 65 years), disabled patients, mild to moderate liver impairment: Recommended dose of 6.25 mg PO once daily prior to bedtime (regardless of sex) Avoid use: Severe liver impairment
Zolpidem tartrate^a Edluar³⁹ (2009) 5 mg sublingual tablet 10 mg sublingual tablet Class IV CS Intermezzo⁴⁰ (2011) 1.75 mg sublingual tablet 3.5 mg sublingual tablet Class IV CS	Edluar: Indicated for <u>sleep onset insomnia</u> , short-term treatment. (study duration 4 to 5 weeks) Intermezzo: Insomnia with problems falling back asleep after awakening in the night	Sublingual tablet(s) should be placed under the tongue and allowed to completely dissolve. The tablet(s) should <u>not</u> be swallowed, or taken with water. Avoid taking with or right after a meal Edluar: Adults: Taken <u>immediately prior to bedtime</u> , with ≥ 7 to 8 hours prior to anticipated wake-up time. Dose may be increased to 10 mg PO once daily if the lower dose is ineffective, but may increase the risk of impairment during the next day for activities that require alertness (eg, driving) Women: Initiate at 5 mg PO once daily due to decreased clearance in women Men: Initiate at either 5 or 10 mg PO once daily Max dose: 10 mg PO daily Adults (≥ 65 years), disabled patients, liver impairment: Recommended dose of 5 mg PO once daily prior to bedtime (regardless of sex)

Abbreviations: CR, controlled-release; CS, controlled substance; CYP, cytochrome; PO, by mouth

^a Although not included within the FDA-approved indication, zolpidem tartrate has demonstrated to reduce sleep latency for ≤ 35 days in clinical trials

Table 2. FDA-Approved Pharmacologic Agents for the Treatment of Insomnia in Adults

Generic Name Brand (approval year) and Preparation Controlled substance class	Labeled Indication	Dosing Recommendation
	when there is ≥ 4 hours before the anticipated wake-up time; as-needed use	Intermezzo: Adults: Take if there is ≥ 4 hours before the anticipated wake-up time to help with returning to sleep after awakening in the middle-of-the-night Women (recommended and max dose): 1.75 mg PO once daily at night as needed Men (recommended and max dose): 3.5 mg PO once daily at night as needed Adults (≥ 65 years), liver impairment: Recommended dose of 1.75 mg PO once daily at night as needed (regardless of sex)
Zolpidem tartrate^a Zolpimist⁴¹ (2008) 5 mg/actuation oral spray; supplied as: 30 sprays/4.5 mL 60 sprays/7.7 mL Class IV CS	Indicated for sleep onset insomnia, short-term treatment. (study duration 4 to 5 weeks)	Adults: Taken PO <u>immediately prior to bedtime</u> , with ≥ 7 to 8 hours prior to anticipated wake-up time. Dose may be increased to 2 sprays (10 mg) PO once per night if the lower dose is ineffective, but may increase the risk of impairment during the next day for activities that require alertness (eg, driving). Avoid taking with or right after a meal Women: Initiate at 1 spray (5 mg) PO once daily due to decreased clearance in women Men: Initiate at 1 to 2 sprays (5 to 10 mg) PO once daily Max dose: 2 sprays (10 mg) PO once daily Adults (≥ 65 years), disabled patients, liver impairment: Recommended dose of 1 spray (5 mg) PO once daily prior to bedtime (regardless of sex)
Benzodiazepines		
Flurazepam⁴⁵ (1970) 15 mg oral capsule 30 mg oral capsule Class IV CS	Treatment of insomnia identified as frequent nighttime awakening, trouble falling asleep, and/or premature morning awakenings	Adults: Take PO <u>immediately prior to bedtime</u> with ≥ 7 to 8 hours prior to anticipated wake-up time. Dose may be increased to 30 mg PO once daily if the lower dose is ineffective Women: Initiate at 15 mg PO once daily due to decreased clearance in women Men: Initiate at either 15 or 30 mg PO once daily Max dose: 30 mg PO once daily Adults (≥ 65 years), disabled patients: Recommended dose of 15 mg PO once daily
Estazolam⁴⁷ (1990) 1 mg oral tablet	Short-term treatment of insomnia identified	Adults: Start at 1 mg PO once daily, <u>taken immediately prior to bedtime</u> . Dose may be increased to 2 mg PO daily if lower dose is ineffective. Avoid taking with or right after a meal.

Abbreviations: CR, controlled-release; CS, controlled substance; CYP, cytochrome; PO, by mouth

^a Although not included within the FDA-approved indication, zolpidem tartrate has demonstrated to reduce sleep latency for ≤ 35 days in clinical trials

Table 2. FDA-Approved Pharmacologic Agents for the Treatment of Insomnia in Adults

Generic Name Brand (approval year) and Preparation Controlled substance class	Labeled Indication	Dosing Recommendation
2 mg oral tablet Class IV CS	as frequent nighttime awakening, trouble falling asleep, and/or premature morning awakenings	Max dose: 2 mg PO once daily Adults (≥ 65 years), disabled patients: Start at 1 mg PO once daily for healthy older adults. In small older adults or disabled patients, an initial dose of 0.5 mg should be considered
Temazepam Restoril⁴⁶ (1981) 7.5 mg oral capsule 15 mg oral capsule 22.5 mg oral capsule 30 mg oral capsule Class IV CS	Short-term treatment of <u>unspecified insomnia</u> . Use should not exceed 7–10 days (study duration 2 weeks)	Adults: Start at 7.5 mg to 15 mg PO once daily, <u>taken immediately prior to bedtime</u> . Dose may be increased to 30 mg PO daily if lower dose is ineffective Max dose: 30 mg PO once daily Adults (≥ 65 years), disabled patients: Start at 7.5 mg PO once daily
Quazepam Doral⁴⁸ (1985) 15 mg oral tablet (scored) Class IV CS	Treatment of insomnia identified as frequent nighttime awakening, trouble falling asleep, and/or premature morning awakenings	Adults: Start at 7.5 mg PO once daily, <u>taken immediately prior to bedtime</u> . Dose may be increased to 15 mg PO daily if lower dose is ineffective Max dose: 15 mg PO once daily Adults (≥ 65 years), disabled patients: Start at 7.5 mg PO once daily
Triazolam Halcion⁴⁹ (1982) 0.25 mg oral tablet (scored) Class IV CS	Short-term treatment of <u>unspecified insomnia</u> . Use should not exceed 7–10 days	Adults: Start at 0.25 mg PO once daily, <u>taken immediately prior to bedtime</u> . Dose may be increased to 0.5 mg PO daily if lower dose is ineffective. Max dose: 0.5 mg PO once daily Adults (≥ 65 years): Start at 0.125 mg PO once daily, <u>taken immediately prior to bedtime</u> . Dose may be increased to 0.25 mg PO daily if lower dose is ineffective

Abbreviations: CR, controlled-release; CS, controlled substance; CYP, cytochrome; PO, by mouth

^a Although not included within the FDA-approved indication, zolpidem tartrate has demonstrated to reduce sleep latency for ≤ 35 days in clinical trials

Table 2. FDA-Approved Pharmacologic Agents for the Treatment of Insomnia in Adults

Generic Name Brand (approval year) and Preparation Controlled substance class	Labeled Indication	Dosing Recommendation
<i>Tricyclic antidepressant/ Histamine receptor antagonist</i>		
Doxepin Silenor⁵⁰ (1969) 3 mg oral tablet 6 mg oral tablet	Indicated for <u>sleep maintenance</u> (study duration ≤ 3 months)	Adults: Recommended dose of 3 mg to 6 mg PO once daily, <u>taken 30 minutes prior to bedtime</u> . Avoid taking within 3 hours of eating a meal to minimize the risk of experiencing next day effects Max dose: 6 mg PO once daily Adults (≥ 65 years): Start at 3 mg PO once daily, <u>taken 30 minutes prior to bedtime</u> . Dose may be increased to 6 mg PO daily if lower dose is ineffective
<i>Orexin receptor antagonists</i>		
Suvorexant Belsomra⁴² (2014) 5 mg oral tablet 10 mg oral tablet 15 mg oral tablet 20 mg oral tablet Class IV CS	Indicated for <u>sleep maintenance</u> and/or <u>sleep onset</u> insomnia	Adults (including those ≥ 65 years of age): Start at 10 mg PO daily, <u>taken within 30 minutes prior to bedtime</u> , with ≥ 7 hours prior to anticipated wake-up time. Dose may be increased if the lower dose is ineffective, but was well-tolerated. It should not be administered more than once during a single night. Avoid taking with or immediately after a meal Max dose: 20 mg PO once daily Moderate CYP3A inhibitors: Start at 5 mg PO daily; the dose should not exceed 10 mg PO daily Women and obese patients: Drug exposure is increased in these subpopulations. Consider the risk of adverse events before increasing the dose, especially in obese women. Avoid use: Do not use with strong CYP3A inhibitors
Lemborexant DayVigo⁵¹ (2019) 5 mg oral tablet 10 mg oral tablet Class IV CS	Indicated for <u>sleep maintenance</u> and/or <u>sleep onset</u> insomnia	Adults (including those ≥ 65 years of age): Start at 5 mg PO daily, <u>taken immediately prior to bedtime</u> , with ≥ 7 hours prior to anticipated wake-up time. Dose may be increased if the lower dose is ineffective, but was well-tolerated. It should not be administered more than once during a single night. Avoid taking with or immediately after a meal Max dose: 10 mg PO once daily Moderate liver impairment (starting and max dose): 5 mg PO daily Avoid use: Do not use in patients with severe liver impairment, and those taking strong or moderate CYP3A inhibitors and inducers

Abbreviations: CR, controlled-release; CS, controlled substance; CYP, cytochrome; PO, by mouth

^a Although not included within the FDA-approved indication, zolpidem tartrate has demonstrated to reduce sleep latency for ≤ 35 days in clinical trials

Table 2. FDA-Approved Pharmacologic Agents for the Treatment of Insomnia in Adults

Generic Name Brand (approval year) and Preparation Controlled substance class	Labeled Indication	Dosing Recommendation
Daridorexant Quviviq ⁵⁹ (2022) 25 mg oral tablet 50 mg oral tablet Class IV CS	Indicated for <u>sleep maintenance</u> and/or <u>sleep onset</u> insomnia	Adults (including those ≥ 65 years of age): Start at 25 mg to 50 mg PO daily, <u>taken within 30 minutes prior to bedtime</u> , with ≥ 7 hours prior to anticipated wake-up time. It should not be administered more than once during a single night. Avoid taking with or immediately after a meal Max dose: 50 mg PO once daily Moderate liver impairment, moderate CYP3A 4 inhibitors (max dose): 25 mg PO daily Avoid use: Do not use in patients with severe liver impairment, and those taking strong CYP3A4 inhibitors, and moderate or strong CYP3A4 inducers
<i>Melatonin receptor agonist</i>		
Ramelteon Rozerem ⁶⁰ (2005) 8 mg oral tablet	Indicated for <u>sleep onset insomnia</u> (study duration ≤ 6 months)	Adults (including those ≥ 65 years of age): 8 mg PO daily, <u>taken within 30 minutes prior to bedtime</u> . Avoid taking with or immediately after a high-fat meal Max dose: 8 mg PO once daily Avoid use: Do not use in patients with severe liver impairment, and use <i>cautiously</i> in patients with moderate liver impairment. Avoid use with fluvoxamine, and use <i>cautiously</i> in patients taking other CYP1A2 inhibitors.

Abbreviations: CR, controlled-release; CS, controlled substance; CYP, cytochrome; PO, by mouth

^a Although not included within the FDA-approved indication, zolpidem tartrate has demonstrated to reduce sleep latency for ≤ 35 days in clinical trials

6.0 GUIDELINE RECOMMENDATIONS

The selection of treatment for insomnia should be individualized based on patient's values, preferences and accessibility.^{3,11} **Of importance, authors of the 2017 AASM guideline state that a recommendation against use of an agent is not equivalent to an established lack of effectiveness.³ Instead, this tends to be due to insufficient evidence supporting the rationale in favor of the treatment.³**

6.1 Summary of Nonpharmacologic Recommendations

All reviewed guidelines that address psychological/behavioral treatments recommend CBT-I as first-line therapy in adults with chronic insomnia, including a 2021 guideline by AASM.^{2,7,11-13}

- The 2019 VA/DoD guideline prefers CBT-I over pharmacotherapy (weak recommendation strength) and highlights the importance of CBT-I in patients with insomnia and other psychiatric comorbidities.²
- The 2021 AASM and 2019 VA/DoD guidelines suggest offering brief therapies for insomnia (BTIs), also referred to as brief behavioral therapy for insomnia (BBT-I). BTIs are shortened versions of CBT-I (generally 1–4 sessions) that are focused on modifying behavioral factors that contribute to insomnia.^{2,11}
- Only AASM (2021) suggests stimulus control, sleep restriction therapy, and relaxation therapy as monotherapy for adults with chronic insomnia.^{2,11}
- Guidelines tend to discourage the use of sleep hygiene as a singular approach to the management of chronic insomnia; it is recommended to be used in combination with other treatment modalities (eg, CBT-I).^{2,11}
- AASM recognizes that some patients may require hypnotics, either alone or in combination with CBT-I, for the management of chronic insomnia.³

Short-term pharmacotherapy is recommended after a trial of CBT-I, or generally, when an individual is unresponsive or unable to participate in CBT-I due to accessibility or other barriers.^{2,3,7,12,13}

Pharmacotherapy may be used as adjunctive therapy to CBT-I.³ Before initiation of a short-course of pharmacologic therapy, providers should consider a patient's response to prior treatments, the accessibility of CBT-I, and the patient's preference.⁶¹

6.2 Summary of Pharmacologic Recommendations

Generally, the recommended pharmacologic options among guidelines include the benzodiazepines (eg, temazepam, triazolam), z-drugs (eszopiclone, zolpidem, zaleplon), ramelteon, low-dose doxepin, and suvorexant.^{2,3,7,11-13} Selection of pharmacotherapy depends on patient-specific factors. The therapeutic indication of the medication should be paired to the primary sleep issue expressed by the patient (ie, sleep onset vs. sleep maintenance; see Section 5.2). A medication's pharmacokinetic properties should also be tailored to the patient. For example, if benzodiazepines are going to be used in older adults (≥ 55 years of age), the British Association for Psychopharmacology (BAP) (2019) recommends a short-acting agent to minimize the "hangover effects" due to the age-related decrease in metabolism.^{12,62} However, the American Geriatrics Society (AGS) does not recommend benzodiazepines and other hypnotic sedatives as first-line treatment in older adults with chronic insomnia due to the increased risk of falls,

hip fractures, and vehicle accidents resulting in hospitalization and/or death.⁶³ Referral to a sleep specialist should be considered for patients that are unresponsive to pharmacotherapy.²

In the 2017 AASM guideline, agents are recommended according to the insomnia subtype (ie, sleep onset or sleep maintenance) and may or may not differ from the FDA-approved indication depending on the dosage compared to placebo (see **Table 3**).³ For example, suvorexant is FDA-approved for sleep maintenance and/or sleep onset; in contrast, AASM recommends this agent only for sleep maintenance, because sleep onset significantly improved only with the highest dose (20 mg, vs. 5 mg, 10 mg, or 15 mg) in clinical trials.³ For the benzodiazepines, triazolam and temazepam, the FDA does not specify a subtype of insomnia for which these agents are indicated; however, AASM recommends 0.25 mg triazolam for sleep onset, and 15 mg temazepam for sleep onset and sleep maintenance due to benefits demonstrated in placebo-controlled studies.³

