

Insomnia Guideline

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Last guideline approval: January 2019

Guidelines are systematically developed statements to assist patients and providers in choosing appropriate health care for specific clinical conditions. While guidelines are useful aids to assist providers in determining appropriate practices for many patients with specific clinical problems or prevention issues, guidelines are not meant to replace the clinical judgment of the individual provider or establish a standard of care. The recommendations contained in the guidelines may not be appropriate for use in all circumstances. The inclusion of a recommendation in a guideline does not imply coverage. A decision to adopt any particular recommendation must be made by the provider in light of the circumstances presented by the individual patient.

Guideline Summary

- **Behavioral treatment is recommended as first-line treatment** for chronic insomnia and includes cognitive behavioral therapy for insomnia (CBT-I) and sleep hygiene.
- Complementary and alternative treatment options that are recommended for insomnia include acupuncture, mindfulness meditation, light box therapy, listening to music, and moderate exercise.
- If behavioral treatment alone has been ineffective, short-term (not to exceed 6 weeks) **pharmacologic treatment may be considered as an adjunct** to ongoing behavioral treatment of insomnia.
 - First-line: doxepin (preferred), melatonin (alternative)
 - Second-line: trazodone
 - First-line in the elderly: melatonin, ramelteon*
* Ramelteon is nonformulary and may incur higher out of pocket costs for patients. Advise patients to contact Member Services with coverage questions
- The following pharmacologic treatments are **not** recommended for insomnia:
 - Benzodiazepines and Z-drugs
 - Diphenhydramine (Benadryl)
- Changes in sleep patterns, such as difficulty in sleep initiation and reductions in total sleep time and sleep efficiency, are a normal part of the aging process.

Background

The recommendations in this guideline apply to adults aged 18 years or older. Pregnant women are out of scope for this guideline; consider consultation with Women's Health.

Insomnia is a sleep disorder characterized by difficulty falling and/or staying asleep for a month or longer. Individuals with insomnia may have one or more of the following symptoms:

- Difficulty falling asleep
- Waking up often during the night and having trouble going back to sleep
- Waking up too early in the morning
- Feeling tired upon waking

Acute insomnia is insomnia lasting less than 6 weeks.

Chronic insomnia is insomnia occurring at least 3 nights a week for more than 6 weeks.

Insomnia Assessment and Diagnosis

Insomnia is a diagnosis of exclusion. Patients who report difficulty initiating sleep, difficulty maintaining sleep, waking too early, or experiencing non-restorative sleep should be assessed to evaluate for:

- Comorbid medical conditions (e.g., pulmonary disease, heart failure, chronic pain)
- Comorbid psychiatric disorders (e.g., depression, anxiety, post-traumatic stress disorder, substance abuse)
- Other sleep disorders (e.g., obstructive sleep apnea, restless legs syndrome, circadian rhythm sleep-wake disorders)

It is important to **screen the patient for depression, substance use, and alcohol use**, as about 1 in 3 patients reporting insomnia have co-occurring psychiatric illness (typically depression or anxiety) and 1 in 6 have alcohol- or drug-induced sleep problems.

It is also important to **review the patient’s current medications**. Table 1 lists medications that may interfere with sleep.

- Medication effects on sleep are complex. Medications can cause sleep disturbances via:
 - Stimulating or activating properties
 - Changes in sleep architecture (e.g., slow wave sleep and REM suppression)
 - Physiological changes (e.g., increased urination)
- Medication effects on sleep vary greatly by individual. For example, some patients who take fluoxetine report insomnia as an adverse effect, whereas other patients experience daytime somnolence.
- For patients who are having difficulty falling or staying asleep, consider:
 - The time of day the patient takes the medication
 - Whether there is an appropriate alternative
- For patients who are experiencing medication withdrawal effects, advise that the related sleep disturbance is temporary.

Drug class	Difficulty falling asleep	Difficulty staying asleep	Medication withdrawal effects
Albuterol	X	X	
Alpha-receptor agonists			X
Antidepressants: SSRIs, SNRIs, bupropion	X (particularly fluoxetine, venlafaxine, duloxetine, bupropion)	X	X
Beta-blockers		X	X
Corticosteroids	X	X	
Diuretics		X	
Opioids			X
Stimulants	X	X	

Patients should be encouraged to keep a sleep diary—such as this one from the [National Sleep Foundation](#)—for 1 to 2 weeks to help identify sleep-wake times, general patterns, and day-to-day variation.

Insomnia Monitoring

The Insomnia Severity Index (ISI) is recommended for monitoring changes in insomnia over time. The seven-question ISI is available as an Epic documentation flowsheet and asks patients to subjectively rate aspects of their insomnia, such as impact on daily activities and their level of anxiety about it.

The ISI is a primary measure of the severity of insomnia used to monitor changes in symptoms over time; it is not intended to be used for diagnosis. One study (Yang 2009) found that a 6-point reduction in ISI score represents a clinically meaningful improvement in insomnia. The ISI is useful for evaluating whether behavioral and pharmacologic treatment has improved a patient's insomnia symptoms.

