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CLINICAL GUIDELINE

Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians

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Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the management of chronic insomnia disorder in adults.

Methods: This guideline is based on a systematic review of randomized, controlled trials published in English from 2004 through September 2015. Evaluated outcomes included global outcomes assessed by questionnaires, patient-reported sleep outcomes, and harms. The target audience for this guideline includes all clinicians, and the target patient population includes adults with chronic insomnia disorder. This guideline grades the evidence and recommendations by using the ACP grading system, which is based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Recommendation 1: *ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. (Grade: strong recommendation, moderate-quality evidence)*

Recommendation 2: *ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful. (Grade: weak recommendation, low-quality evidence)*

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Insomnia is a major health care problem in the United States. It is defined as dissatisfaction with sleep quantity or quality and is associated with difficulty initiating or maintaining sleep and early-morning waking with inability to return to sleep (1). Approximately 6% to 10% of adults have insomnia that meets diagnostic criteria (1–4). Insomnia is more common in women and older adults (5, 6) and can occur independently or be caused by another disease. People with the disorder often experience fatigue, poor cognitive function, mood disturbance, and distress or interference with personal functioning (2, 4). An estimated $30 billion to $107 billion is spent on insomnia in the United States each year (7). Insomnia also takes a toll on the economy in terms of loss of workplace productivity, estimated at $63.2 billion in the United States in 2009 (8).

Chronic insomnia, also referred to as "chronic insomnia disorder" in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), is diagnosed according to the DSM-5 (9) and the International Classification of Sleep Disorders (10), which have similar criteria for making the diagnosis. These criteria specify that symptoms must cause clinically significant functional distress or impairment; be present for at least 3 nights per week for at least 3 months; and not be linked to other sleep, medical, or mental disorders (1). Symptoms of insomnia differ between older adults and the younger population. Older adults are more likely to report problems with waking after sleep onset (difficulty maintaining sleep) than they are to report problems with sleep onset latency (time to fall asleep).

The goal of treatment for insomnia is to improve sleep and alleviate distress or dysfunction caused by the disorder. Insomnia can be managed with psychological therapy, pharmacologic therapy, or a combination of both. Psychological therapy options include cognitive behavioral therapy for insomnia (CBT-I); multicomponent behavioral therapy or brief behavioral therapy (BBT) for insomnia; and other interventions, such as stimulus control, relaxation strategies, and sleep restriction (see **Appendix Table 1**, available at

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www.annals.org, for a description of these interventions). Cognitive behavioral therapy for insomnia is multimodal cognitive behavioral therapy targeted specifically to insomnia. It consists of a combination of cognitive therapy, behavioral interventions (such as sleep restriction and stimulus control), and educational interventions (such as sleep hygiene). Various delivery methods are available, including in-person individual or group therapy, telephone- or Web-based modules, and self-help books. Trained clinicians or mental health professionals can administer CBT-I.

Pharmacologic therapy in the United States includes drugs approved by the U.S. Food and Drug Administration (FDA) for insomnia treatment, including benzodiazepines (triazolam, estazolam, temazepam, flurazepam, and quazepam); nonbenzodiazepine hypnotics (zaleplon, zolpidem, and eszopiclone); the recently approved orexin receptor antagonist suvorexant; the melatonin receptor agonist ramelteon; the antidepressant doxepin; off-label use of drugs, such as other antidepressants, antihistamines, and antipsychotics; and melatonin.

Complementary and alternative approaches, including acupuncture and Chinese herbal medicine, have also been used to treat insomnia.

GUIDELINE FOCUS AND TARGET POPULATION

The purpose of this American College of Physicians (ACP) guideline is to present recommendations based on the evidence on the efficacy, comparative effectiveness, and safety of treatments for chronic insomnia disorder. The target audience for this guideline includes all clinicians, and the target patient population includes all adults with chronic insomnia disorder. These recommendations are based on 2 background evidence review papers (11, 12) and an evidence review sponsored by the Agency for Healthcare Research and Quality (AHRQ) (13).

METHODS

Systematic Review of the Evidence

The evidence review was conducted by the AHRQ's Minnesota Evidence-based Practice Center. The summary of methods for the evidence review is provided in the **Appendix** (available at www.annals.org), and additional details are included in the accompanying background evidence review papers (11, 12) and the full evidence report (13). Reviewers searched several databases for randomized, controlled trials (RCTs) published in English from 2004 through September 2015. The study population included adults (aged ≥18 years) with chronic insomnia disorder (insomnia definitions that match diagnostic criteria for insomnia disorder).

The systematic evidence review evaluated psychological therapies, including CBT-I, multicomponent behavioral therapy or BBT for insomnia, stimulus control, relaxation strategies, and sleep restriction; pharmacologic therapies, including doxepin, triazolam, estazolam, temazepam, flurazepam, quazepam, zaleplon, zolpidem, eszopiclone, ramelteon, suvorexant, off-label use of drugs (such as antidepressants and antipsychotics), and melatonin; and complementary and alternative approaches, including acupuncture and Chinese herbal medicine. Evaluated outcomes included global outcomes assessed by questionnaires (such as treatment response), patient-reported and intermediate sleep outcomes, and harms.