Table 3. Pharmacologic Benefit According to Insomnia Subtype, AASM vs. FDA^{3,37-44,46,49,50,60}

Pharmacologic Agent	Sleep Maintenance	Sleep Onset	Difficulty returning to sleep after awakening during the night	Unspecified Insomnia
Ramelteon		AASM (WR) FDA indicated		
Doxepin	AASM (WR) FDA indicated			
Eszopiclone	AASM (WR) FDA indicated			
Zaleplon		AASM (WR) FDA indicated		
Zolpidem	AASM (based on zolpidem 10 mg tablet and 12.5 mg CR tablet) (WR) FDA indicated for Ambien CR	FDA indicated for Ambien, Zolpimist, Edluar	FDA indicated for Intermezzo	
Triazolam		AASM (WR)		FDA indicated
Temazepam	AASM (WR)			FDA indicated
Suvorexant	AASM (WR) FDA indicated			

Abbreviations: AASM, American Academy of Sleep Medicine; FDA, US Food and Drug Administration; WR, weak recommendation in favor of the treatment

All pharmacologic agents recommended for insomnia in adults generally have a *weak* recommendation strength across the reviewed guidelines meaning that there is less confidence in the recommendation either due to a limited number of evidence providing convincing supportive rationale, or that the agent

cannot be confidently recommended in all patients and should be referred to physician judgement/expertise based on the individualized benefit/risk profile and patient values/preferences.^{2,3} The 2016 ACP guideline does not provide drug-specific recommendations, but instead provides clinical considerations with respect to pharmacological options and recommends that a shared decision-making approach, considering benefits, harms, and costs of short-term use of medications be employed when deciding to add pharmacological therapy.⁷

- Current guidelines predate the FDA-approval of the newer orexin receptor antagonists, daridorexant and lemborexant; thus, no recommendations are currently provided for these agents.^{2,3,7,11-13}
- US guidelines recommend against the use of OTC dietary supplements, including melatonin, sleep aids, or antihistamines due to inadequate supportive evidence and/or safety concerns.^{2,3}
 - Kava (*Piper methysticum*) is strongly recommended against by the VA/DoD (2019) due to the known risk of liver toxicity.² In 2002, the FDA issued a safety advisory for kava-containing dietary supplements to warn consumers about the potential for rare, but serious liver-related harm, including hepatitis, cirrhosis, and liver failure.⁶⁴
- In the 2017 European guideline, melatonin is weakly recommended against due to a lack of supporting efficacy.¹³
- BAP (2019) recommends melatonin as first-line only for older adults (aged > 55 years) with chronic insomnia after pharmacologic agents have been deemed necessary.¹²
 - This recommendation may in part be due to in Europe, an extended-release melatonin tablet (Circadin) is available via prescription for the short-term treatment (≤ 13 weeks) of chronic insomnia in adults ≥ 55 years of age.⁶⁵

Due to the potential safety concerns, the off-label use of sedating antipsychotic agents (eg, quetiapine, olanzapine, ziprasidone) and the antidepressant, trazodone are generally weakly recommended against for the treatment of chronic insomnia in the absence of other mental health comorbidities, especially as first-line agents.^{2,3,12,13} The American Psychiatric Association (APA) has a similar recommendation against the regular use of antipsychotic agents as first-line therapy for insomnia due to conflicting evidence.⁶⁶ Although the reviewed guidelines recommend against use of these agents, this should not be construed as these agents have no therapeutic utility for adults with chronic insomnia and other psychiatric conditions (eg, schizophrenia, bipolar disorder).^{12,67} In patients with psychiatric comorbidities and chronic insomnia, providers should use their clinical judgement to address the needs of the individual patient, taking into consideration the potential adverse effects.¹²

6.3 Recommendations for Duration of Pharmacotherapy

The guidelines for the treatment of chronic insomnia in adults recommend *short-term* pharmacotherapy.^{2,7,13,68} ACP (2016) defines short-term as < 4 to 5 weeks of treatment.⁷ The recommendation for a short-term duration appears to be determined by a lack of significant long-term placebo-controlled trials, not due to an alteration in the risk/benefit profile after 4 weeks of treatment.^{13,69} A few longer duration placebo-controlled trials suggest that the use of certain hypnotics (ie, zolpidem, eszopiclone, ramelteon) for ≤ 6 months and temazepam for ≤ 2 months are not strongly correlated to the development of dependence (ie, withdrawal or tolerance).^{12,69} A 2021 position statement by the World Sleep Society (WSS) mentions that although some long-term studies exist, it is

not enough evidence to recommended these agents (ie, zolpidem, eszopiclone, ramelteon) for long-term use.⁶⁸

Despite the chronicity of insomnia, a limited number of guidelines address the long-term treatment with pharmacotherapy, likely due to the lack of available long-term evidence.^{2,7,13} According to the guidelines that do address long-term pharmacologic management, the continued use of medications should be determined by individualized benefit/risk decisions and periodic reassessments.^{7,12} The 2017 AASM guideline states that long-term treatment with benzodiazepine receptor agonists should be reserved for patients that are unresponsive or unable to use CBT-I, have been screened for agent-specific contraindications, continue to show long-term benefit, and are evaluated on a regular basis.³ ACP (2016) suggests treating other potential causes of insomnia (eg, depression, substance abuse disorders, pain, sleep apnea) before deciding to continue pharmacotherapy beyond 4–5 weeks.⁷ After a trial of CBT-I, if the decision to continue pharmacologic agents exceeds 4–5 weeks, ACP recommends that the requirement for pharmacologic therapy should be evaluated at periodic intervals.⁷

European guidelines suggest the need for long-term therapy may be based on a trial of discontinuing the pharmacologic agent and evaluating the response, or switching to intermittent dosing for those taking benzodiazepine receptor agonists on a daily basis.^{12,13} In these cases, especially with benzodiazepines, a gradual taper is recommended to minimize the risk of rebound insomnia and withdrawal symptoms.³⁴ The concomitant use of CBT-I during the medication taper may improve positive outcomes, and is encouraged to be used for long-term symptom management of chronic insomnia after completing a standard duration of CBT-I.^{7,12,13,34} Benefits achieved with CBT-I tend to be sustained after completing treatment, whereas, the insomnia symptoms suppressed by the pharmacologic agents may return after cessation of the medication.^{3,34} **Table 4** summarizes the reviewed guideline recommendations for the management of chronic insomnia in adults.

Table 4. Guideline Recommendations for the Management of Chronic Insomnia in Adults

Guideline Name (Professional Organization; Year) and Recommendations
UNITED STATES GUIDELINES
Behavioral and Psychological Treatments for Chronic Insomnia Disorder in Adults (AASM; 2021)¹¹

The aim of this guideline is to aid physicians in selecting a specific behavioral and/or psychological therapy for the treatment of adults with chronic insomnia (with or without other comorbidities). Interventions were compared to a control (eg, placebo) or “minimal intervention.”¹¹

The strength of recommendations were classified as either “strong” or “conditional”. “Strong” recommendation was described as, “almost all patients should receive the recommended course of action. Adherence to this recommendation could be used as a quality criterion or performance indicator.”¹¹ “Conditional” is explained as, “most patients should receive the suggested course of action; however, different choices may be appropriate for different patients. The clinician must help each patient determine if the suggested course of action is clinically appropriate and consistent with his or her values and preference.”¹¹

Strong recommendation(s) for:

- For the treatment of chronic insomnia in adults, multicomponent **CBT-I** is **recommended**
 - Studies used to formulate the recommendation were primarily those in which a trained professional delivered CBT-I to patients *with or without comorbidities*

Conditional recommendation(s) for:

- Multicomponent BTIs are suggested for adults with chronic insomnia
- Stimulus control, sleep restriction therapy, and relaxation therapy (*used alone*) are suggested for the treatment of adults with chronic insomnia

Conditional recommendation(s) against:

- For the treatment of adults with chronic insomnia, physicians are advised to not use sleep hygiene as monotherapy
 - Sleep hygiene is recommended as part of a multicomponent approach (eg, in combination with CBT-I)

Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and OSA (VA/DoD; 2019)^{a 2}

The goal of this guideline is to help physicians and other healthcare providers to deliver patient-centered care for the treatment of OSA and chronic insomnia in adults (≥ 18 years of age).² At the time this guideline was published, daridorexant and lemborexant were not yet FDA-approved.

Recommendation strength was defined as “strong” or “weak.” The GRADE of a recommendation was based on the LOE, balance of desired and undesired effects, values/preferences, other factors as appropriate (eg, costs, feasibility), relative strength, and direction (for or against).² A “strong” recommendation typically indicates a high level of confidence in the quality of evidence, an intervention that displays clear difference between harms and benefits, and values/preferences among patients

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; BBT-I, brief behavioral therapy for insomnia; BTIs, brief therapies for insomnia; CBT-I, cognitive-behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; GABA-A, gamma-aminobutyric acid-type A; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ISI, Insomnia Severity Index; LOE, level of evidence; OSA, obstructive sleep apnea; OTC, over-the-counter; QoL, quality of life; VA, Department of Veterans Affairs

Table 4. Guideline Recommendations for the Management of Chronic Insomnia in Adults

or providers are similar.² A “weak” recommendation is often a suggestion due to the lower level of confidence after the GRADE assessment, but may still be a clinically important consideration.²

Behavioral/psychological interventions

Strong recommendation(s) for:

- CBT-I is **recommended** for the treatment of chronic insomnia in adults

Weak recommendation(s) for:

- BTIs (referred to as brief behavioral therapy for insomnia [BBT-I]) are suggested for the treatment of chronic insomnia in adults
- For first-line therapy, CBT-I is suggested over pharmacotherapy for adults with chronic insomnia
- CBT-I is suggested for adults with chronic insomnia and other comorbid psychiatric conditions

Weak recommendation(s) against:

- Sleep hygiene, as monotherapy is suggested against for the treatment of chronic insomnia in adults

Complementary and integrative health interventions

Weak recommendation(s) for:

- Auricular acupuncture with seed and pellet is suggested for the treatment of chronic insomnia in adults

Weak recommendation(s) against:

- Cranial electrical stimulation is suggested against for the treatment of adults with chronic insomnia

Pharmacotherapy (prescription)

Weak recommendation(s) for:

- Low-dose doxepin (ie, 3 mg or 6 mg) is suggested in adults that require a short-course of pharmacotherapy for chronic insomnia
- A z-drug (zolpidem, eszopiclone, zaleplon) is suggested in adults that require a short-course of pharmacotherapy for chronic insomnia

Weak recommendation(s) against:

- Antipsychotic agents (eg, quetiapine), benzodiazepines (eg, flurazepam, triazolam, estazolam), and trazodone are suggested against for the treatment of adults with chronic insomnia

Insufficient evidence to recommend for or against use:

- Ramelteon and suvorexant

OTC Pharmacotherapy

Strong recommendation(s) against:

- Kava is recommended against for the treatment of chronic insomnia in adults
-

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; BBT-I, brief behavioral therapy for insomnia; BTIs, brief therapies for insomnia; CBT-I, cognitive-behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; GABA-A, gamma-aminobutyric acid-type A; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ISI, Insomnia Severity Index; LOE, level of evidence; OSA, obstructive sleep apnea; OTC, over-the-counter; QoL, quality of life; VA, Department of Veterans Affairs

Table 4. Guideline Recommendations for the Management of Chronic Insomnia in Adults

Weak recommendation(s) against:

- Diphenhydramine, **melatonin**, valerian, and chamomile are **suggested against** for the treatment of adults with chronic insomnia

**Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults
(AASM; 2017)³**

The purpose of this guideline is to assist physicians in selecting pharmacologic agents for the treatment of chronic insomnia in adults after pharmacologic management has been determined to be appropriate.³ It was not created to provide recommendations of one agent over another.³ The approval of daridorexant and lemborexant came after the publication of this guideline.

The strength of recommendations for pharmacotherapies were classified as either “strong” or “weak.” “Strong” recommendations should be followed by physicians, in the majority of situations, when pharmacotherapy is appropriately indicated.³ “Weak” recommendations have a lower level of certainty and require additional physician insight (eg, knowledge, experience) to provide individualized care based on the patient’s values and preferences.³

- CBT-I should be delivered to all patients with chronic insomnia as an initial treatment intervention. Pharmacotherapy should be considered for patients that are unwilling/unable to participate in CBT-I, continue to have insomnia symptoms despite active participation in a CBT-I program, or in certain situations, “as a temporary adjunct to CBT-I”.³ (ungraded recommendation)

The following recommendations are “weak” meaning that the recommendation for or against use is a **suggestion**, and include the trial doses that were used to formulate the recommendation(s):

Sleep Maintenance Insomnia (vs. no treatment)^b:

Weak recommendation(s) for:

Orexin receptor agonists

- Suvorexant (10, 15/20, and 20 mg) (LOE: low; benefits outweigh harms)

Z-drugs

- Eszopiclone (2 mg or 3 mg) (LOE: very low; benefits outweigh harms)
- Zolpidem (10 mg) (LOE: very low; benefits outweigh harms)

Benzodiazepines

- Temazepam (15 mg) (LOE: moderate; benefits outweigh harms)

Heterocyclics

Weak recommendation(s) against:

Heterocyclics

- Trazodone (50 mg) (LOE: moderate; harms outweigh benefits)

Anticonvulsants

- Tiagabine (4 mg) (LOE: very low; harms outweigh benefits)

OTC

- Diphenhydramine (50 mg) (LOE: low; benefits approximately equivalent to harms)
- **Melatonin** (2 mg) (LOE: very low; benefits approximately equivalent to harms)
- L-tryptophan (250 mg) (LOE: high; harms outweigh benefits)

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; BBT-I, brief behavioral therapy for insomnia; BTIs, brief therapies for insomnia; CBT-I, cognitive-behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; GABA-A, gamma-aminobutyric acid-type A; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ISI, Insomnia Severity Index; LOE, level of evidence; OSA, obstructive sleep apnea; OTC, over-the-counter; QoL, quality of life; VA, Department of Veterans Affairs

Table 4. Guideline Recommendations for the Management of Chronic Insomnia in Adults

○ Low-dose doxepin (3 mg or 6 mg) (LOE: low; benefits outweigh harms)	○ Valerian (dosages vary) (LOE: low; benefits approximately equivalent to harms)
Sleep Onset Insomnia (vs. no treatment)^b:	
<i>Weak recommendation(s) for:</i>	<i>Weak recommendation(s) against:</i>
<u>Z-drugs</u>	<u>Heterocyclics</u>
○ Eszopiclone (2 mg or 3 mg) (LOE: very low; benefits outweigh harms)	○ Trazodone (50 mg) (LOE: Moderate; harms outweigh benefits)
○ Zaleplon (10 mg) (LOE: low; benefits outweigh harms)	<u>Anticonvulsants</u>
○ Zolpidem (10 mg) (LOE: very low; benefits outweigh harms)	○ Tiagabine (4 mg) (LOE: very low; harms outweigh benefits)
<u>Benzodiazepines</u>	<u>OTC</u>
○ Triazolam (0.25 mg) (LOE: high; benefits approximately equivalent to harms)	○ Diphenhydramine (50 mg) (LOE: low; benefits approximately equivalent to harms)
○ Temazepam (15 mg) (LOE: moderate; benefits outweigh harms)	○ Melatonin (2 mg) (LOE: very low; benefits approximately equivalent to harms)
<u>Melatonin agonists</u>	○ L-tryptophan (250 mg) (LOE: high; harms outweigh benefits)
○ Ramelteon (8 mg) (LOE: very low; benefits outweigh harms)	○ Valerian (dosages vary along with combinations) (LOE: low; benefits