Insomnia Severity Index

1. In the past 2 weeks, have you experienced difficulty falling asleep? (none, mild, moderate, severe, very severe)
2. In the past 2 weeks, have you experienced difficulty staying asleep? (none, mild, moderate, severe, very severe)
3. In the past 2 weeks, have you experienced problems with waking up too early? (none, mild, moderate, severe, very severe)
4. How SATISFIED/DISSATISFIED are you with your current sleep pattern? (very satisfied, satisfied, moderately satisfied, dissatisfied, very dissatisfied)
5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life? (not at all noticeable, a little, somewhat, much, very much noticeable)
6. How WORRIED/DISTRESSED are you about your current sleep problem? (not at all worried, a little, somewhat, much, very much worried)
7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g., daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood) CURRENTLY? (not at all interfering, a little, somewhat, much, very much interfering)

ISI total score categories and interpretation

- **0–7 = No clinically significant insomnia.** Reassure the patient that sleep experience is normal and educate about sleep hygiene.
- **8–14 = Subthreshold insomnia.** Educate about sleep hygiene and provide a sleep diary.
- **15–21 = Clinical insomnia (moderate severity).** Perform history and physical to evaluate for diagnosis. **Consider** combination CBT-I and acute insomnia medications (up to 2 weeks).
- **22–28 = Clinical insomnia (severe).** Perform clinical interview. **Offer** combination CBT-I and acute insomnia medications. Taper medications at 2–4 weeks.

Insomnia Treatment Foundations

Normal sleep pattern changes in healthy elderly individuals

It is important to set expectations with patients about the normal changes in sleep patterns that occur in healthy elderly individuals. These changes include:

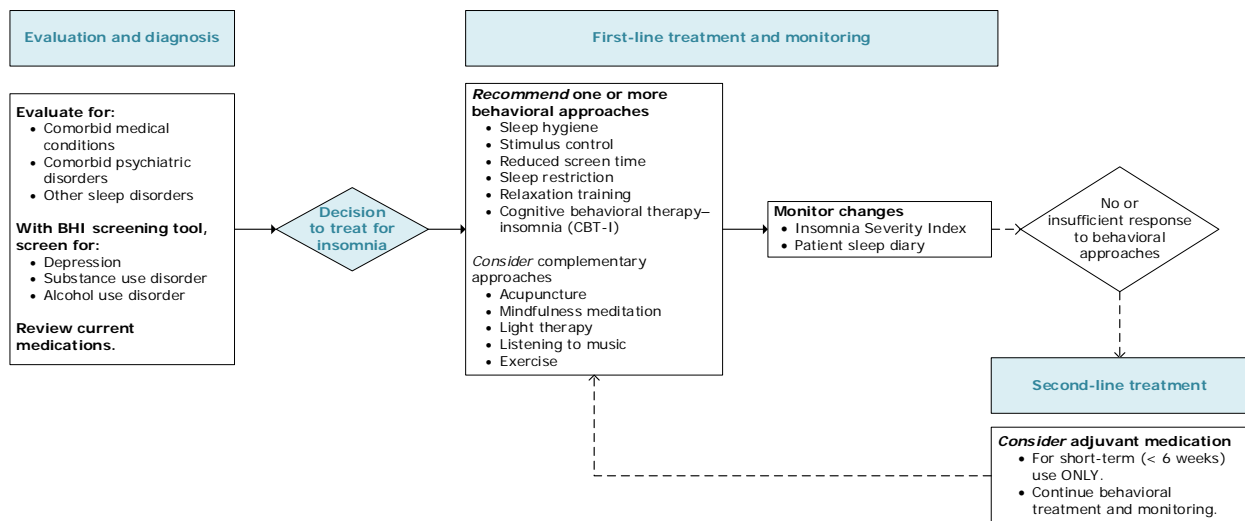
- More difficulty with sleep initiation
- Reduced total sleep time and sleep efficiency
- Decreased delta wave or slow wave sleep
- Increased sleep fragmentation
- Increased time spent in bed awake after retiring
- Changes in circadian rhythm that cause sleepiness in the early evening and earlier waking
- Increased frequency of daytime naps, which makes it harder to sleep at night

Step-wise approach to insomnia treatment

The following step-wise approach is recommended for treatment of insomnia. Note that prescribing medication is the last step and is only appropriate if behavioral treatments have not been successful.

The SmartPhrase [.avsinsomniaptinfo](#) provides an overview of insomnia therapies for patients.

A step-wise approach to insomnia



Behavioral treatment

Behavioral therapy is recommended as the initial treatment for insomnia. There is good evidence that behavioral therapy is effective in treating insomnia and that the improvement gained is long-term.

Behavioral strategies can include:

- Sleep hygiene
- Stimulus control
- Reducing screen time
- Sleep restriction
- Relaxation training
- Cognitive behavioral therapy – insomnia (CBT-I)

Sleep hygiene

Sleep hygiene focuses on teaching good sleeping habits to patients (e.g., keeping a regular schedule, exercising during the day, avoiding napping) and can help to identify and address specific habits, behaviors, and environmental factors that can impact sleep.

- Create a bedtime routine. Get ready for bed, get into bed, and get up at the same time every day, even on weekends. Establishing a routine helps regulate your inner clock. Try not to take naps during the day.
- Avoid too much mental or physical stimulation an hour or so before going to bed. Don't finish office work or get into a big discussion about finances or other stressful topics right before getting ready to sleep.
- Get some exercise each day. You might find that exercising 3 to 4 hours before going to bed helps you to sleep better. However, don't exercise vigorously later than 3 hours before your bedtime.
- Follow a healthy diet. Don't drink beverages that have caffeine, even soft drinks, after 2 p.m. Drinking alcohol, using tobacco, and taking certain medicines can also make it hard to fall asleep. If you drink alcohol before bed, you might have periods of wakefulness during the night, after the alcohol wears off.

Stimulus control

Stimulus control helps the patient to form a positive, clear association between the bed and sleep, and to establish a stable sleep-wake schedule.

- Take time to relax before getting into bed. Doing something you enjoy, like reading, taking a warm bath, or using other relaxation techniques can reduce stress and quiet your mind for sleep.
- Your bedroom should be cool, dark, and quiet for sleeping. If street lights shine in your room, or you need to sleep during the day because of your work schedule, put room-darkening shades, blinds, or drapes on the windows.
- Your bedroom should be as quiet as possible. If you can't block outside noise, cover it up with familiar inside sounds, like the steady hum of a fan.
- Move the clock away from your bed, so you can't see it easily. Try putting it under your bed so you can still hear the alarm when it goes off.
- If you share your room or bed with someone who is restless, snores, keeps the light on late for reading, or steals your covers, arrange to sleep separately until you establish a regular sleeping pattern.
- Only use your bedroom for sleeping and sexual activity. Don't use your bedroom for working, having discussions, watching TV, or using your computer.
- If, after 30–45 minutes of trying, you have trouble falling asleep or getting back to sleep, get up and leave the room for a while. Doing something relaxing in another room, such as reading, might help you feel sleepy so you can go back to bed.

Reducing screen time

Observational studies show an association between screen time and mobile phone use during the day or at bedtime and an increase in sleep disturbances among school age children, adolescents, and adults.

Limiting screen exposure 2 hours before bedtime is recommended to minimize any harmful effects on sleep and well-being. There is no evidence that blue light modulation provides any benefit in decreasing sleep problems related to screen time.

Sleep restriction

The goal of sleep restriction is to increase sleep efficiency as close to 100% as possible, so that most of the time in bed is spent sleeping versus lying awake, tossing and turning. Current baseline sleeping time is recorded in sleep logs (e.g., of the 8 hours spent in bed, 5 hours were restful sleep). Then the patient restricts their total time in bed to their baseline sleeping time, staying up later at night but getting up at the same time each day. The purpose of this therapy is to increase the level of tiredness before sleep so that patients can break the mindset that they have difficulty falling asleep. Once a good sleep pattern is established, the amount of sleep can gradually be increased each night.

Relaxation training

Relaxation training includes techniques such as progressive muscle relaxation, guided imagery, and abdominal breathing. The purpose is to lower physical and mental stimulation that can interfere with sleep.

Cognitive behavioral therapy – insomnia (CBT-I)

CBT-I is a combination of cognitive therapy and behavioral treatments, with or without relaxation training. The goal is to change unrealistic expectations and negative thoughts about sleep. There is evidence that CBT-I for insomnia is effective for adults, including perimenopausal women and the elderly.

Face-to-face CBT-I

Patients who are interested in CBT-I may be referred to Behavioral Health Services (BHS) for individual or group CBT-I treatment. However, availability of face-to-face CBT-I at KPWA is limited.

Online CBT-I

Online CBT-I may be an attractive option, as in-person access may be a significant barrier to care. Evidence suggests that internet-delivered CBT-I leads to improvements in sleep efficiency, sleep onset latency, total sleep time, and wake time after sleep, as well as improvements in depression and anxiety. The effects were comparable to those found for face-to-face CBT-I and were generally maintained at 4–48 weeks follow-up.

Internet-delivered CBT-I programs include:

- CBTi coach (free app from Veterans Affairs) <https://mobile.va.gov/app/cbt-i-coach>
- Sleepio (\$) <https://www.sleepio.com/cbt-for-insomnia/>
- CBT-I for Insomnia (\$) <https://www.cbtforinsomnia.com/>

Other resources

Sleeping Better: Help for Long Term Insomnia is a video and booklet that can be accessed by patients online via the KP Member site. Providers can also order the DVD and booklet to be sent directly to a patient's home. Using Order Entry in Epic, order by title (DVD: Sleeping Better) or number (PE569).

Complementary/alternative therapy

- **Acupuncture** is recommended, used alone or with antidepressants, for improving the sleep quality of adults with depression-related insomnia.
- **Mindfulness meditation** is recommended for improving sleep quality.
- **Listening to music** is recommended for improving subjective sleep quality.
- **Light therapy** may have a small to moderate effect on improving some insomnia outcomes.
- **Exercise** is recommended for a minimum of 150 minutes per week at moderate intensity, preferably broken into 20- to 30-minute sessions, at least 5 days per week.

Adjunctive pharmacologic treatment if no response to behavioral treatment

If behavioral treatment has been ineffective, short-term (not to exceed 6 weeks) pharmacologic treatment may be considered.

Safety considerations and sleep outcomes of common insomnia medications

Table 2 provides information on potential benefits and safety considerations for the most commonly used medications for sleep and may be useful in conversations with patients who request specific medications, particularly those that are **not** recommended in this guideline. The table compares over the counter (OTC) medications, benzodiazepines and Z-drugs, and sedating antidepressants.

- Antidepressants show the greatest improvement in sleep length (sleep duration up to 80 minutes longer than with placebo).
- Improvement in sleep latency is similar for all pharmacologic options (sleep onset 10–20 minutes faster than with placebo).