Additional comments on long-term pharmacologic treatment:

- Authors state long-term treatment with benzodiazepine receptor agonists should be reserved for patients that are unresponsive or unable to use CBT, have been screened for agent-specific contraindications, continue to show long-term benefit, and are evaluated on a regular basis.³

**Management of Chronic Insomnia Disorder in Adults
(ACP; 2016)⁷**

This guideline provides evidence-based clinical recommendations for the treatment of adults (≥ 18 years of age) with chronic insomnia (based on appropriate diagnostic criteria).⁷

The strength of recommendations were classified as either “strong” or “weak”, as determined by GRADE criteria. “Strong” recommendations were defined as “benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits”.⁷⁰ “Weak” recommendations were defined as benefits are “finely balanced” with the associated risks and burden, or the magnitude of the benefits and risks is uncertain.^{7,70} For weak recommendations, patient preferences are vital in determining the most appropriate therapy.⁷⁰

Strong recommendation(s) for:

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; BBT-I, brief behavioral therapy for insomnia; BTIs, brief therapies for insomnia; CBT-I, cognitive-behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; GABA-A, gamma-aminobutyric acid-type A; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ISI, Insomnia Severity Index; LOE, level of evidence; OSA, obstructive sleep apnea; OTC, over-the-counter; QoL, quality of life; VA, Department of Veterans Affairs

Table 4. Guideline Recommendations for the Management of Chronic Insomnia in Adults

- As an initial therapy for chronic insomnia in adults, CBT-I is **recommended** for all patients (LOE: moderate)

Weak recommendation(s) for:

- In those adults with chronic insomnia that are unresponsive to CBT-I alone, a shared decision to add pharmacologic treatment is recommended between the physician and patient based on the benefits, harms, and affordability of short-term medication use (LOE: low)

Additional comments on clinical considerations for pharmacotherapy:

- Short-term use (≤ 4 –5 weeks) of pharmacologic agents is preferred, with the management of long-term insomnia symptoms addressed with the techniques learned from CBT-I
 - After a trial of CBT-I, if the decision to continue pharmacologic agents exceeds 4–5 weeks, the requirement for pharmacologic therapy should be evaluated at periodic intervals
- Before considering pharmacologic agents to be continued, physicians should treat other potential causes of insomnia (eg, depression, pain, substance abuse disorders, sleep apnea) if applicable
- Older adults (> 55 years of age) should be monitored closely when treated with pharmacologic therapy due to the increased sensitivity to adverse effects
- There was a lack of evidence to determine the comparative effectiveness and safety between pharmacologic agents. Thus, no recommendations are made for a specific agent
- Among the general population, the drug efficacy versus placebo is as follows:
 - Eszopiclone (2–3 mg) improved signs and symptoms of insomnia (LOE: low), and wake after sleep onset, total sleep time, and sleep onset latency (LOW: low-to-moderate)
 - Zolpidem
 - Zolpidem (5–15 mg) improved total sleep time and sleep onset latency (LOE: moderate)
 - “As needed” (10 mg) improved total sleep time and sleep onset latency (LOE: moderate) and Clinical Global Impression (LOE: low)
 - Extended-release (12.5 mg) improved wake after sleep onset, total sleep time, sleep onset latency, and Clinical Global Impression (LOE: low)
 - Sublingual (3.5 mg) improved sleep onset latency after awakening during the night (LOE: low)
 - Low-dose doxepin (3 mg and/or 6 mg) improved wake after sleep onset and total sleep time (LOE: low)
 - Suvorexant (15 or 20 mg) improved wake after sleep onset, total sleep time, sleep onset latency, ISI, and response to treatment (LOE: moderate)
- There was insufficient evidence for the use of **melatonin** in older adults and the general population for the treatment of chronic 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; BTIs, brief therapies for insomnia; CBT-I, cognitive-behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; GABA-A, gamma-aminobutyric acid-type A; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ISI, Insomnia Severity Index; LOE, level of evidence; OSA, obstructive sleep apnea; OTC, over-the-counter; QoL, quality of life; VA, Department of Veterans Affairs

Table 4. Guideline Recommendations for the Management of Chronic Insomnia in Adults

EUROPEAN GUIDELINES
An Updated Consensus statement on Evidence-based Treatment of Insomnia, Parasomnias, and Circadian Rhythm Disorders (BAP; 2019) ^{a 12}

The purpose of this guideline is to provide an update on evidence-based recommendations for the management of insomnia, parasomnias, and circadian rhythm disorders.¹² This guideline is not exclusive to adults; it also makes recommendations for sleep-related issues in children.¹² At the time of publication, suvorexant and other orexin receptor antagonists were not available in Europe.¹²

The strength of recommendations vary between “A to D” depending on the level of evidence. “A” was based on high-quality evidence from a meta-analysis of RCTs (Ia), or evidence from > 1 RCT (Ib).¹² “B” was extrapolated from “A” evidence, or based on evidence from >1 non-randomized controlled trial (IIa) or another quasi-experimental trial (IIb).¹² “C” was extrapolated from “A or B” evidence, or based on evidence from observational descriptive studies (eg, correlation studies, case-control studies) (III).¹² “D” was extrapolated from “A, B, or C” evidence, or based on evidence from expert opinions or reports and/or clinical experience (IV).¹²

Grade A Recommendations:

- Treatment for insomnia is recommended due to the reduced QoL, increased functional impairment, and the greater risk of other potential chronic conditions (eg, anxiety, depression, cardiovascular disease, diabetes)
- For **first-line therapy**, CBT-I programs that include stimulus control and sleep restriction are recommended for the treatment of chronic insomnia in adults, including individuals > 55 years of age
 - Digital CBT-I (online, phone-based) and in-person are effective for the treatment of chronic insomnia
 - In routine care, digital CBT-I expands the potential choices for evidence-based alternatives (eg, CBT or pharmacologic agents) for patients and physicians
 - Pharmacologic agents should be considered for patients that are unresponsive to CBT-I, or are unable to participate in CBT-I (eg, lack of availability, unable to engage in therapy) (*no recommendation strength is assigned*)

Pharmacotherapy (prescription)

- When selecting a pharmacologic agent, the efficacy, duration of action, and safety should be considered
- Long-term use of pharmacotherapy to treat chronic insomnia should be clinically indicated based on individualized benefits/risks
- Generally, hypnotic agents should be slowly tapered when discontinuing. The concomitant use of CBT-I during the medication taper has been associated with positive outcomes
- Medications for depression should be considered when insomnia co-exists with another mood disorder
 - Even with low doses, TCAs should be used cautiously due to the potential for toxicity-related overdose
- Low-dose doxepin is effective for the treatment of chronic insomnia
- For older adults on a GABA-A hypnotic (eg, zolpidem, zopiclone), a shorter half-life is preferred to minimize potential hangover effects

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; BBT-I, brief behavioral therapy for insomnia; BTIs, brief therapies for insomnia; CBT-I, cognitive-behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; GABA-A, gamma-aminobutyric acid-type A; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ISI, Insomnia Severity Index; LOE, level of evidence; OSA, obstructive sleep apnea; OTC, over-the-counter; QoL, quality of life; VA, Department of Veterans Affairs

Table 4. Guideline Recommendations for the Management of Chronic Insomnia in Adults

Grade B Recommendations:

Pharmacotherapy (prescription)

- In older adults (> 55 years of age), **extended-release melatonin** is recommended as first-line when hypnotic agents are required
- **Melatonin** may have therapeutic utility for other sleep disorders such as delayed sleep wake phase disorder, jet lag, and non-24-hour sleep rhythm disorder

Grade D Recommendations:

Pharmacotherapy (prescription)

- Additional factors that should be considered when prescribing a pharmacologic agent should be prior efficacy or adverse effects, and substance abuse or dependence history
- Overall, antipsychotic agents should not be used as first-line agents for the treatment of chronic insomnia
- Non-selective histamine antagonists have limited therapeutic utility for the treatment of chronic insomnia and other psychiatric conditions

Additional considerations on long-term pharmacologic treatment:

- Insomnia tends to be chronic and is often treated with hypnotics for extended periods of time in clinical practice (Ib)
- “Studies suggest that dependence (tolerance/withdrawal) is not inevitable”¹² with eszopiclone, zolpidem, and ramelteon for up to 1 year (Ib)
 - To decrease the risk of dependence, intermittent dosing may be beneficial (Ib)

Factors that remain unknown:

- Estimating the required treatment duration; the approach and timing of treatment discontinuation; the dosing schedule for extended periods (nightly vs. intermittent); identification of an individual that is at higher risk for abuse; effects of pharmacologic treatment on the course of the insomnia or other associated illnesses

**European Guideline for the Diagnosis and Treatment of Insomnia
(ESRS; 2017)¹³**

This guideline provides recommendations for the treatment of chronic insomnia (based on ICD-10/ICSD-3 diagnostic criteria) in adults (≥ 18 years of age).¹³ Of note, at the time this guideline was published, ramelteon and the orexin receptor inhibitors were not approved in Europe;¹³ thus, no recommendations are made about these agents. The strength of recommendations were classified as either “strong” or “weak”, as determined by author consensus based on the GRADE criteria assigned to the level of evidence of included meta-analyses.¹³ High quality evidence is defined as evidence that provided a high level of confidence in the estimated effect and unlikely to change based on additional investigation.¹³ Low quality is defined as “any estimate of effect is uncertain”.¹³

Behavioral/psychological interventions

Strong recommendation(s) for:

- Adults at any age are **recommended** to receive **CBT-I** as first-line treatment (LOE: high)

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; BBT-I, brief behavioral therapy for insomnia; BTIs, brief therapies for insomnia; CBT-I, cognitive-behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; GABA-A, gamma-aminobutyric acid-type A; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ISI, Insomnia Severity Index; LOE, level of evidence; OSA, obstructive sleep apnea; OTC, over-the-counter; QoL, quality of life; VA, Department of Veterans Affairs

Table 4. Guideline Recommendations for the Management of Chronic Insomnia in Adults

- Pharmacologic agents should be considered for patients that are unresponsive to CBT-I, or are unable to participate in CBT-I (eg, lack of availability) (no recommendation strength or LOE are assigned)

Complementary and integrative health interventions

Weak recommendation(s) for:

- As adjunct therapies, exercise and light therapy may be helpful (LOE: low)

Weak recommendation(s) for:

- Due to poor quality evidence, “acupuncture, aromatherapy, foot reflexology, homeopathy, meditative movement, moxibustion, and yoga are not recommended for the treatment of” chronic insomnia in adults¹³

Pharmacotherapy (prescription)

Strong recommendation(s) for:

- In adults with chronic insomnia that are taking benzodiazepines or benzodiazepine receptor agonists daily, it is recommended to decrease use to intermittent dosing (LOE: low)

Strong recommendation(s) against:

- Typically, **long-term use (> 4 weeks) of benzodiazepines** (eg, diazepam, temazepam) **z-drugs** (eg, zaleplone, zolpidem) and **sedating antidepressants** (eg, trazodone) are **not recommended** for the treatment of chronic insomnia in adults due to the insufficient evidence and potential risks outweighing benefits (LOE: low)
- Antihistamines (eg, diphenhydramine) are not recommended for the treatment of chronic insomnia in adults due to a lack of evidence (LOE: low)
- Antipsychotics (eg, olanzapine, quetiapine) are not recommended for the treatment of chronic insomnia in adults due to a lack of evidence and the potential for adverse effects (LOE: very low)

Unassigned recommendation strength:

- For short-term use (≤ 4 weeks), benzodiazepines and benzodiazepine receptor agonists are effective for the treatment of chronic insomnia in adults (LOE: high)
 - Shorter half-life agents may produce less morning sedation (LOE: moderate)
- For short-term use, sedating antidepressants (eg, doxepin, trazodone) are effective for the treatment of chronic insomnia in adults (LOE: moderate)

OTC Pharmacotherapy

Weak recommendation(s) against:

- Due to limited efficacy, **melatonin** is **typically not recommended** for the treatment of chronic insomnia in adults (LOE: low)
- Due to poor quality evidence, “valerian and other phytotherapeutics are not recommended for the treatment of” adults with chronic insomnia¹³

^a Recommendations pertaining to the management of other sleep disorders (eg, OSA, parasomnias, circadian rhythm disorders) were not extracted since that topic is outside the scope of this report ^b Some medications are suggested in both sleep maintenance and sleep onset

Abbreviations: AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; BAP, British Association for Psychopharmacology; BBT-I, brief behavioral therapy for insomnia; BTIs, brief therapies for insomnia; CBT-I, cognitive-behavioral therapy for insomnia; DoD, Department of Defense; ESRS, European Sleep Research Society; GABA-A, gamma-aminobutyric acid-type A; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ISI, Insomnia Severity Index; LOE, level of evidence; OSA, obstructive sleep apnea; OTC, over-the-counter; QoL, quality of life; VA, Department of Veterans Affairs

Table 5 summarizes the most common nonpharmacologic and pharmacologic interventions with a favorable recommendation for use across reviewed guidelines.