Medication	Category	Sleep latency ¹	Sleep length ²	Safety considerations ³
Melatonin	OTC – supplement	7 min	8 min	No data on long-term use
Ramelteon (NF)	Melatonin agonist	10–15 min	No difference	Somnolence, fatigue, dizziness, nausea, exacerbation of insomnia, abnormal thinking/behavioral changes (e.g., sleep driving)
Mirtazapine	Antidepressant	10 min	80 min	CNS depression, weight gain
Doxepin	Antidepressant	10 min	80 min	HRME Limit < 6 mg if aged ≥ 65 years.
Trazodone	Antidepressant	10 min	80 min	Orthostatic hypotension
Diphenhydramine	OTC – antihistamine	No change	11 min	HRME Limit use to 2–3 days. May impair physical or mental abilities
Doxylamine	OTC – antihistamine	Not available	Not available	HRME Limit use to 2–3 days. May impair physical or mental abilities
Temazepam	Benzodiazepine ⁴	15 min	33 min	Risk of next-day impairment, unawareness of activities during sleep (e.g., driving)
Zolpidem	Z-drug	22 min	11 min	HRME Risk of next-day impairment, unawareness of activities during sleep (e.g., driving) ⁵
¹ Reduction from placebo. ² Increase from placebo. ³ HRME = high-risk medication in the elderly. ⁴ The only benzodiazepines FDA approved for insomnia are temazepam, flurazepam, and triazolam. ⁵ Women are at higher risk of impairment.				

Pharmacologic options for refractory insomnia in adults

Table 3 shows dosing information for medications that may be used for short-term relief of insomnia that has not improved with behavioral treatment. The medication treatment period should not exceed 6 weeks, as sleep studies have shown that sleep patterns return to pretreatment levels after only a few weeks of regular medication use.

Medication	Category	Initial dose ²	Older adult dose ²	Max. dose ²
Doxepin ³	Antidepressant	3–6 mg (10 mg/mL oral solution)	3–6 mg (10 mg/mL oral solution)	10 mg
Melatonin ⁴	OTC - supplement	3 mg	2 mg	5 mg
Trazodone ⁵	Antidepressant	25–50 mg	25–50 mg	200 mg
Ramelteon ⁶	Melatonin agonist	8 mg	8 mg	8 mg

¹ Pharmacologic therapy is recommended for intermittent short-term use only.
² Doses are daily before bedtime.
³ First-line. Contraindicated during use of MAO inhibitors and with glaucoma or urinary retention. Preferred when insomnia is related to depression or anxiety.
⁴ First-line option for elderly and for general population. Best for advanced phase sleep disorders or circadian rhythm disorders.
⁵ Second-line. Not FDA approved for insomnia.
⁶ Alternative first-line for elderly. Weak recommendation (third-line) for general population. To be taken within 30 minutes of going to bed. Non-formulary and may incur higher out of pocket costs for patients. Advise patients to contact Member Services with coverage questions.

Medications that are *not* recommended for insomnia due to harms or lack of evidence

Medications with insufficient evidence of efficacy

- Doxylamine
- Mirtazapine
- Supplements and herbals: 5-HTP, tryptophan, valerian, chamomile, hops, kava-kava, passionflower

Medication that causes rebound insomnia and next-day performance impairment

- Diphenhydramine (Benadryl): The SmartPhrase **.avsbenadrylnotrecomforinsomnia** provides information to patients on why Benadryl is not recommended.

Medications with significant harms

- Z-drugs: zolpidem
- Benzodiazepines: temazepam

See the [KPWA Benzodiazepine and Z-drug Safety Guideline](#) for more information.

Adverse effects of benzodiazepines and Z-drugs include:

- Particularly high risk of overdose when combined with sedative drugs, such as opioids or alcohol
- Psychological or physical dependence, which can develop over a few weeks or months
- Tolerance to hypnotic effects, which can develop after only a few days of regular use
- Daytime somnolence
- Dizziness
- Impaired driving performance leading to an increased risk of road traffic accidents
- Depression and increased anxiety

- Slowness of mental processes and body movements
- Increased risk of mortality
- Increased risk of cognitive impairment and delirium
- Increased risk of falls and fractures, especially among older adults

Note: Z-drugs are not “safer” than benzodiazepines, and patients on benzodiazepines should not be switched to Z-drugs to try to improve safety.

Recommendations for Special Populations

Shift workers

- To promote daytime sleep, recommendations include: modifying the sleep environment by using blackout shades and reducing ambient noise with a white noise machine; minimizing exposure to light on the way home; and going directly to sleep to prevent activating wakefulness.
- To promote a regular sleep schedule with a stable circadian rhythm, recommended schedule adjustments include: limiting the number of night shifts worked in a row to 4 or fewer, taking 48 hours off work after a string of night shifts, and avoiding frequently rotating shifts.
- Advise patients to get enough sleep on days off and adjust to a slightly later bedtime (1–2 hours later) on the 2 days before the start of night shifts.
- Treatment options with limited or insufficient evidence include light therapy, exercise, sleep education, and napping before shifts.

Perimenopausal women

- Recommended therapeutic options include CBT-I and moderate exercise.
- Treatment options with limited or insufficient evidence include low-dose hormonal therapy, herbal medications, and soy.
- Perimenopausal hot flashes must be treated separately from insomnia.

Follow-up

Assess for improvement in insomnia severity using the ISI. Do not continue insomnia medication for longer than 6 weeks.

Referral

Consider a referral to **Behavioral Health Services** for any of the following:

- Patient is interested in cognitive behavioral therapy.
- Patient exhibits significant anxiety and/or depression in addition to insomnia.
- Patient is using alcohol or illicit drugs to help with sleeping.