Table 5. Summary of Favorable Interventions for Chronic Insomnia in Adults, Specified by Guideline

	Intervention(s)	Reference Guideline(s) Sponsoring Organization; Year					
		AASM; 2021 ^b	VA/DoD; 2019	BAP; 2019	AASM; 2017	ESRS; 2017	ACP; 2016
Nonpharmacologic	CBT-I	✓	✓	✓	✓	✓	✓
	Sleep hygiene in combination with another therapy	✓	✓				
	BTIs/BBT-I	✓	✓				
Pharmacologic^a	Z-drugs		✓		✓	✓	
	Benzodiazepines				✓	✓	
	Low-dose doxepin		✓	✓	✓		
	Suvorexant				✓		
	Melatonin			✓*			
	Ramelteon				✓		

Abbreviations: AASM, American Academy of Sleep Medicine; BBT-I, brief behavioral therapy for insomnia; BTIs, brief therapies for insomnia; DoD, Department of Defense; VA, Department of Veterans Affairs

^a Short-course therapy (< 4 weeks) is generally recommended

^b The scope of this guideline was to address nonpharmacological interventions only

*Recommended as an extended-release product in older adults (≥ 55 years of age) only

7.0 OVERVIEW OF MELATONIN USE FOR CHRONIC INSOMNIA

Melatonin is an endogenous indolamine hormone secreted primarily by the pineal gland in the suprachiasmatic nucleus (SCN) that helps to maintain the sleep-wake cycle.^{9,14,17} Naturally-produced melatonin levels are secreted in a circadian rhythm under low-light conditions, with levels rising in the evening that eventually peak (around 3–4 AM) and start to decrease during the early morning hours.^{9,12,17,71} The increase in melatonin levels in the evening aids sleep onset by binding to melatonin receptors distributed throughout the body.⁹ The natural production of melatonin decreases with age, and middle-aged and older adults with insomnia have lower levels of melatonin compared to those that obtain adequate amounts of sleep.¹² Melatonin has been proposed to have effects on a number of other chronic conditions such as neurodegenerative conditions, cancer, and autoimmune-related illnesses, as well as a role in limiting oxidative stress.¹⁷

In an effort to imitate the sleep-producing physiologic effects of endogenous melatonin, *exogenous* administration of melatonin, most commonly oral, has been used for the treatment of insomnia and other sleep disorders (eg, jetlag, delayed sleep phase syndrome, non-24 hour sleep wake disorder [N24SWD]) for more than 20 years.^{14,17} In the US, melatonin is available as an OTC dietary supplement, regulated under DSHEA.¹⁷ Its accessibility as an OTC product has made melatonin a commonly used product to treat insomnia in adults.¹⁸ However, relative to prescription products, there is a greater potential concern for impurities or contaminants in OTC products.² Prescription formulations of

melatonin are available in other countries. In Europe, an extended-release melatonin tablet (Circadin) is available for the short-term treatment (≤ 13 weeks) of chronic insomnia in adults ≥ 55 years of age.^{9,65} Physicians may prefer the use of low-dose melatonin to treat insomnia in adults due to the favorable side effect profile, especially in older adults that are more sensitive to adverse effects.¹⁸

In the US, 2 FDA-approved synthetic prescription melatonin agonists, ramelteon and tasimelteon are also available.^{52,60} They bind to melatonin receptors (MT₁ and MT₂), which seem to be involved in regulating sleep and circadian rhythms.^{52,60,65} Ramelteon is indicated for the treatment of insomnia in adults, whereas tasimelteon is indicated for N24SWD in adults and nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) for patients aged 3–15 years or ≥ 16 years of age depending on the formulation.^{52,60} Since tasimelteon is approved for other conditions that are not insomnia, further discussion of this product is outside the scope of this report. In the subsequent sections that follow (7.1, 7.2, and 7.3), guideline recommendations for ramelteon are provided for contextual purposes, but this report focuses on recommendations for melatonin, as well as the safety and efficacy of melatonin from systematic reviews (SRs).

7.1 Guideline Recommendations for Melatonin Use

The US guidelines that address the use of melatonin and ramelteon for the treatment of chronic insomnia in adults can be found in **Table 4**.

- The 2019 VA/DoD guideline did not provide a recommendation for or against the use of ramelteon;² however, the 2017 AASM guideline included ramelteon as a recommended option for patients with sleep onset insomnia (weak recommendation).³
- Ramelteon is not approved for use in Europe;⁷² thus recommendations for this agent are not provided in the reviewed European guidelines.^{12,13}
- The VA/DoD (2019) and AASM (2017) both *weakly recommend against* the use of melatonin.^{2,3}
- The 2017 AASM guideline *suggests against* the use of melatonin for sleep onset and/or sleep maintenance for adults with chronic insomnia (based on 2 mg dose trials).³
- BAP (2019) recommends extended-release melatonin as a *first-line pharmacologic option* after a trial of CBT-I in older adults (> 55 years of age) with chronic insomnia due to the favorable side effect profile (no motor or memory impairment) and modest efficacy in sleep quality and onset.¹²
- The 2017 ESRS guideline generally *recommends against* the use of melatonin, including immediate-release and extended-release for the treatment of insomnia due to poor efficacy (weak recommendation).¹³

7.2 Melatonin Efficacy for Insomnia: Evidence from Systematic Reviews

Low et al (2019) conducted an umbrella review of systematic reviews (SRs) and meta-analyses on the efficacy and safety of melatonin and ramelteon for the treatment of primary or comorbid insomnia among individuals of all ages.¹⁸ In the majority of reviews, efficacy was measured by the improvement in sleep latency, also known as sleep onset, and total sleep time (TST).¹⁸ Many reviews also included the use of PSG as an outcome measure.¹⁸ The quality of the included SRs ranged from critically low to moderate based on the AMSTAR 2 criteria.¹⁸

Of the 18 included reviews, 14 evaluated the efficacy of melatonin immediate-and/or extended-release (dose ranged from 0.1–75 mg) compared to placebo.¹⁸ Nine of the 12 reviews that measured sleep onset, either self-reported or with PSG, reported a significant reduction with melatonin compared to placebo.¹⁸ This effect on sleep onset was also observed with the extended-release formulation, Circadin.¹⁸ Additionally, all 3 included reviews with ramelteon demonstrated a significant reduction in sleep onset versus placebo.¹⁸ The 2 reviews that also measured TST, showed a significant improvement in TST with ramelteon compared to placebo.¹⁸

Less consistent positive results for melatonin on TST was observed in the included reviews. In 3 of the 8 reviews that measured TST, melatonin produced a statistically significant difference compared to placebo.¹⁸ Substantial heterogeneity existed between studies, including the type of population (eg, older adults, those admitted to an intensive care unit, adults or children with intellectual disabilities), type of insomnia (primary vs. comorbid), and timing of melatonin administration (ranged from 15 minutes to 2 hours before bed), which may impact the observed results on sleep parameters.¹⁸

Another SR by **Almond et al (2021)** in older adults (≥ 65 years of age) evaluated the efficacy and safety of OTC products including melatonin, among others for the treatment of primary insomnia.¹⁵ Three RCTs on the use of melatonin with a duration between 19 days to 8 weeks were included.¹⁵ Across included studies, the population was predominately female with a mean age ranging from 71.7 to 76 years, with or without a prior history of melatonin deficiency.¹⁵ Melatonin significantly improved insomnia symptoms (eg, sleep efficiency, TST, number of awakenings, wake time after sleep onset) in 2 studies.¹⁵ However, in a randomized controlled crossover trial among those categorized as normal sleepers (those that self-reported no issues with sleeping) and those as problem sleepers (those that self-reported age-related sleep maintenance issues),⁷³ melatonin significantly reduced the number of awakenings in normal sleepers compared to placebo, but demonstrated no significant improvement for other sleep parameters (eg, latency, sleep duration, sleep efficiency) in either group.¹⁵

An SR conducted by **Moreira-Fumero et al (2020)** evaluated the efficacy of melatonin for improving the discontinuation rate of benzodiazepines and/or hypnotics in adults with primary insomnia.¹⁶ Four studies were included; 2 were descriptive (prospective cohort) and 2 were placebo-controlled RCTs.¹⁶ The diagnostic methods and criteria across studies varied. Diagnoses were based on self-reporting, questionnaires, interviews, or by defined diagnostic criteria (DSM-4).¹⁶ One study focused on older adults (≥ 65 years of age), while another enrolled participants on long-term benzodiazepine use (at least 6 months) for the treatment of insomnia.¹⁶

Although one study failed to report the benzodiazepine and/or hypnotic agents that were being discontinued, the remaining included studies noted these agents were alprazolam, brotizolam, bromazepam, clonazepam, lorazepam, lormetazepam, nitrazepam, and oxazepam.¹⁶ All included studies used melatonin, either immediate-release or extended-release, with dosages ranging from 2 mg to 5 mg taken up to 30 minutes before bedtime, or at bedtime.¹⁶ The treatment duration varied from 21–180 days.¹⁶

Among the 2 RCTs, the total withdrawal (number of participants no longer taking a benzodiazepine at end of the study duration) in the melatonin arm was 77.8% and 64.3%, whereas, it was 25% and 0% in the placebo-treated group, respective to each study.¹⁶ Among the 2 descriptive studies, 30.8% and 65% of the study participants, respective to each study, achieved total withdrawal of the benzodiazepine while taking melatonin for sleep.¹⁶ One of these descriptive studies demonstrated that 30.8% of the

study participants were able to reduce their dose of a benzodiazepine by 50% to 75%, standardized to a diazepam equivalent dose (DED), while the other cohort study showed 20% of participants who did not achieve total withdrawal were able to reduce their benzodiazepine dose by 25% to 66%.¹⁶ In addition to concomitant melatonin use as a strategy to discontinue benzodiazepines and/or hypnotics, study participants were recommended to gradually taper the medication in 3 of the studies.¹⁶ SR authors note that these results should be interpreted cautiously due to the small sample size of the included studies.¹⁶

7.2.1 Melatonin for Comorbid Insomnia

Jafari-Koulaee et al (2021) evaluated the efficacy of oral melatonin to improve sleep quality and insomnia symptoms in patients with cancer (eg, breast, gastrointestinal, head and neck).¹⁴ The SR included 6 studies, comprising of 4 RCTs, 1 prospective study, and 1 quasi-experimental study.¹⁴ The mean age of included participants ranged from 52 to 59 years.¹⁴ Melatonin dosages were 3 mg, 6 mg, or 20 mg, typically taken 1 to 2 hours before bed.¹⁴ The duration of studies varied between 10 days to 4 months and outcomes on sleep quality and insomnia symptoms were measured with validated tools such as the Pittsburgh Sleep Quality Index (PSQI)³⁰ and the Athens Insomnia Scale (AIS).^{14,32}

In 4 of the 6 studies, melatonin demonstrated a significant improvement in sleep quality and insomnia-related symptoms.¹⁴ In the two other studies, melatonin 6 mg improved sleep efficiency in the short-term (3 days prior to surgery to 8 days post-surgery), but was comparable to placebo for improvements in sleep quality.¹⁴ To improve sleep quality in this patient population, the authors of the SR explain that the melatonin dose and duration of use may depend on patient-specific factors such as the cancer treatment (chemotherapy vs. surgical).¹⁴ They suggest higher doses (20 mg) of melatonin for a shorter duration in cancer patients that are receiving chemotherapy treatment, whereas lower doses for a longer duration (up to a month) may be more appropriate for cancer patients who “have not undergone special treatment for at least one month”.¹⁴

Lastly, an SR conducted by **Oliveira et al (2018)** evaluated the efficacy and safety of several treatment options including melatonin for insomnia in adults with schizophrenia.¹⁹ Insomnia is a common complainant of individuals with schizophrenia, with more severe symptoms experienced during relapses or the manifestation of positive symptoms.¹⁹ Four placebo-controlled RCTs were included in the SR, 2 of which evaluated the use of melatonin, with dosages ranging from 2 mg to 12 mg, either extended-release or immediate-release, 1 study evaluated extended-release paliperidone, an atypical antipsychotic, and 1 study assessed the z-drug, eszopiclone.¹⁹ The study durations varied from approximately 2 weeks to 8 weeks.¹⁹ Study participants had a confirmed diagnosis of schizophrenia according to DMS-4 criteria, and insomnia was determined either according to established diagnostic criteria (DSM-4) or based on sleep index tools (eg, Insomnia Severity Index [ISI])³¹.¹⁹ Enrolled patients in 1 of the melatonin RCTs had initial insomnia, defined as sleep onset latency of ≥ 30 minutes for a duration of at least 2 weeks that resulted in clinical suffering.⁷⁴ The median age across all included studies was 39.3 years and was predominately male (62.8%).¹⁹

In the 2 studies that evaluated melatonin, compared to placebo, melatonin was associated with a statistically significant improvement in sleep efficiency, TST, and a reduction in nighttime awakenings with no observable “hangover effects”.¹⁹

7.3 Safety of Melatonin for Insomnia: Evidence from Systematic Reviews

In the **Low et al (2019)** SR, melatonin was not associated with a significant increase in adverse effects compared to placebo in the majority of included trials (9 out of 14).¹⁸ None of the included studies reported any serious adverse effects related to melatonin use.¹⁸ Among the 5 studies that reported adverse effects for melatonin, the most commonly reported adverse effects were somnolence and headache, which were also occasionally reported with ramelteon use.¹⁸ Of the included studies, no adverse effects were reported with Circadin, and both ramelteon and Circadin were associated with minimal to no withdrawal symptoms or adverse effects.¹⁸

The SR by **Almond et al (2021)** demonstrated that melatonin is well-tolerated in older adults (≥ 65 years of age), with very minimal adverse effects.¹⁵ Excessive drowsiness was reported with melatonin use, but may be considered minimal relative to the side effects with diphenhydramine, which include oversedation and anticholinergic activity.¹⁵ The 2019 American Geriatrics Society (AGS) Beers Criteria recommends avoiding first-generation antihistamines such as diphenhydramine as a hypnotic in older adults due to the anticholinergic adverse effects (eg, dry mouth, confusion, constipation),⁶² which some evidence suggests may be associated with an increased risk of cognitive impairment.¹⁵ The AGS Beers Criteria do not make a recommendation regarding the use of melatonin in older adults.⁶²

Another SR of placebo-controlled RCTs conducted by **Besag (2019)** evaluated the safety of melatonin for the treatment of primary or secondary sleep disorders.¹⁷ Open-label and observational studies, including retrospective chart reviews were included to assess the long-term safety of melatonin.¹⁷ A total of 37 RCTs were included; melatonin dosages varied from 0.15 mg/day to 12 mg/day, and study duration ranged from 1 to 29 weeks, with most of the studies having a shorter duration (≤ 4 weeks).¹⁷ The participants included infants (at least 1 year of age) to older adults (up to 93 years of age).¹⁷

Sixteen of the RCTs reported no adverse events for melatonin compared to placebo.¹⁷ Of the remaining RCTs, the most common adverse events were daytime sedation, headache, dizziness, other sleep-related adverse effects (eg, red eyes, nightmares, vivid dreams), and hypothermia.¹⁷ Melatonin did not produce a statistically significant difference compared to placebo in the frequency of reported adverse events, but the majority of included RCTs only reported the frequencies of the adverse events and did not perform a statistical analysis.¹⁷ A very small number of adverse events were considered to be associated with melatonin use, and although rarely reported, serious adverse events (eg, fatigue, mood swings, agitation, nightmares, palpitations, skin sensitivity) were often an exacerbation of a pre-existing condition or associated with the study population (eg, agitation for patients with attention-deficit hyperactivity disorder [ADHD]).¹⁷

Similar to RCTs, the uncontrolled studies rarely reported any serious adverse events, with none considered to be associated with melatonin use.¹⁷ Adverse events tended to be self-limited and resolved within a couple of days without any adjustments to the melatonin dose or after cessation of the offending agent.¹⁷ The rates of adverse events did not seem to be associated to the dose or formulation of the product (immediate-release vs. extended-release).¹⁷

The following theoretical safety concerns with melatonin use have a paucity of evidence and are often inconclusive, but have been presented by the authors of the SR:

- **Seizures:** There is no conclusive evidence that melatonin causes seizures; however, some evidence suggests melatonin may have neuroprotective properties and may lessen the severity of seizures, possibly due to the effect of better sleep quality.¹⁷
- **Delayed puberty in children:** There is concern that long-term use of melatonin in pre-pubertal children may increase the risk of delayed puberty due to the natural decline that occurs in endogenous melatonin concentrations immediately before the onset of sexual maturity.¹⁷ There is no conclusive evidence that exogenous melatonin impacts sexual development in pre-pubertal children, and there is a paucity of evidence for long-term RCTs in teenaged adults and younger children.¹⁷
- **Effects on reproductive and endocrine hormones** (eg, luteinizing hormone, growth hormone, follicle-stimulating hormone): There is inconsistent evidence on the effects of melatonin to inhibit or stimulate growth hormone secretion, which has caused some experts (in 2003) to recommend a conservative approach for melatonin use in pediatrics, including adolescents.¹⁷ Studies of melatonin's ability to dysregulate these hormones have had contradictory results, with long-term outcomes not established.¹⁷ However, increased melatonin levels appear to be related to poor semen quality in males, and amenorrhea in females.¹⁷
- **Glucose tolerance and insulin resistance:** Melatonin is known to act as a natural regulator of circadian processes, including metabolic functions.¹⁷ Genetic studies identified a variant in the melatonin receptor gene (*MTNR1B*) that encodes the MT₂ receptor that has been associated with dysfunctional glucose regulation, decreased insulin concentrations, and an increased risk of developing type 2 diabetes.¹⁷ Despite the genetic correlation, the limited studies available show contradictory results for the role of melatonin on endocrine metabolic functions.¹⁷ Due to the paucity of evidence, those with diabetes or metabolic syndrome or who are intolerant to glucose are encouraged to be monitored for any adverse effects with melatonin use.¹⁷
- **Asthma or other inflammatory conditions:** It is speculated that melatonin may negatively affect asthma and other inflammatory conditions due to the ability of pro-inflammatory cytokines to increase in the presence of melatonin.¹⁷ Limited evidence suggests conflicting results; a long-term open label study considering asthma suggests melatonin does not produce any improvement or exacerbation of asthma symptoms.¹⁷

The SR by **Oliveira et al (2018)** evaluated the use of melatonin, eszopiclone, and paliperidone in adults with schizophrenia suffering from insomnia, including the assessment of medication-related adverse effects.¹⁹ Each agent was evaluated by 1 study each to determine the adverse effects experienced by this patient population.¹⁹ In the melatonin study, based on subjective measures, participants noted better daytime functioning and increased “morning freshness”, and experienced fewer morning headaches with melatonin use versus placebo, likely due to experiencing better sleep quality.¹⁹ Melatonin was comparable to placebo for long-term sedating effects such as drowsiness after administration, time to awaken in the morning, head heaviness in the morning upon awakening, number and/or quality of dreams remembered, and “freshness during the day”.¹⁹

8.0 SAFETY INFORMATION FOR PRESCRIPTION INSOMNIA AGENTS USED IN ADULTS

Below is a summary of commonly reported adverse events (AEs) as reported in the prescribing information for the FDA-approved pharmacotherapies used to treat insomnia in adults. Older adults

(≥ 65 years of age) and/or disabled patients may be more sensitive to certain agents (eg, benzodiazepines, z-drugs) and their associated AEs.^{45,48,51,59} Due to the increased risk of excessive sedation, confusion, and/or falling, older adults should be closely monitored and typically started on a lower dose than younger individuals (refer to **Table 2** for initiation dosages).^{45,46,48,49,51}

8.1 Common Adverse Events

Benzodiazepines

- Estazolam (AE ≥1%): somnolence, hypokinesia, abnormal coordination, and dizziness⁴⁷
 - A similar side effect profile was observed in older adults (≥ 60 years of age). However, caution should be used in older adults that are smaller in size or disabled due to the risk of excessive sedation.⁴⁷
- Flurazepam (AE frequency not reported): abnormal coordination (eg, staggering, ataxia), falling, dizziness, sedation/drowsiness, light-headedness⁴⁵
- Triazolam (AE ≥ 4%; twice the rate of the placebo group): drowsiness, light-headedness, dizziness, abnormal coordination (eg, ataxia)⁴⁹
- Quazepam (AE ≥1%): headache, drowsiness, fatigue, dry mouth, dizziness, dyspepsia⁴⁸
- Temazepam (AE ≥2%): drowsiness, headache, fatigue, nervousness, lethargy, dizziness, nausea, hangover, anxiety⁴⁶

Z-drugs

- Eszopiclone (AE ≥2%): unpleasant taste, somnolence, headache, infections (respiratory and viral), dry mouth, rash, dizziness, anxiety, hallucinations⁴³
 - A similar side effect profile was observed in older adults taking the 2 mg dose.⁴³
- Zaleplon (AE ≥4%): headache, dizziness, drowsiness, nausea, abdominal pain, asthenia⁴⁴
- Zolpidem tartrate
 - Ambien short-term (<10 days; AE ≥1%): headache, drowsiness, dizziness, diarrhea³⁷
 - long-term (25–35 days; AE ≥3%): drowsiness, dizziness, lethargy, drugged feeling, allergy, dry mouth, back pain, diarrhea, sinusitis, pharyngitis³⁷
 - Ambien CR (AE > 10% in older adults or adults): headache, dizziness, next-day somnolence³⁸
 - Edluar short-term (<10 days; AE ≥1%): headache, drowsiness, dizziness, diarrhea³⁹
 - long-term (25–35 days; AE ≥3%): drowsiness, dizziness, lethargy, drugged feeling, allergy, dry mouth, back pain, diarrhea, sinusitis, pharyngitis³⁹
 - Intermezzo (AE ≥1%): headache, nausea, fatigue⁴⁰
 - Zolpimist short-term (<10 days; AE ≥1%): headache, drowsiness, dizziness, diarrhea⁴¹
 - long-term (25–35 days; AE ≥3%): drowsiness, dizziness, lethargy, drugged feeling, allergy, dry mouth, back pain, diarrhea, sinusitis, pharyngitis⁴¹

Tricyclic antidepressant/ Histamine receptor antagonist

- Doxepin (most common treatment-related AE ≥2% in doxepin-treated patients, and more frequently than placebo-treated patients): somnolence/sedation, upper respiratory tract infection, nausea⁵⁰

Orexin receptor antagonists

- Suvorexant (AE $\geq$ 5%; at least twice the rate of the placebo group): somnolence⁴²
 - A similar adverse effect profile was observed in older adults ($\geq$ 65 years of age). However, as a result of drowsiness, individuals, especially older adults, have an increased risk of falling.⁴²
- Lemborexant (AE $\geq$ 5%; at least twice the rate of the placebo group): somnolence⁵¹
 - The incidence of somnolence was higher in older adults taking 10 mg compared to younger patients on the same dose.⁵¹ However, when used at the lower dose (5 mg), the incidence of somnolence was similar between older adults and those younger than 65 years of age.⁵¹ Caution should be used when exceeding the 5 mg dose in older adults, especially due to the increased risk of falling as a result of excessive sedation and/or drowsiness.⁵¹
- Daridorexant (AE $\geq$ 5%; at an incidence greater than or equal to the placebo group): headache, fatigue, somnolence⁵⁹
 - The incidence of fatigue and somnolence/sedation increased with age.⁵⁹

Melatonin receptor agonist

- Ramelteon (AE $\geq$ 3%; more common than in the placebo-treated patients): somnolence, fatigue, dizziness, nausea, exacerbated insomnia⁶⁰
 - A similar side effect profile was observed in older adults ($\geq$ 65 years of age) compared to younger patients. A double-blind, placebo-controlled RCT in older adults demonstrated that ramelteon (dosed during the night) had no negative impacts on mobility, memory, and balance compared to placebo, although the exact effects on balance during the night in older adults remains unknown.⁶⁰

8.2 Warnings and Precautions

Table 6 contains contraindications, warnings, and precautions among the common prescription drugs or drug-classes recommended in reviewed guidelines for the treatment of insomnia in adults. Additional details related to black box warnings or serious precautions are provided below. As a reminder, prescribing information should be reviewed for individual drugs; contraindications, warnings, and precautions may vary for specific agents within a drug class or by drug formulation.

8.2.1 Black Box Warnings

Drug-classes carrying black box warnings include the benzodiazepines and z-drugs (eszopiclone, zolpidem, and zaleplon). Benzodiazepines have black box warnings for the risks of respiratory depression, excessive sedation, coma, and death regarding combination use with opioids; risk of abuse, misuse, and addiction; and the potential for withdrawal symptoms.⁴⁵⁻⁴⁹ Due to the risks of respiratory depression, sedation, coma, and potential death, concomitant use of benzodiazepines with opioids should be reserved for patients that have failed alternative options, and should be closely monitored.⁴⁵⁻
⁴⁹ The risks of addiction, abuse, and misuse can result in overdose and death.⁴⁵⁻⁴⁹ Typically, abuse and misuse occurs in individuals exceeding the maximum recommended dose and taking other concomitant agents such as alcohol and/or illicit agents.⁴⁵⁻⁴⁹ In patients at a higher risk of abuse, misuse, and addiction, providers should counsel patients about the appropriate use of the medication and about associated risks, especially prior to treatment initiation.⁴⁵⁻⁴⁹ The lowest effective dose should be used

and other addiction-promoting substances (eg, opioids, alcohol, stimulants) should be avoided or used cautiously while using benzodiazepines.⁴⁵⁻⁴⁹ In the event benzodiazepines are no longer required, they should be gradually tapered to avoid potentially life-threatening withdrawal symptoms.⁴⁵⁻⁴⁹ Usually individuals taking higher doses or those with chronic use have an increased risk of experiencing withdrawal symptoms due to the manifestation of physical dependence.⁴⁵⁻⁴⁹ In some situations, withdrawal symptoms have persisted for ≥ 12 months.⁴⁵⁻⁴⁹

All prescription pharmacologic agents have been associated with the development of complex sleep behaviors (eg, sleep walking, sleep-driving) during use, which can result in serious injury or death; prescribing information for most hypnotics (eg, orexin inhibitors) list complex sleep behaviors as a precaution or warning.^{37-51,59,60} However, the non-benzodiazepine hypnotic z-drugs, including the various formulations of zolpidem, carry a black box warning for complex sleep behaviors.^{37-41,43,44} Patients do not tend to remember these events, which may occur at any time during use, regardless of prior treatment experience.^{42,51,59,60} Although these events may occur at recommended doses, exceeding the recommended dose or taking the agent with CNS depressants, including alcohol, seems to increase the risk of these events.⁴⁷ In patients who experience complex sleep behaviors, the agent should be discontinued immediately.^{42,51,59}

8.2.2 Cognitive, Behavioral, and Other Abnormalities

Except for the orexin receptor antagonists, the other hypnotics FDA-approved for insomnia include a warning for the potential risk of cognitive and daytime behavioral abnormalities (eg, agitation, depersonalization).^{37-41,43-50,60} The majority of agents include a warning for worsening depression and suicide, especially in patients with comorbid depression.^{37-45,48-51,59,60} The manifestation of any changes should be evaluated immediately, and precautions such as limiting the amount of dispensed medication may be required.^{37-45,48-51,59,60}

In addition, most agents carry a risk for next-day impairment, especially with higher doses, or if administered with less than 7-8 hours of sleep the night before, or with concomitant CNS depressant use (eg, benzodiazepines, alcohol, opioids).^{37-45,48-51,59,60} Patients are advised to minimize driving, operating heavy machinery, or engaging in activities that require mental attention the day after administration.^{37-45,48-51,59,60} Labeling for all agents suggests that if insomnia symptoms persist beyond 7–10 days with a given pharmacologic treatment, the patient should be evaluated for other pre-existing psychiatric and/or medical comorbidities that are manifesting insomnia symptoms, especially if symptoms worsen with treatment or new behavioral or mental symptoms develop.^{37-51,59,60}

Except for benzodiazepines, the majority of agents contain a warning/precaution against use in patients that have impaired respiratory function, particularly those with severe OSA due to the depression of the respiratory drive.^{37,42,50,51,59,60} In addition, such warnings/precautions state that the agents were not studied in the OSA patient population.^{37,42,50,51,59,60}

Orexin receptor antagonists have a unique warning regarding possible sleep paralysis and periodic brief episodes of leg weakness (seconds to a couple of minutes).^{42,51,59} In addition, the majority of benzodiazepines, z-drugs, and ramelteon have warnings for severe anaphylactic reactions (angioedema) that, if experienced, require the agent to be discontinued.^{37,43-48,60} A warning unique to ramelteon is the potential for reproductive hormone effects.⁶⁰ Ramelteon has been associated with lower testosterone

concentrations and higher levels of prolactin, although effects from long-term use on the reproductive axis remain unknown.⁶⁰

8.2.3 Withdrawal Symptoms

Although not classified as a black box warning like benzodiazepines, withdrawal symptoms have occurred with the abrupt discontinuation or rapid dose de-escalation of z-drugs.^{37,43,44} Symptoms have varied from rebound insomnia to characteristic withdrawal symptoms, including abdominal discomfort, sweating, nausea, tremors, and seizures.^{37,43,44} The risk of abuse and dependence is higher in those with a prior history of substance abuse (alcohol or drug); thus, those with a current or previous history of substance abuse should be monitored closely during use.^{37,43,44} An increased risk of abuse and dependence may also be a consideration in the dose and duration of treatment.⁴³

Table 6. Contraindications, Warnings, and Precautions for the Prescription Guideline-Recommended Pharmacologic Agents used for the Treatment of Insomnia in Adults^a

Benzodiazepines ⁴⁵⁻⁴⁹	Z-drugs ^{37-41,43,44}	Ramelteon ⁶⁰	Low-dose Doxepin ⁵⁰	Orexin Receptor Antagonists ^{42,51,59}
Contraindications				
Hypersensitivity to active substance, including angioedema				Avoid in patients with narcolepsy
Pregnant women or those anticipated of becoming pregnant (<i>Estazolam, temazepam, and flurazepam only</i>)	Prior history of complex sleep behaviors after consumption of the agent (eg, sleep-walking, sleep-driving, eating, making phone calls)	Use with fluvoxamine: resulted in 190-fold increase in AUC, and an estimated 70-fold increase in C _{max}	Avoid in patients currently taking MAOIs or in those with prior use within the past 14 days	
Use with strong CYP3A inhibitors (<i>Estazolam and triazolam only</i>)			“Untreated narrow angle glaucoma or severe urinary retention” ⁵⁰	
Warnings and Precautions				
Cognitive and behavioral abnormalities Behavioral changes such as agitation, manias, depersonalization (depending on agent), along with hallucinations have been reported with use. Amnesia, anxiety and other neuro-psychiatric symptoms may occur sporadically. New changes should be evaluated immediately				Sleep paralysis, disturbing hallucinations, and cataplexy-like symptoms Brief periods of weakness in the legs may occur during the daytime or at night. In addition, sleep paralysis and vivid images may occur with use
Evaluate other comorbidities A primary psychiatric and/or medical condition should be evaluated if the insomnia persists longer than 7 to 10 days with drug therapy, especially if worsening insomnia symptoms develop with use				
Complex sleep behaviors ^b				

Grey shading indicates a **black box warning**.