Consider a referral to **Sleep Medicine** if another sleep disorder is suspected:

- Acting out dreams
- Sleepwalking
- Narcolepsy
- Shifted sleep schedule (delayed sleep phase, night-shift work)

Note: Prior to referral to Sleep Medicine, patient must complete an Epworth Sleepiness Scale, available as a documentation flowsheet in Epic.

Evidence Summary

The Insomnia Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

As part of our improvement process, the Kaiser Permanente Washington guideline team is working towards developing new clinical guidelines and updating the current guidelines every 2–3 years. To achieve this goal, we are adapting evidence-based recommendations from high-quality national and international external guidelines, if available and appropriate. The external guidelines should meet several quality standards to be considered for adaptation. They must: be developed by a multidisciplinary team with no or minimal conflicts of interest; be evidence-based; address a population that is reasonably similar to our population; and be transparent about the frequency of updates and the date the current version was completed.

In addition to identifying the recently published guidelines that meet the above standards, a literature search was conducted to identify studies relevant to the key questions that are not addressed by the external guidelines.

External guidelines meeting KPWA criteria for adaptation/adoption

- 2017 Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline
- 2017 European guideline for the diagnosis and treatment of insomnia
- 2016 Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline from the American College of Physicians
- 2015 AHRQ: Management of Insomnia Disorder; Comparative Effectiveness Review (number 159)

Key questions addressed in the KPWA guideline

1. What is the effectiveness and safety of antidepressants for the management of insomnia in adults?

A recent Cochrane review and meta-analysis (Everitt 2018) assessed the effectiveness and tolerability of antidepressants for insomnia in adults. The review included 23 randomized controlled trials (RCTs) involving 2,806 adults with a primary diagnosis of insomnia. The included trials compared any antidepressant used as monotherapy at any dose, versus placebo, any other medications used for insomnia (e.g., benzodiazepines and Z drugs), a different antidepressant, waiting list control, or usual treatment. The primary efficacy outcomes were any improvement in sleep quality or satisfaction with sleep, total sleep duration, sleep onset latency, number of awakenings, total nocturnal awakening time, and sleep efficiency. The safety outcomes were the number and type of adverse events.

The overall results of the analysis show the following:

- Small improvement in sleep quality with short-term use of low-dose doxepin and trazodone compared with placebo.
- No evidence to support the use for amitriptyline for insomnia.
- Insufficient evidence to determine the effects of SSRIs compared with placebo due to the small number of studies.
- Insufficient evidence to determine the tolerability or the long-term safety and efficacy of antidepressants for insomnia due to limited reporting of adverse events and lack of long-term follow-up data.

Earlier systematic reviews with a meta-analysis (Liu 2017) or without a meta-analysis (Yeung 2015) also suggest that:

- Short-term use of low-dose doxepin at 3–6 mg has a small to medium effect size compared to placebo for sleep maintenance and sleep duration.
- Moderate-dose doxepin is associated with rebound insomnia and more side effects.
- Headache and next-day somnolence are the most common side effects.

Conclusion

- There is insufficient published data to support either short- or long-term use of antidepressants in the management of insomnia.
- Weak evidence suggests that short-term use of low-dose doxepin may improve some objective polysomnography outcomes compared with placebo, but is associated with some adverse effects, mainly increased somnolence and rebound insomnia.
- There is no published evidence to date to determine the safety and efficacy of long-term use of any antidepressant for insomnia.
- All low-dose doxepin studies were industry-sponsored, which is a potential source of bias.

2. What is the effectiveness and safety of prescription or non-prescription melatonin/melatonin agonists in managing insomnia in adults?

A recent meta-analysis (Auld 2017) compared the effectiveness of melatonin versus placebo in improving sleep onset latency in patients with primary sleep disorders, including primary insomnia. The analysis included 12 trials with a total of 1,510 patients aged 55–80 years; not all patients were included in the meta-analyses due to variations in the outcomes measured. The daily doses of melatonin ranged from 0.1 mg to 10 mg with a treatment duration time ranging from 2 to 5 weeks.

The pooled results showed that the most convincing evidence for exogenous melatonin use was in reducing sleep onset latency in primary insomnia ($p = 0.002$), delayed sleep phase syndrome ($p < 0.0001$), and regulating the sleep-wake patterns in blind patients compared with placebo.

Another meta-analysis (Kuriyama 2014) assessed the efficacy and safety of ramelteon for the treatment of chronic insomnia in adults. The analysis included 13 trials involving 5,812 patients with insomnia or insomnia symptoms. Eleven studies were published in peer-reviewed journals, 10 had parallel design, and 3 had a cross-over design. The mean study duration was 38 days (range 6–80 days), the participants' age range was 18–93 years with a mean of 48.2, and 62% of the participants were women. The timing of drug administration before bedtime ranged from 0 to 30 minutes. Most trials included in the analysis had a habitual bedtime of 8:30 p.m. to 1:00 a.m. and sleep latency of at least 20–45 minutes as eligibility requirements.

The primary outcomes of the analysis were subjective sleep latency (sSL), sleep quality, and subjective total sleep time (sTST). Secondary outcomes included latency to persistent sleep (LPS), total sleep time (TST), sleep efficiency (SE), proportion of rapid eye movement (REM) sleep, wakefulness after sleep onset (WASO), subjective WASO, number of nighttime awakenings (NAW), subjective NAW, and adverse events.