Abbreviations: CNS, central nervous system; CYP, cytochrome; MAOIs, monoamine oxidase inhibitors; OSA, obstructive sleep apnea

^a Prescribing information should be reviewed for individual drugs; this contains select warnings and precautions. In addition, contraindications, warnings, and precautions may vary for specific agents within a drug class or by drug formulation

^b **Complex sleep behaviors is a black box warning for the z-drugs**

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The experience of complex sleep behaviors (eg, participating in activities while not completely awake) has occurred with use. May occur after the initial or subsequent administration, with or without combination use of other CNS depressants				
<u>Next-day impairment and CNS depression</u>				
Next day impairment, including inability to drive is increased and activities that require concentration should be avoided. Do not administer with other CNS depressants (eg, alcohol) due to the increase risk of daytime impairment				
<u>Combination use with opioids</u> May cause excessive respiratory depression, sedation, coma, and death. Combination use should be reserved for patients in which alternative options are insufficient	<u>Limited respiratory function conditions</u> Use should be avoided or used cautiously (depending on agent) in patients with compromised respiratory function, including those with severe OSA because it has not been studied in this patient population and hypnotics tend to depress respiratory function			
<u>Worsening depression/suicidal ideation</u> Patients, especially those with other comorbid depression, should be monitored for exacerbating symptoms and the risk of suicide				
<u>Anaphylactic reactions</u> Do not rechallenge in patients that experience angioedema			<u>Combination use with CNS depressants or sedating antihistamines</u> A dose reduction may be required if used with other sedating medications due to the additive effects	
<u>Addiction, abuse, and misuse</u> Use has been associated with increased risks of addiction,	<u>Withdrawal symptoms</u> Withdrawal symptoms have manifested due to the sudden cessation of	<u>Reproductive hormone effects</u> May cause decreased testosterone and increased		

Grey shading indicates a **black box warning**.

Abbreviations: CNS, central nervous system; CYP, cytochrome; MAOIs, monoamine oxidase inhibitors; OSA, obstructive sleep apnea

^a Prescribing information should be reviewed for individual drugs; this contains select warnings and precautions. In addition, contraindications, warnings, and precautions may vary for specific agents within a drug class or by drug formulation

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abuse, and misuse, which may result in overdose and death.	the agent or rapid dose reduction. Symptoms may include abdominal discomfort, vomiting and anxiety	prolactin concentrations. Effects from long-term use on the reproductive axis remains unknown		
<u>Dependence and withdrawal symptoms</u> To avoid withdrawal symptoms, the agent should be tapered before discontinuing				

Grey shading indicates a **black box warning**.

Abbreviations: CNS, central nervous system; CYP, cytochrome; MAOIs, monoamine oxidase inhibitors; OSA, obstructive sleep apnea

^a Prescribing information should be reviewed for individual drugs; this contains select warnings and precautions. In addition, contraindications, warnings, and precautions may vary for specific agents within a drug class or by drug formulation

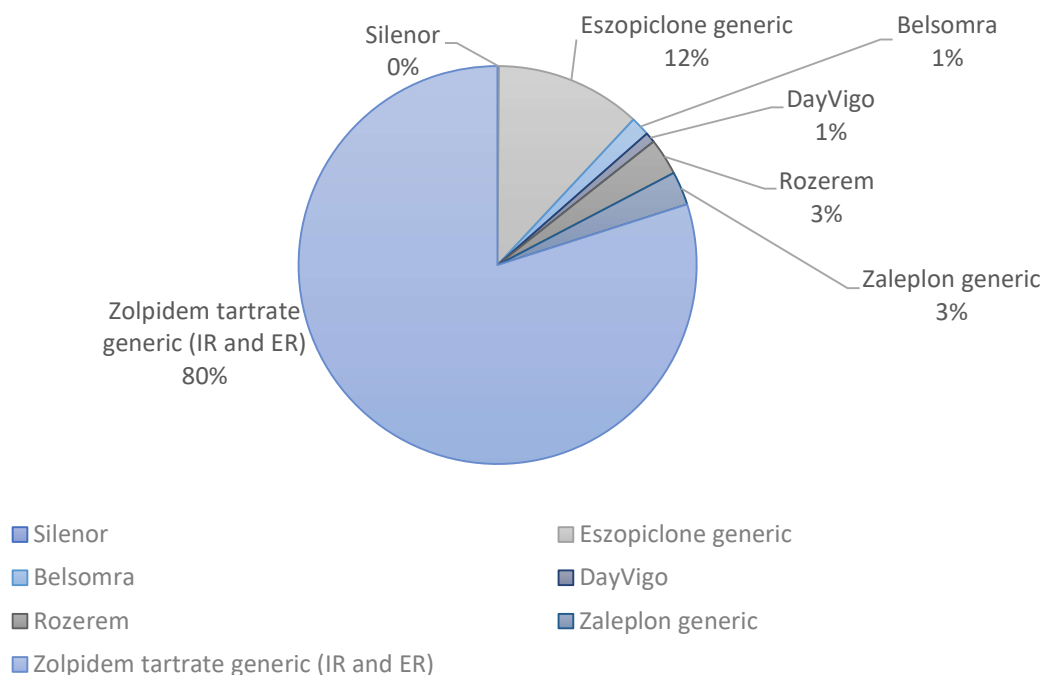
^b **Complex sleep behaviors is a black box warning for the z-drugs**

9.0 UTAH MEDICAID PHARMACY UTILIZATION DATA

FDA-approved insomnia agents with preferred status on the Utah Medicaid Preferred Drug List (PDL; June 1, 2022 version), include flurazepam, temazepam 15 mg and 30 mg, eszopiclone, Rozerem (brand for ramelteon), zaleplon, zolpidem tablet, and zolpidem CR. The orexin receptor antagonists, DayVigo (brand for lemborexant), Belsomra (brand for suvorexant), and Quviviq (brand for daridorexant) are non-preferred. Additional non-preferred agents include estazolam, triazolam as brand (Halcion) or generic, temazepam as brand (Restoril) or generic 7.5 mg and 22.5 mg, all brand products for zolpidem (ie, Ambien, Edluar, Intermezzo, Zolpimist, and Ambien CR), doxepin as brand (Silenor) or generic, Lunesta (brand for eszopiclone), and generic ramelteon.

Pharmacy utilization data for approved insomnia agents were extracted for the Utah Medicaid fee-for-service (FFS) adult population (≥ 18 years of age) from May 2021 through April 2022. To target benzodiazepine use for insomnia, utilization data was extracted for adults who had *at least* 1 insomnia-related ICD-10 diagnosis code (F51.0X or G47.0X) within 30 days prior to the indexed benzodiazepine claim, in an attempt to minimize observable utilization for other benzodiazepine indications (eg, anxiety, seizures). **Table 7** provides the pharmacy utilization data for the non-benzodiazepines. **Figure 1** is a visual representation of the non-benzodiazepine pharmacy claims filled during the 1 year period.

Figure 1. Non-benzodiazepine Hypnotic Pharmacy Claims, May 2021 through April 2022



Over the 1-year period (May 2020 through April 2022), the most-utilized agent among the non-benzodiazepine hypnotic drug class was zolpidem tartrate (80% of claims, both immediate-release and extended-release), followed by generic eszopiclone (12% of claims). Among zolpidem tartrate claims, 88% were for the immediate-release formulation and 12% were for the extended-release formulation. Utilization was lowest for Belsomra, DayVigo, and Silenor, which are non-preferred products on the PDL.

Table 7. Utah Medicaid FFS Pharmacy Claims for Non-benzodiazepine Hypnotics Among Adults (≥18 years of age) from May 2021 through April 2022^a

Generic Name	Product(s) and Formulation	Claims	Patients
Doxepin	SILENOR TAB 3 MG	< 5	< 5
	SILENOR TAB 6 MG	< 5	< 5
Eszopiclone	ESZOPICLONE TAB 1 MG	104	55
	ESZOPICLONE TAB 2 MG	97	43
	ESZOPICLONE TAB 3 MG	306	81
	LUNESTA TAB 3 MG	< 5	< 5
Lemborexant	DAYVIGO TAB 5 MG	17	7
	DAYVIGO TAB 10 MG	18	6
Ramelteon	ROZEREM TAB 8MG	128	42
Suvorexant	BELSOMRA TAB 5 MG	< 5	< 5
	BELSOMRA TAB 10 MG	15	6
	BELSOMRA TAB 15 MG	6	< 5
	BELSOMRA TAB 20MG	45	9
Zaleplon	ZALEPLON CAP 5 MG	14	9
	ZALEPLON CAP 10 MG	103	28
Zolpidem Tartrate	ZOLPIDEM TAB 5 MG	573	199
	ZOLPIDEM TAB 10 MG	2447	551
	ZOLPIDEM ER TAB 6.25 MG	110	13
	ZOLPIDEM ER TAB 12.5 MG	290	64
Total		4282	1000

Blue color indicates **brand** product

Abbreviations: AHFS, American Hospital Formulary Service; CAP, capsule; ER, extended-release; FFS, fee-for-service; MG, milligram; NDC, national drug code; TAB, tablet

^a Filled products were identified based on NDCs from the most recent (as of the day of this report) AHFS table of NDCs

Table 8 provides the pharmacy utilization data for the benzodiazepines among adults in the Medicaid FFS population from May 2021 through April 2022. Of importance, as a drug class, benzodiazepines are used for other indications aside from insomnia such as anxiety and seizures. Although we attempted to target utilization for the treatment of insomnia, the utilization may also reflect use for these other indications. The most-utilized agent among the benzodiazepine drug class with an FDA-approved indication for insomnia was temazepam, 15 mg followed by the 30 mg dosage.

Table 8. Utah Medicaid FFS Pharmacy Claims for Benzodiazepines Among Adults (≥18 years of age) with an Insomnia-related Diagnosis Code from May 2021 through April 2022^a

Generic Name	Product(s) and Formulation	Claims	Patients
Temazepam	TEMAZEPAM CAP 15 MG	45	17
	TEMAZEPAM CAP 22.5 MG	< 5	< 5
	TEMAZEPAM CAP 30 MG	21	11
Triazolam	TRIAZOLAM TAB 0.25 MG	< 5	< 5
Total		70	30

Abbreviations: AHFS, American Hospital Formulary Service; CAP, capsule; FFS, fee-for-service; ICD-10, International Classification of Diseases, Tenth Revision; MG, milligram; NDC, national drug code; TAB, tablet

^a Utilization is from the pool of patients with at least 1 insomnia-related ICD-10 code (F51.0X or G47.0X) within 30 days of the indexed benzodiazepine claim. Filled products were identified based on NDCs from the most recent (as of the day of this report) AHFS table of NDCs

10.0 CONSIDERATIONS FOR AGENTS USED TO TREAT ADULT INSOMNIA

The Utah Medicaid DUR Board may consider the following recommendations:

- 1) Currently, a prescription-grade melatonin agonist, Rozerem (brand of ramelteon) is listed as preferred on the Utah Medicaid PDL. This medication is FDA-approved for sleep onset insomnia; thus, coverage of OTC melatonin may not be needed at this time to fill a treatment need for a melatonin receptor agonist since patients already have access (without requiring a prior authorization [PA]) to ramelteon. However, certain Medicaid PA (for Hetlioz in particular) requires a previous trial of melatonin. None of the reviewed SRs reported head-to-head evidence comparing ramelteon to melatonin; thus one agent cannot be recommended over another. However, some SRs or guidelines do describe potential usefulness/benefits of melatonin as follows:
 - a) Melatonin may be beneficial for older adults (≥ 65 years of age) due to the low risks of adverse effects.¹⁵ Alternatively, melatonin concomitant with benzodiazepines may help facilitate dose reductions or cessation of benzodiazepines in patients that are using these agents for sleep.¹⁶
 - i) Melatonin is likely a safe option in older adults due to consistent evidence from SRs demonstrating minimal adverse effects (eg, excessive drowsiness), especially related to motor impairment.^{12,15}
 - ii) BAP (2019) recommends extended-release melatonin as a first-line pharmacologic agent in older adults (≥ 55 years of age) after a trial of CBT-I.¹²
 - (1) In this patient population, extended-release melatonin has demonstrated a reduction in time to sleep onset and increased patient-reported sleep quality, although the improvements tend to be minor.¹²
 - (2) An important consideration of melatonin use is that unlike in other countries,⁶⁵ a prescription-grade melatonin is not available in the US.
 - (a) Unlike prescription products, manufacturers of dietary supplements are not required to submit proven efficacy, safety, or quality standards to the FDA prior to marketing, thus, there is the potential for impurities in OTC dietary supplements.^{2,55}

- iii) In an SR conducted by **Morera-Fumero et al (2020)**, concomitant melatonin use was found to either aid with complete withdrawal of benzodiazepine consumption or reduce the benzodiazepine dose in those unable to achieve complete withdrawal.¹⁶
- 2) For zolpidem and zaleplon, which are preferred products and commonly used among the Medicaid population, the board may consider a point of sale edit that requires certain populations to initiate therapy at the lower end of the dosage range as recommended in product labeling. Labeling permits up-titration thereafter; so initiation doses should not be interpreted as the maximum recommended dosage unless specified.
 - a) At the point of sale, a patient may be defined as initiating therapy if they have not filled zolpidem or zaleplon within the previous 60 days
 - b) Women should initiate zolpidem at 5 mg, or 6.25 mg for the CR product^{37,38}
 - c) For those ≥ 65 years of age, the maximum dose for eszopiclone is 2 mg;⁴³ initiation dose for zaleplon is 5 mg, and maximum dose is 10 mg;⁴⁴ and the recommended dose for zolpidem is 5 mg, and 6.25 mg for the CR product^{37,38}
- 3) The board may consider adding a non-controlled substance for sleep maintenance insomnia as preferred on the PDL, so that non-controlled substances are more easily accessible compared to controlled substances. Doxepin (Silenor), a non-controlled substance is approved for sleep maintenance but is currently non-preferred on the PDL.
 - a) The majority of hypnotics have a known increased risk of physical dependence, tolerance, and abuse, and as a result, are classified as Schedule IV controlled substances,³⁴ except doxepin and ramelteon which are non-controlled substances.³⁷⁻⁵²
 - b) Rozerem, the brand for ramelteon is the only non-controlled substance that is currently listed as preferred on the PDL; however, its approved indication is for the treatment of sleep onset insomnia.⁶⁰ Thus, there is no non-controlled product for sleep maintenance insomnia listed as preferred on the PDL.
- 4) Additional data extraction work beyond the scope of this review, but that may be interesting to investigate further could include:
 - a) Number of treatment-naïve women or patients over 65 years of age who may have initiated a z-drug at higher than recommended initiation doses according to product labeling
 - b) Patients on controlled substance hypnotics (eg, zolpidem) with an ICD-10 diagnosis code for substance abuse

11.0 SUMMARY

The ICSD-3 defines insomnia as trouble initiating and/or maintaining sleep, or premature awakening that results in symptoms during wakefulness (eg, decreased energy, fatigue, problems with attention, irritability).²⁻⁴ Insomnia may occur as an independent condition, or comorbid with other diseases (eg, anxiety, sleep apnea).^{4,7} Consistent, inadequate amounts of sleep have been associated with adverse health consequences such as weight gain, diabetes, hypertension, cardiovascular disease, and depression, as well as impaired immunity, reduced performance, and increased risk of errors/accidents.¹

The goals of insomnia management are to improve sleep, mitigate psychological or physical distress/dysfunction that results from the disorder,⁷ and improve function.¹² Nonpharmacologic interventions, primarily CBT-I, pharmacologic interventions, or a combination of both modalities are typically used to treat chronic insomnia in adults.^{7,8} The pharmacologic agents with a FDA-approved

indication for the treatment of insomnia belong to numerous drug classes including z-drugs (zaleplon, eszopiclone, zolpidem), benzodiazepines (eg, triazolam, estazolam), tricyclic antidepressant/histamine receptor antagonist (ie, doxepin), orexin receptor antagonists (eg, suvorexant, lemborexant), and melatonin receptor agonists (ie, ramelteon).⁷⁻⁹ Pharmacologic agents often produce a quicker response in symptom resolution compared to nonpharmacologic therapies, but the effects can fade after cessation of the agent.^{8,34}

All reviewed guidelines that address psychological/behavioral treatments recommend CBT-I as first-line therapy in adults with chronic insomnia.^{2,7,11-13} AASM recognizes that some patients may require hypnotics, either alone or in combination with CBT-I, for the management of chronic insomnia.³ Before initiation of a short-course of pharmacologic therapy, providers should consider a patient's response to prior treatments, the accessibility of CBT-I, and the patient's preference.⁶¹ The guidelines for the treatment of chronic insomnia in adults recommend *short-term* pharmacotherapy (< 4 to 5 weeks of treatment).^{2,7,13,68} Some patients, especially those with other chronic comorbidities, may require continued treatment for insomnia due to persistent symptoms.³⁴

A limited number of guidelines address the long-term treatment with pharmacotherapy, likely due to the lack of available long-term evidence.^{2,7,13} According to the guidelines that do address long-term pharmacologic management, the continued use of medications should be determined by individualized benefit/risk decisions at periodic reassessments.^{7,12} The 2017 AASM guideline states that long-term treatment with benzodiazepine receptor agonists should be reserved for patients that are unresponsive or unable to use CBT-I, have been screened for agent-specific contraindications, continue to show long-term benefit, and are evaluated on a regular basis.³ ACP (2016) suggests treating other potential causes of insomnia (eg, depression, substance abuse disorders, pain, sleep apnea) before deciding to continue pharmacotherapy beyond 4–5 weeks.⁷ After a trial of CBT-I, if the decision to continue pharmacologic agents exceeds 4–5 weeks, ACP recommends that the requirement for pharmacologic therapy should be evaluated at periodic intervals.⁷ European guidelines suggest the need for long-term therapy may be based on a trial of discontinuing the pharmacologic agent and evaluating the response, or switching to intermittent dosing for those taking benzodiazepine receptor agonists on a daily basis.^{12,13}

The accessibility of melatonin as an OTC product has made it a commonly used product to treat insomnia in adults.¹⁸ Unlike prescription products, manufacturers of dietary supplements are not required to submit proven efficacy, safety, or quality standards to the FDA prior to marketing, thus, there is the potential for impurities in OTC dietary supplements.^{2,55} Dietary supplements that have been evaluated and passed by third party companies (eg, USP, CL) for established quality standards may be considered of higher quality;⁴ however, these companies may test only a limited number of all possible impurities in products.⁵⁸ Nonetheless, physicians may prefer the use of low-dose melatonin to treat insomnia in adults due to the tolerable side effect profile, especially in older adults who are more sensitive to adverse effects.¹⁸

Among reviewed SRs, melatonin improved insomnia symptoms (sleep onset, TST, nighttime awakenings) compared to placebo, even among patients with comorbidities, including schizophrenia and cancer.^{14,15,18,19} Among patients desiring to discontinue benzodiazepines for the treatment of insomnia, concomitant melatonin use was associated with higher rates of partial (reduced dose) or complete benzodiazepine cessation.¹⁶ Regarding safety, melatonin was generally well-tolerated with very few AEs, even among older adults (≥ 65 years of age).^{15,17-19} The most commonly reported AEs were headache

and somnolence.^{15,17-19} Reports of serious AEs related to melatonin use were very few; one SR noted that the incidence of serious AEs was more likely related to an exacerbation of a pre-existing condition or associated with the study population rather than melatonin use itself.¹⁷

Benzodiazepines have black box warnings for the risks of respiratory depression, excessive sedation, coma, and death regarding combination use with opioids, risk of abuse, misuse, and addiction, and the potential for withdrawal symptoms.⁴⁵⁻⁴⁹ Non-benzodiazepine hypnotic z-drugs, carry a black box warning for complex sleep behaviors (eg, sleep walking, sleep-driving), while prescribing information for other hypnotics (eg, orexin receptor antagonists) list complex sleep behaviors as a precaution or warning.^{37-41,43,44} Similar to benzodiazepines, withdrawal symptoms have been associated with z-drugs when abrupt discontinuation or rapid dose de-escalation occurs.^{37,43,44} Other warnings for the majority of agents includes worsening depression and suicide, behavioral and cognitive abnormalities (eg, hallucinations), CNS-depressant effects and/or next-day impairment in the presence or absence of other CNS depressants, and to use caution or avoid in patients with compromised respiratory function (eg, sleep apnea).^{37-51,59,60}

There is variability among guidelines regarding pharmacologic therapies that are recommended in favor for their use. The 2017 AASM guideline has the broadest set of agents recommended for consideration in adult insomnia, which generally includes low-dose doxepin, eszopiclone, ramelteon, temazepam, triazolam, suvorexant, zaleplon, and zolpidem.³ Recommendations are specific to the insomnia subtype (ie, sleep onset or maintenance insomnia). Only the BAP guideline provided a recommendation in favor of melatonin; the recommendation was specific to extended-release melatonin exclusively for older adults.¹² Melatonin may be beneficial for older adults (≥ 65 years of age) due to the low risk of adverse effects.¹⁵ In the majority of reviewed SRs, compared to placebo, melatonin improved various sleep parameters including sleep onset, TST, decreased nighttime awakenings, and sleep efficiency among adults, including those with advanced age.^{14,15,18,19} However, trial results tended to be inconsistent and based on small sample sizes.^{14,15,18,19} A prescription-grade melatonin agonist, Rozerem, the brand of ramelteon is listed as preferred on the Utah Medicaid PDL. This medication is FDA-approved for sleep onset insomnia; thus, the coverage of OTC melatonin for adult insomnia may not be needed at this time.

REFERENCES

1. Watson NF, Badr MS, Belenky G, et al. Recommended Amount of Sleep for a Healthy Adult: A Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep*. 2015;38(6):843-4.
2. Chowdhuri S, Ulmer C, Mysliwiec V, Spevak C, et al. VA/DoD Clinical 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 April 22, 2022. Available at: <https://www.healthquality.va.gov/guidelines/CD/insomnia/VADoDSleepCPGFinal508.pdf>
3. 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.
4. Perez MN, Salas RME. Insomnia. *Continuum (Minneapolis Minn)*. 2020;26(4):1003-1015.
5. 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 May 10, 2022. Available at: <https://www.uptodate.com/contents/risk-factors-comorbidities-and-consequences-of-insomnia-in-adults>.
6. Salisbury-Afshar E. Management of Insomnia Disorder in Adults. *Am Fam Physician*. 2018;98(5):319-322.
7. 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.
8. UpToDate.com. Overview of the treatment of insomnia in adults [by JW Winkelman]. [Online database.] Waltham, MA: Wolters Kluwer. Last updated March 2022. Accessed April 27, 2022. Available at: <https://www.uptodate.com/contents/overview-of-the-treatment-of-insomnia-in-adults>
9. Neubauer DN, Pandi-Perumal SR, Spence DW, Buttoo K, Monti JM. Pharmacotherapy of Insomnia. *J Cent Nerv Syst Dis*. 2018;10:1179573518770672.
10. CADTH.ca. Strings Attached: CADTH's Database Search Filters (Guidelines — OVID Medline, Embase, PsycINFO). [Online database.] Ottawa, ON Canada: Canadian Agency for Drugs and Technologies in Health. Last updated February 11, 2021. Accessed April 25, 2022. Available at: <https://www.cadth.ca/cadth-search-filters-database>.
11. 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*. 2021;17(2):255-262.
12. 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.

13. 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.
14. Jafari-Koulaee A, Bagheri-Nesami M. The effect of melatonin on sleep quality and insomnia in patients with cancer: a systematic review study. *Sleep Med.* 2021;82:96-103.
15. Almond SM, Warren MJ, Shealy KM, Threatt TB, Ward ED. A Systematic Review of the Efficacy and Safety of Over-the-Counter Medications Used in Older People for the Treatment of Primary insomnia. *Sr Care Pharm.* 2021;36(2):83-92.
16. Morera-Fumero AL, Fernandez-Lopez L, Abreu-Gonzalez P. Melatonin and melatonin agonists as treatments for benzodiazepines and hypnotics withdrawal in patients with primary insomnia. A systematic review. *Drug Alcohol Depend.* 2020;212:107994.
17. Besag FMC, Vasey MJ, Lao KSJ, Wong ICK. Adverse Events Associated with Melatonin for the Treatment of Primary or Secondary Sleep Disorders: A Systematic Review. *CNS Drugs.* 2019;33(12):1167-1186.
18. Low TL, Choo FN, Tan SM. The efficacy of melatonin and melatonin agonists in insomnia - An umbrella review. *J Psychiatr Res.* 2019;121:10-23.
19. Oliveira P, Coroa M, Madeira N. Treatment Options for Insomnia in Schizophrenia: A Systematic Review. *Pharmacopsychiatry.* 2019;52(4):165-169.
20. Mukherjee S, Patel SR, Kales SN, et al. An Official American Thoracic Society Statement: The Importance of Healthy Sleep. Recommendations and Future Priorities. *Am J Respir Crit Care Med.* 2015;191(12):1450-8.
21. UpToDate.com. Insufficient sleep: evaluation and management [by K Maski]. [Online database.] Waltham, MA: Wolters Kluwer. Last updated February 2021. Accessed April 28, 2022. Available at: <https://www.uptodate.com/contents/insufficient-sleep-evaluation-and-management>.
22. Ramar K, Malhotra RK, Carden KA, et al. Sleep is essential to health: an American Academy of Sleep Medicine position statement. *J Clin Sleep Med.* 2021;17(10):2115-2119.
23. Hirshkowitz M, Whiton K, Albert SM, et al. National Sleep Foundation's updated sleep duration recommendations: final report. *Sleep Health.* 2015;1(4):233-243.
24. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest.* 2014;146(5):1387-1394.
25. Riemann D, Benz F, Dressle RJ, et al. Insomnia disorder: State of the science and challenges for the future. *J Sleep Res.* 2022;
26. National Institutes of Health State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults, June 13-15, 2005. *Sleep.* 2005;28(9):1049-57.
27. Reynolds CF, 3rd, O'Hara R. DSM-5 sleep-wake disorders classification: overview for use in clinical practice. *Am J Psychiatry.* 2013;170(10):1099-101.
28. 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 April

- 27, 2022. Available at: <https://www.choosingwisely.org/clinician-lists/american-academy-sleep-medicine-polysomnography-for-chronic-insomnia/>.
29. 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 April 27, 2022. Available at: <https://www.uptodate.com/contents/evaluation-and-diagnosis-of-insomnia-in-adults>.
30. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. *J Psychosom Res*. 2002;53(3):737-40.
31. 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.
32. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. Athens Insomnia Scale: validation of an instrument based on ICD-10 criteria. *J Psychosom Res*. 2000;48(6):555-60.
33. ChoosingWisely.org. Don't routinely order sleep studies (polysomnogram) to screen for/diagnose sleep disorders in workers suffering from chronic fatigue/insomnia [American College of Occupational and Environmental Medicine]. [Online database.] Philadelphia, PA: ABIM Foundation. Last updated February 24, 2014. Accessed April 27, 2022. Available at: <https://www.choosingwisely.org/clinician-lists/american-college-occupational-environmental-medicine-routine-sleep-studies-for-sleep-disorders/>.
34. UpToDate.com. Pharmacotherapy for insomnia in adults [by DN Neubauer]. [Online database.] Waltham, MA: Wolters Kluwer. Last updated March 4, 2022. Accessed May 3, 2022. Available at: <https://www.uptodate.com/contents/pharmacotherapy-for-insomnia-in-adults>.
35. UpToDate.com. Cognitive behavioral therapy for insomnia in adults [by JL Martin]. [Online database.] Waltham, MA: Wolters Kluwer. Last updated December 2021. Accessed April 28, 2022. Available at: <https://www.uptodate.com/contents/cognitive-behavioral-therapy-for-insomnia-in-adults>.
36. FDA.gov. 2017. FDA Drug Safety Communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR. [Internet website.] US Food and Drug Administration (FDA). Last updated December 11, 2017. Accessed May 5, 2022. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-approves-new-label-changes-and-dosing-zolpidem-products-and>.
37. Sanofi-aventis US LLC. Ambien (zolpidem tartrate) tablets, for oral use [Package Insert]. Revised February 2022. Bridgewater, NJ: sanofi-aventis US LLC.
38. 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.
39. Meda Pharmaceuticals Inc. Edluar (zolpidem tartrate) sublingual tablets, for oral use [Package Insert]. Revised August 2019. Somerset, NJ: Meda Pharmaceuticals Inc.
40. Patheon Pharmaceuticals Inc. Intermezzo (zolpidem tartrate) sublingual tablets, for oral use [Package insert]. Revised August 2019. Cincinnati, OH: Patheon Pharmaceuticals Inc.

41. Aytu BioScience Inc. Zolpimist (zolpidem tartrate) spray, for oral use [Package insert]. Revised August 2019. Englewood, CO: Aytu BioScience Inc.,.
42. Merck & Co. Inc. Belsomra (suvorexant) tablets, for oral use [Package insert]. Revised March 2020. Whitehouse Station, NJ: Merck & Co. Inc.,.
43. Sunovion Pharmaceuticals Inc. Lunesta (eszopiclone) tablets, for oral use [Package insert]. Revised August 2019. Marlborough, MA: Sunovion Pharmaceuticals Inc.
44. Pfizer Inc. Sonata (zaleplon) capsules, for oral use [Package insert]. Revised August 2019. New York, NY: Pfizer Inc.
45. Mylan Pharmaceuticals Inc. Flurazepam hydrochloride capsules, for oral use [Package insert]. Revised February 2021. Morgantown, WV: Mylan Pharmaceuticals Inc.
46. SpecGx LLC. Restoril (temazepam) capsules, for oral use [Package insert]. Revised February 2021. Webster Groves, MO: SpecGx LLC.
47. Actavis Pharma Inc. Estazolam tablets, for oral use [Package Insert]. Revised January 2021. Parsippany, NJ: Actavis Pharma Inc.
48. Galt Pharmaceuticals LLC. Doral (quazepam) tablets, for oral use [Package insert]. Revised February 2021. Atlanta, GA: Galt Pharmaceuticals LLC.
49. Pfizer Inc. Halcion (triazolam) tablets, for oral use [Package insert]. Revised October 2021. New York, NY: Pfizer Inc.
50. Currax Pharmaceuticals LLC. Silenor (doxepin) tablets, for oral use [Package insert]. Revised October 2020. Morristown, NJ: Currax Pharmaceuticals LLC.
51. Eisai Inc. Dayvigo (lemborexant) tablets, for oral use [Package insert]. Revised March 2022. Woodcliff Lake, NJ: Eisai Inc.
52. Vanda Pharmaceuticals Inc. Hetlioz (tasimelteon) capsules and suspension, for oral use [Package Insert]. Revised December 2020. Washington, D.C.: Vanda Pharmaceuticals Inc.
53. Lie JD, Tu KN, Shen DD, Wong BM. Pharmacological Treatment of Insomnia. *P t*. 2015;40(11):759-71.
54. FDA.gov. 2022. Dietary Supplements. [Internet website.] US Food and Drug Administration (FDA). Last updated February 18, 2022. Accessed May 3, 2022. Available at: <https://www.fda.gov/food/dietary-supplements>.
55. UpToDate.com. Overview of herbal medicine and dietary supplements [by R Saper]. [Online database.] Waltham, MA: Wolters Kluwer. Last updated October 26, 2021. Accessed May 9, 2022. Available at: <https://www.uptodate.com/contents/overview-of-herbal-medicine-and-dietary-supplements>.
56. Natural Products Insider.com. 2013. FDA GMP inspectors cite 70% of dietary supplement firms [by J Long]. [Internet website.] Natural Products Insider. Last updated May 20, 2013. Accessed May 17, 2022. Available at: <https://www.naturalproductsinsider.com/regulatory/fda-gmp-inspectors-cite-70-dietary-supplement-firms>.