The overall results indicated that the short-term use of ramelteon was associated with improvement in some sleep parameters in patients with insomnia but, as the authors indicated, the clinical impact was small and long-term trials are needed before solid conclusions can be established. Several adverse events were reported, but the only significant difference observed between ramelteon and placebo was in somnolence (RR 1.97 [95% CI, 1.21–3.20]).

Conclusion

Several published meta-analyses of placebo-controlled RCTs evaluated the efficacy and safety of melatonin in subjects with primary sleep disorders. The number of published RCTs and their sizes were small, and all compared melatonin versus placebo. There were variations between the published studies in the dosing, timing, frequency, and type of melatonin formulation used, as well as the assessment tools and outcome measures used in the trials. The meta-analyses pooling the results of the published RCTs varied in their inclusion/exclusion criteria. The overall results suggest that there is weak evidence for a short-term small clinical effect of melatonin in general on some sleep parameters when compared to a placebo.

- There is weak evidence from a small number of trials that exogenous melatonin may be more beneficial than placebo in reducing sleep onset latency time in subjects with primary insomnia or delayed sleep phase syndrome. It may also be more beneficial, compared to placebo, in regulating sleep-wake patterns in blind individuals.
- Short-term use of melatonin appears to be safe, but the evidence on its safety is weak.

- There is insufficient evidence to determine the efficacy and safety of long-term use of melatonin in adults with insomnia.
- It is advised to use the lowest possible dose of immediate-release formulation melatonin for older adults.
- There is weak evidence showing that the short-term use of ramelteon was associated with improvement in some sleep parameters in patients with insomnia, when compared to placebo.
- The reported significant adverse effect of ramelteon was somnolence.
- There is insufficient evidence on the comparative efficacy and safety of melatonin or ramelteon versus other pharmacological or non-pharmacologic treatments/interventions for insomnia.
- There are no data available that directly compared the efficacy and safety of ramelteon with that of the much lower recommended dose (0.3 mg) of melatonin.

3. What is the effectiveness and safety of other prescription or non-prescription medications—including antihistamines, diphenhydramine, supplements (such as 5-HTP and tryptophan either as a supplement or in food intake), and herbal medications (such as valerian, chamomile, hops, kava-kava, and passionflower)—in managing insomnia in adults?

- There is insufficient evidence to support the efficacy and safety of antihistamine use for insomnia.
- Weak evidence shows that diphenhydramine may have a limited beneficial effect on sleep, but with an increased risk of next-day performance impairments and potential rebound insomnia after its discontinuation.
- There is insufficient published evidence to support the use of doxylamine for the management of insomnia.
- There is insufficient evidence to determine that valerian has any benefit in managing insomnia in adults.
- There is weak evidence from one RCT that an herbal compound composed of valerian (0.8% valerenic acid), hop (cone dry extract containing 0.4% minimum of total flavonoids), and jujube (seeds dry extract) may improve self-reported sleep quality in healthy adults with insomnia. The study, however, did not evaluate the long-term effects of using the herbal compound.
- There is insufficient evidence to determine that other herbal therapies, including chamomile, kava-kava, and wuling, have any benefit in managing insomnia in adults.

4. What is the effectiveness and safety of non-pharmacological therapies and complementary/alternative interventions in managing insomnia in adults?

Physical exercise

A systematic review and meta-analysis (Banno 2018) examined the effectiveness/efficacy of exercise in adults with insomnia. Seventeen trials were included in the qualitative synthesis and 9 trials with a total of 557 participants were included in the quantitative synthesis. The primary outcomes of the analysis were sleep quality, sleep efficiency, and insomnia severity. There were variations between the 9 trials in the population studied (adult, elderly, perimenopausal, or cancer patients), population sizes (range 17–123), modality of exercise (walking, mild exercise, aerobics or tai chi), frequency of exercise (range from 1 day/week to 7 days/week), and duration of the study (2–6 months). The comparison groups mainly underwent no or routine activity. Other comparisons were made versus CBT-I in one trial and pharmacological therapy in another.

The pooled results showed that total Pittsburgh Sleep Quality Index (PSQI) scores were significantly improved with exercise when compared with routine activity. The results should be cautiously interpreted due to significant heterogeneity between the studies, and the low quality and high risk of bias of the included trials.

Acupuncture

A systematic review and meta-analysis (Dong 2017) evaluated the effectiveness of acupuncture as a monotherapy for treating depression-related insomnia. The results suggest that acupuncture may have a benefit in treating depression-related insomnia in adults. The meta-analysis had valid methodology and analysis, but its results must be interpreted with caution due to the high risk of bias of the included studies (only 2 of the 18 trials were at low risk of bias) and due to the significant heterogeneity between the studies in all comparisons made. There was variation between the studies in the inclusion criteria, diagnostic criteria, patient characteristics, acupoints used, and duration of treatment (which ranged from 18 days to 3 months), as well as other differences that would affect the outcomes.

Listening to music

A network meta-analysis (Feng 2018) of clinical trials evaluated the effect of music in adults with primary insomnia. The analysis included 20 trials with 1,339 participants and 12 intervention arms, including acupuncture, language induction, listening to music, a combination of these interventions, music-assisted relaxation with or without stimulus control, usual care, Western medicine, and/or placebo music. The great majority of the trials were conducted in China.

The primary outcome of the analysis was sleep quality as scored by PSQI, and the secondary outcomes included sleep onset latency and sleep efficiency.