57. USP.org. 2022. USP Verified Mark. [Internet website.] United States Pharmacopeial Convention. Accessed May 9, 2022. Available at: <https://www.usp.org/verification-services/verified-mark>.
58. ConsumerLab.com. 2022. About ConsumerLab.com. [Internet website.] White Plains, NY: ConsumerLab.com, LLC. Accessed May 17, 2022. Available at: <https://www.consumerlab.com/about/>.
59. Idorsia Pharmaceuticals US Inc. Quviviq (daridorexant) tablets, for oral use [Package insert]. Revised April 2022. Radnor, PA: Idorsia Pharmaceuticals US Inc.
60. Takeda Pharmaceuticals America Inc. Rozerem (ramelteon) tablets, for oral use [Package insert]. Revised November 2021. Lexington, MA: Takeda Pharmaceuticals America Inc.
61. ChoosingWisely.org. Don't offer hypnotics as the only initial therapy for chronic insomnia in adults. Use cognitive behavioral therapy for insomnia (CBT-I), whenever possible, and use medications only when necessary [American Academy of Sleep Medicine]. [Online database.] Philadelphia, PA: ABIM Foundation. Last updated December 21, 2021. Accessed May 9, 2022. Available at: <https://www.choosingwisely.org/clinician-lists/aasm-hypnotics-for-chronic-insomnia/>.
62. 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.
63. ChoosingWisely.org. Don't use benzodiazepines or other sedative-hypnotics in older adults as first choice for insomnia, agitation or delirium [American Geriatrics Society]. [Online database.] Philadelphia, PA: ABIM Foundation. Last updated April 23, 2015. Accessed May 9, 2022. Available at: <https://www.choosingwisely.org/clinician-lists/american-geriatrics-society-benzodiazepines-sedative-hypnotics-for-insomnia-in-older-adults/>.
64. FDA.gov. 2002. Consumer advisory: kava-containing dietary supplements may be associated with severe liver injury. [Internet website.] US Food and Drug Administration (FDA). Last updated March 25, 2002. Accessed May 3, 2022. Available at: <https://wayback.archive-it.org/7993/20171114232640/https://www.fda.gov/Food/RecallsOutbreaksEmergencies/SafetyAlertsAdvisories/ucm085482.htm>.
65. RAD Neurim Pharmaceuticals EEC Limited. Circadin (melatonin) prolonged-release tablets [Summary of Product Characteristics]. Revised May 2018. Berkshire, United Kingdom: RAD Neurim Pharmaceuticals EEC Limited.
66. ChoosingWisely.org. Don't routinely prescribe antipsychotic medications as a first-line intervention for insomnia in adults [American Psychiatric Association]. [Online database.] Philadelphia, PA: ABIM Foundation. Last updated August 21, 2014. Accessed May 9, 2022. Available at: <https://www.choosingwisely.org/clinician-lists/american-psychiatric-association-antipsychotics-for-insomnia/>.
67. 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*. 2017;13(2):155-157.
68. Morin CM, Inoue Y, Kushida C, Poyares D, Winkelman J. Endorsement of European guideline for the diagnosis and treatment of insomnia by the World Sleep Society. *Sleep Med*. 2021;81:124-126.

69. Everitt H, Baldwin DS, Stuart B, et al. Antidepressants for insomnia in adults. *Cochrane Database Syst Rev*. 2018;5(5):Cd010753.
70. 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.
71. Quera-Salva MA, Claustat B. [Melatonin: Physiological and pharmacological aspects related to sleep: The interest of a prolonged-release formulation (Circadin®) in insomnia]. *Encephale*. 2018;44(6):548-557.
72. European Medicines Agency. 2008. Takeda withdraws its marketing authorisation application for Ramelteon. [Internet website.] Amsterdam, The Netherlands: European Medicines Agency. Last updated September 25, 2008. Accessed May 11, 2022. Available at: <https://www.ema.europa.eu/en/news/takeda-withdraws-its-marketing-authorisation-application-ramelteon>.
73. Baskett JJ, Broad JB, Wood PC, et al. Does melatonin improve sleep in older people? A randomised crossover trial. *Age Ageing*. 2003;32(2):164-70.
74. Suresh Kumar PN, Andrade C, Bhakta SG, Singh NM. Melatonin in schizophrenic outpatients with insomnia: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(2):237-41.
75. Rösner S, Englbrecht C, Wehrle R, Hajak G, Soyka M. Eszopiclone for insomnia. *Cochrane Database Syst Rev*. 2018;10(10):Cd010703.
76. Lexi.com. Quazepam (Lexi-Drugs): Mechanism of action and pharmacokinetics. [Online database.] Hudson, OH: Lexicomp. Last updated April 22, 2022. Accessed May 17, 2022. Available at: <http://online.lexi.com>.
77. Lexi.com. Triazolam (Lexi-Drugs): Mechanism of action and pharmacokinetics. [Online database.] Hudson, OH: Lexicomp. Last updated April 22, 2022. Accessed May 17, 2022. Available at: <http://online.lexi.com>.
78. Lexi.com. Flurazepam (Lexi-Drugs): Mechanism of action and pharmacokinetics. [Online database.] Hudson, OH: Lexicomp. Last updated May 2, 2022. Accessed May 17, 2022. Available at: <http://online.lexi.com>.
79. Lexi.com. Estazolam (Lexi-Drugs): Mechanism of action and pharmacokinetics. [Online database.] Hudson, OH: Lexicomp. Last updated April 25, 2022. Accessed May 17, 2022. Available at: <http://online.lexi.com>.
80. Lexi.com. Temazepam (Lexi-Drugs): Mechanism of action and pharmacokinetics. [Online database.] Hudson, OH: Lexicomp. Last updated May 4, 2022. Accessed May 17, 2022. Available at: <http://online.lexi.com>.

APPENDIX A – LITERATURE SEARCHES

Clinical Practice Guidelines

The following searches were performed in Ovid Medline and Epistemonikos on April 26, 2022. In the final result row for each search, this number of citations were reviewed at the title/abstract level. For citations that were not excluded at the title/abstract review level, full-text articles were retrieved, and relevant articles were included in this report.

Table 9. Ovid Medline Literature Search Strategy for Adult Insomnia

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to April 25, 2022>		
Search strategy (date of search: April 26, 2022)		
#	Searches	Results
1	exp clinical pathway/ or exp clinical protocol/ or clinical protocols/ or exp consensus/ or exp consensus development conference/ or exp consensus development conferences as topic/ or critical pathways/ or exp guideline/ or guidelines as topic/ or exp practice guideline/ or practice guidelines as topic/ or health planning guidelines/ or treatment guidelines/ or Clinical Decision Rules/	419033
2	(guideline or practice guideline or consensus development conference).pt	46542
3	(position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw	41141
4	(standards or guideline or guidelines).ti,kf,kw. or ((practice or treatment* or clinical) adj guideline*).ab. or (CPG or CPGs).ti. or consensus*.ti,ab,kf,kw.	345776
5	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw	24153
6	recommendat*.ti,kf,kw. or guideline recommendation*.ab.	53214
7	(care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.	73816
8	(algorithm* adj2 (pharmacotherap* or therap* or treatment* or intervention*)).ti,ab,kf,kw.	11771
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	815748
10	exp **Sleep Initiation and Maintenance Disorders**/	11874
11	(insomnia or sleep-dis*).ti.	20016
12	10 or 11	24051
13	Exp *Adult/ or (adult*).ti,ab	1446706
14	9 and 12 and 13	139
15	Limit 14 to yr="2016 – Current"	84

Table 10. Epistemonikos Literature Search Strategy for Adult Insomnia

Database(s): Epistemonikos Session Results

Search strategy (date of search: April 26, 2022)

#	Searches	Results
1	((practice guideline) OR (guide*) OR (guidance OR guideline*)) [Title or Abstract]	114642
2	AND (insomnia OR sleep-disorder* OR sleep-disturbance*) [Title or Abstract]	304
3	AND (adult*) [Title or Abstract]	74
4	From 2016 – 2022	51

Systematic Reviews of Melatonin

Table 11. Epistemonikos Literature Search Strategy for Systematic Reviews of Melatonin

Database(s): Epistemonikos Session Results

Search strategy (date of search: April 26, 2022)

#	Searches	Results
1	Melatonin [Title or Abstract]	1338
2	AND (insomnia* OR sleep) [Title or Abstract]	575
3	Limited to Systematic Reviews	190
4	From 2018 – 2022	94

APPENDIX B – SUPPLEMENTARY TABLE

Table 12. Pharmacokinetic and Pharmacodynamic Characteristics

Generic Name (Brand Name)	MOA	T _{max}	Half-life	Metabolism	Excretion
<i>Z-drugs</i>					
Eszopiclone (Lunesta) ⁴³	Non-selectively binds to GABA-A subtypes (1, 2, and 3) ⁷⁵	1 hour; delayed by an estimated 1 hour if taken with a high-fat meal	6 hours	Hepatic oxidation and demethylation via CYP3A4 and CYP2E1	75% excreted in the urine as metabolites, with < 10% as parent substance
Zaleplon (Sonata) ⁴⁴	Allosterically modulate GABA-A subtypes (alpha-1 subunit) ⁷⁵	1 hour; delayed by an estimated 2 hours if taken with a high-fat meal	1 hour	Aldehyde oxidase (primarily) and CYP3A4	70% excreted in the urine as metabolites, with < 1% as unchanged Approximately 17% in feces, primarily as metabolites
Zolpidem tartrate (Ambien) ³⁷ <i>Immediate-release tablet</i>		1.6 hours; delayed to 2.2 hours (60%) if taken with food	Approximately 2.5 hours, depending on the dose	Hepatic via primarily CYP3A4, CYP1A2, CYP2C9	Excreted primarily in the urine as metabolites
Zolpidem tartrate (Ambien CR) ³⁸ <i>Controlled-release tablet</i>		1.5 hours; delayed by an estimated 2 hours if taken with or immediately after a meal	2.8 hours		
Zolpidem tartrate (Eduar) ³⁹ <i>Sublingual tablet</i>		1.4 hours; delayed to 1.75 hours (28%) when taken after a high-fat meal	Approximately 2.85 hours, depending on dose		
Zolpidem tartrate (Intermezzo) ⁴⁰ <i>Sublingual tablet</i>		An estimated 35 to 75 minutes; delayed to 3 hours if taken with food	An estimated 2.5 hours		
Zolpidem tartrate (Zolpimist) ⁴¹ <i>Oral spray</i>		0.9 hours; delayed to 2.6 hours (225%) if taken with	2.6 hours		

Abbreviations: CR, controlled-release; CYP, cytochrome; MOA, mechanism of action

Table 12. Pharmacokinetic and Pharmacodynamic Characteristics

Generic Name (Brand Name)	MOA	T _{max}	Half-life	Metabolism	Excretion
		or immediately after a high-fat meal			
Benzodiazepines					
Flurazepam ⁴⁵ (Generic only)	Binds to GABA-A receptors on the postsynaptic GABA neuron to increase the inhibition on neuronal excitability ⁷⁶⁻⁸⁰	30 to 60 minutes	2.3 hours	Hepatic to active (N-desalkylflurazepam) and inactive metabolites	Excreted primarily in the urine as metabolites
Estazolam ⁴⁷ (Generic only)		2 hours	10 to 24 hours	Hepatic via CYP3A	Excreted primarily in the urine as metabolites (> 70%), with < 5% as unchanged Approximately 4% in feces
Temazepam (Restoril) ⁴⁶		1.2 to 1.6 hours	3.5 to 18.4 hours	Hepatic conjugation	Excreted primarily in the urine (80% to 90%) as metabolites
Quazepam (Doral) ⁴⁸		Approximately 2 hours	39 hours	Hepatic via CYP3A4, CYP2C19, and CYP2C9 ⁷⁶	Excreted in the urine (31%) and in feces (23%)
Triazolam (Halcion) ⁴⁹		2 hours	1.5 to 5.5 hours	Hepatic hydroxylation via CYP3A	Excreted in the urine with 80% primarily as metabolites
Tricyclic antidepressant/ Histamine receptor antagonist					
Doxepin (Silenor) ⁵⁰	Histamine-1 receptor antagonist	3.5 hours; delayed by an estimated 3 hours if taken with a high-fat meal	15.3 hours	Hepatic oxidation and demethylation via CYP2C19 (major), CYP2D6 (major), CYP1A2, and CYP2C9	Excreted primarily in the urine as metabolites; < 3% as the parent substance or nordoxepin
Dual orexin receptor antagonists					
Suvorexant (Belsomra) ⁴²	Suppress wakefulness by antagonizing orexin receptors (OX1R and OX2R) and preventing orexin A and orexin B	2 hours (ranges from 30 minutes to 6 hours); delayed by an estimated 1.5 hours if taken with a high-fat meal	12 hours	Hepatic via CYP2C19 and mainly CYP3A	Excreted primarily in the feces (66%), and 23% in the urine

Abbreviations: CR, controlled-release; CYP, cytochrome; MOA, mechanism of action

Table 12. Pharmacokinetic and Pharmacodynamic Characteristics

Generic Name (Brand Name)	MOA	T _{max}	Half-life	Metabolism	Excretion
Lemborexant (DayVigo) ⁵¹	from binding to orexin receptors	1 to 3 hours; delayed by 2 hours if taken immediately after a high- fat meal	17 to 19 hours, depending on dose	Hepatic via CYP3A4 (major), and CYP3A5	Excreted primarily in the feces (57.4%) and 29.1% in the urine with <1% as unchanged
Daridorexant (Quviviq) ⁵⁹		1 to 2 hours; delayed by 1.3 hours if taken with a high-fat meal	8 hours	Hepatic via CYP3A4 (major)	Excreted primarily in the feces (an estimated 57%) and approximately 28% in the urine, mainly as metabolites. Small amounts of the parent substance has been identified in the feces or urine
Melatonin receptor agonist					
Ramelteon (Rozerem) ⁶⁰	Antagonizes melatonin receptors (MT ₁ and MT ₂), with some selectivity to the MT ₃ receptor	0.75 hours (ranges from 0.5 to 1.5 hours); delayed by 45 minutes when taken with a high-fat meal	1 to 2.6 hours	Hepatic via glucuronidation and oxidation via CYP1A2 (major), CYP3A4, and CYP2C	Excreted primarily in the urine (84%) as metabolites Approximately 4% in the feces <0.1% of the parent substance was identified in the feces or urine

Abbreviations: CR, controlled-release; CYP, cytochrome; MOA, mechanism of action