The results of the analysis suggest that listening to music and music-assisted relaxation had a significant advantage over other interventions on overall sleep quality and sleep onset latency. This was a network meta-analysis with direct and indirect comparisons, and the results should be interpreted with caution.

An earlier Cochrane review (Jespersen 2015) also showed that music may be effective for improving subjective sleep quality in adults with insomnia symptoms. The review had a valid methodology and analysis; however, the studies had high risk of bias for at least one domain. The authors concluded that the intervention is safe and easy to administer, but more research is needed to establish the effect of listening to music on other aspects of sleep as well as on the daytime consequences of insomnia.

Light therapy

A systematic review and meta-analysis (van Maanen 2016) examined the effect of light therapy on sleep problems in general and on specific types of sleep problems (circadian rhythm sleep disorders, insomnia, and sleep problems related to dementia).

The review included 53 studies (N=1,154 participants) of any design, and any publication language, date, or status. There were also no restrictions regarding the age of the participants or the type of sleep disorder. Only 10 of the 52 studies reviewed were conducted among patients with insomnia; all were very small in size and only 3 were randomized and controlled. The authors did not provide a meta-analysis of studies conducted among adult patients with a diagnosis of insomnia but pooled the results of a subset of studies with circadian outcomes.

Overall, the authors concluded that light therapy may have a small to moderate effect on insomnia, and that the highest light intensities are associated with larger effects.

These results should be interpreted with caution due to the limitations of the meta-analysis, variability in the design of the included studies, heterogeneity, and several other weaknesses in the systematic review.

Conclusion

The published literature provides:

- Low- to moderate-quality evidence suggesting that exercise may be beneficial in improving sleep duration and quality in adults with insomnia.
- Insufficient evidence to determine the effectiveness of acupuncture on primary insomnia.
- Low-quality evidence suggesting that acupuncture used alone or in combination with antidepressants may improve the sleep quality of adult patients with depression-related insomnia.

- Low-quality evidence suggesting that mindfulness meditation may improve sleep quality in patients with insomnia.
- Low- to moderate-quality evidence suggesting that listening to music may be effective for improving subjective sleep quality in adults with insomnia symptoms.
- Low-quality evidence showing that light therapy may have a small to moderate effect on improving some insomnia outcomes.

5. What pharmacological and nonpharmacological therapies are effective and safe in managing insomnia in the elderly?

A review of the published literature on the safety and efficacy of medications used to treat insomnia in older adults (Schroeck 2016) concluded the following:

- Cognitive behavioral therapy and sleep hygiene are considered initial therapy for insomnia and should continue throughout treatment.
- Benzodiazepines are discouraged in the geriatric population, especially for long-term use. Although non-benzodiazepines have improved safety profiles compared with benzodiazepines, their side effects include dementia, serious injury, and fractures, which should limit their use.
- Ramelteon has a minimal adverse effect profile and is effective for sleep onset latency and increased total sleep time, making it a valuable first-line option for older patients after sleep hygiene has failed.
- Sedating low-dose antidepressants should only be used for insomnia when the patient has comorbid depression.
 - Trazodone seems to be the safest because it lacks anticholinergic activity.
 - Mirtazapine may be beneficial when the patient has a fragility syndrome, due to its side effect of appetite stimulation.
- Antipsychotic agents, pramipexole, and tiagabine have all been used for insomnia, but none has been extensively studied in an older population and all have considerable adverse effects, limiting their use to patients with insomnia and a corresponding comorbid condition.
- Gabapentin may be useful in patients with restless legs syndrome or chronic neuropathic pain and insomnia.
- Diphenhydramine should be avoided in the elderly.
- Valerian and melatonin are unregulated products that have a small impact on sleep latency and can produce residual sedation.

Optimal dosage of melatonin in older adults

A qualitative systematic review (Vural 2014) was conducted to define the optimal dosage of exogenous melatonin administration in disorders related to altered melatonin levels in adults aged 55 years and above by determining the dose-response effect of exogenous administered melatonin on endogenous levels.

The review included 16 articles, 9 of which were randomized controlled trials (RCTs). The mean age varied from 55.3 to 77.6 years. Melatonin dosage varied from 0.1 mg/kg to 50 mg/kg and was administered orally in all studies.

Pre- and post-intervention levels revealed a significant elevation of the post-intervention melatonin levels in a dose-dependent fashion. The maximum concentrations measured in serum and urine were all elevated compared with placebo, and a higher elevation in older adults than in younger adults was demonstrated. There were no differences between times to reach maximum concentration in serum and urine, but the melatonin levels with higher doses were maintained longer above a certain threshold than were lower doses.

The authors recommended the use of the lowest possible dose of immediate-release formulation melatonin to best mimic the normal physiological circadian rhythm of melatonin and to avoid prolonged, supra-physiological blood levels.

Adverse effects of long-term use of melatonin

There is insufficient evidence to determine the adverse effects of long-term use of melatonin.

Conclusion

- There is moderate-quality evidence that manual-based CBT-I delivered by non-clinician sleep coaches may improve sleep in older adults with chronic insomnia.
- There is insufficient evidence to determine the efficacy and safety of long-term use of melatonin in older adults with insomnia.
- It is advised to use the lowest possible dose of immediate-release formulation melatonin for older adults.

6. What pharmacological and non-pharmacological therapies are effective and safe for managing perimenopause-related insomnia?

- There is low- to moderate-quality evidence from one relatively small trial (MsFLASH—McCurry 2016) that telephone-based CBT-I may improve sleep in perimenopausal and postmenopausal women with insomnia and hot flashes.
- There is conflicting evidence on the benefit of low-dose hormone therapy on sleep quality in menopausal women. The observed benefit appears to be limited to women with vasomotor symptoms. However, this finding should be interpreted cautiously, as the published studies varied in terms of participants' characteristics, formulations of hormonal therapy used, measures used to assess the quality of sleep, and the subjectivity or objectivity of the outcome measures.
- There is insufficient evidence to determine the effectiveness of herbal medications such as soy in managing insomnia in perimenopausal women.
- There is low-quality evidence suggesting that moderate physical activity (aerobic exercise) may improve the self-reported sleep quality in perimenopausal women with mild to moderate poor quality of sleep.
- There is insufficient evidence to determine the effect of yoga on sleep quality or insomnia severity.
- There is insufficient evidence to determine the effect of more intense physical activity on sleep quality or insomnia severity in perimenopausal women.
- Low-quality evidence from one small RCT suggests that acupuncture may have a short-term benefit in improving sleep quality and efficiency in women with perimenopausal insomnia.

7. What strategies or measures are effective in managing insomnia in shift workers?

Pharmacological therapy

Results of a Cochrane systematic review and meta-analysis (Liira 2014) include:

- Low-quality evidence suggesting that the use of melatonin (1–10 mg) after the night shift may increase sleep length during daytime and nighttime sleep when compared to placebo. The authors did not find a dose-response effect, nor any significant effect on other sleep quality parameters. Participants in most melatonin trials were health care volunteers without severe shift work disorder symptoms, so the trial results may not be generalized to all types of shift work sleep disorders.
- Low-quality evidence from one trial suggests that the hypnotic medication zopiclone did not result in significantly longer daytime sleep length compared to placebo.
- Moderate-quality evidence from two trials indicating that armodafinil taken before the night shift may reduce sleepiness by one point on the Karolinska Sleepiness Scale but is associated with adverse effects, including headache and nausea. The drug was administered in a gradually increasing dose during the night shift period (50, 100, and 150 mg).
- One trial that compared modafinil to placebo showed a superior effect of the drug in reducing sleepiness during the night shift among workers with shift work sleep disorder diagnosis. The observed effect was more pronounced during the first hours of the shift and

was partly diminished towards its end. Headache and nausea were the most frequently reported adverse effects and were dose-dependent.

- Results from one trial suggesting that caffeine plus pre-shift naps taken before the night shift may decrease sleepiness. The design does not allow for evaluating the effect of each intervention separately.

Non-pharmacological interventions

- There is insufficient evidence to determine the effect of light therapy on improving alertness and mood in shift workers.
- There is insufficient evidence to draw any conclusion on the effect of physical exercise and sleep education interventions to reduce sleepiness during shift work or to improve the quality or length of sleep.
- Limited published literature shows no significant effects for one- or two-nap opportunities on reaction time or sleepiness, respectively.

8. Is there any evidence to determine if there is an effect of screen time on insomnia in adults, and whether there are any measures to manage that effect?

- Observational studies among adults, school-age children, and adolescents show a negative relation between use of technology during the day or at bedtime and sleep disturbances.
- Observational studies suggest that bedtime mobile phone use may be negatively associated with sleep outcomes in adults.
- There is insufficient published evidence on the management of insomnia associated with screen time/electronic device use.

9. What is the comparative effectiveness of internet-based cognitive behavioral therapy for insomnia (CBT-I) and traditional CBT-I in improving sleep efficiency and reducing the severity of insomnia in the short and long term among adults with insomnia?

- The internet-based programs for delivering CBT-I varied between studies, but overall the trials incorporated both behavioral and cognitive strategies (sleep restriction and stimulus control) that were delivered in more than one session. There were variations between the trials in the components of applied therapies, the duration and number of sessions, and the duration of patient follow-up, all of which may influence the results pooled in the published meta-analyses.
- Overall, the published literature (including meta-analyses by Seyffert 2016, Ye 2016, and Zachariae 2016, and an RCT by Ritterband 2017) indicates that internet-delivered CBT-I leads to improvements in several sleep-related variables, including sleep efficiency, sleep onset latency, total sleep time, and wake time after sleep.
- The results of a meta-analysis of 10 trials (Ye 2015) also suggest that internet-delivered CBT-I may lead to improvements in anxiety and depression symptoms in patients with insomnia.
- The short-term improvements observed for different sleep parameters remained significant at 6 months' follow-up. One trial (Kaldo 2015) showed that the significant difference between the intervention and control groups was stable for 1 year.

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Guideline Development Process and Team

Development process

The guideline team developed the Insomnia Guideline using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis. For details, see Evidence Summary and References.

This edition of the guideline was approved for publication by the Guideline Oversight Group in January 2019.

Team

The Insomnia Guideline development team included representatives from the following specialties: Behavioral Health, Family Medicine, Gerontology, Pharmacy, Residency, Sleep Medicine, and Social Work.

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Disclosure of conflict of interest

Kaiser Permanente requires that team members participating on a guideline team disclose and resolve all potential conflicts of interest that arise from financial relationships between a guideline team member or guideline team member's spouse or partner and any commercial interests or proprietary entity that provides or produces health care–related products and/or services relevant to the content of the guideline.

Team members listed above have disclosed that their participation on the Insomnia Guideline team includes no promotion of any commercial products or services, and that they have no relationships with commercial entities to report.