Table. The American College of Physicians' Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

Grading the Evidence and Developing Recommendations

This guideline was developed by the ACP Clinical Guidelines Committee according to the ACP guideline development process, details of which can be found in the ACP methods paper (14). The Clinical Guidelines Committee used the evidence tables in the accompanying systematic review and full report (11, 12) when reporting the evidence and graded the recommendations by using the ACP system, which is based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (**Table**).

Peer Review

The AHRQ evidence review was sent to invited peer reviewers and posted on the AHRQ Web site for public comments. The guideline was peer reviewed through the journal and was posted online for comments from ACP Regents and Governors, who represent physician members at the national level.

BENEFITS OF TREATMENTS FOR CHRONIC INSOMNIA DISORDER

The efficacy, safety, and comparative effectiveness of psychological and pharmacologic treatments for chronic insomnia disorder are summarized in **Appendix Tables 2** to **5** (available at www.annals.org) and in the accompanying evidence reviews (11, 12). Evidence is described for the general adult population as well as for older adults (aged >55 years).

Psychological Treatment

Evidence for most psychological therapies was limited, and there was insufficient evidence to determine the comparative effectiveness of different psychological treatments for chronic insomnia disorder in the general population or in older adults.

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General Population

Moderate-quality evidence showed that CBT-I improved remission, treatment response, sleep onset latency, wake after sleep onset, sleep efficiency, and sleep quality in the general population (15–34). Improvements were seen across the various methods of CBT-I delivery, including in-person individual therapy (18, 24, 33, 35, 36), in-person group therapy (19, 20, 31), telephone-based modules (21), Web-based modules (17, 22, 23, 25), and self-help books (26, 29, 37); however, evidence was insufficient to determine the superiority of one method over another.

Low-quality evidence showed that stimulus control improved sleep onset latency and total sleep time in the general population (38, 39).

Older Population

For older adults, moderate-quality evidence showed that CBT-I improved Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI) scores compared with controls, and low- to moderate-quality evidence showed that CBT-I improved sleep onset latency, wake after sleep onset, and sleep efficiency (40–46).

Low- to moderate-quality evidence showed that multicomponent behavioral therapy or BBT improved sleep onset latency, wake after sleep onset, sleep efficiency, and sleep quality in older adults (47–50). Low-quality evidence showed that stimulus control improved total sleep time in older adults (51, 52).

Pharmacologic Treatment

Evidence was insufficient to determine the benefits of pharmacologic therapy with benzodiazepines in the general population or in older adults. Few trials met the inclusion criteria for the evidence review, largely because many assessed short durations of treatment.

General Population

Low-quality evidence showed that eszopiclone improved remission, and low- to moderate-quality evidence showed that it improved sleep onset latency, total sleep time, and wake after sleep onset compared with placebo in the general population (53–55). Zaleplon did not improve total sleep time in the general population (low-quality evidence) (56, 57). Moderate-quality evidence showed that zolpidem improved sleep onset latency and total sleep time in the general population (56–61). Zolpidem taken "as needed" improved Clinical Global Impression scores (62) (low-quality evidence), sleep onset latency, and total sleep time (moderate-quality evidence) in the general population (62–64). Zolpidem extended-release improved Clinical Global Impression scores, sleep onset latency, total sleep time, and wake after sleep onset in the general population (low-quality evidence) (65). Low-quality evidence showed that sublingual zolpidem reduced sleep onset latency after middle-of-the-night waking (66). Moderate-quality evidence showed that suvorexant increased treatment response and improved sleep onset latency, total sleep time, and wake after sleep onset compared with placebo in mixed general populations (67). Doxepin improved total sleep time and wake after sleep onset in the general population (low-quality evidence) (68).

Older Population

In older adults, low-quality evidence showed that eszopiclone improved remission, total sleep time, and wake after sleep onset (69). Low-quality evidence showed that zolpidem reduced sleep onset latency in older adults (70). Suvorexant increased treatment response and improved sleep onset latency, total sleep time, and wake after sleep onset compared with placebo in mixed older populations (moderate-quality evidence) (67). Low-quality evidence showed that ramelteon reduced sleep onset latency in older adults (71). Doxepin improved mean ISI scores, sleep onset latency, total sleep time, and wake after sleep onset in older adults (low- to moderate-quality evidence) (72, 73).

Complementary and Alternative Treatments

There was insufficient evidence to determine the safety or efficacy of complementary and alternative treatments for insomnia disorder in the general population or in older adults (13).

COMPARATIVE EFFECTIVENESS OF DIFFERENT TYPES OF INTERVENTIONS

Overall, evidence was insufficient to determine the comparative efficacy of pharmacologic treatments for insomnia disorder in the general population or in older adults.

HARMS OF TREATMENTS FOR CHRONIC INSOMNIA DISORDER

A full summary of the evidence supporting the harms of treatments for chronic insomnia disorder is provided in Appendix Tables 2 to 5 and the accompanying evidence reviews (11, 12).

Psychological Treatment

Specific adverse effects were not reported for psychological interventions, and withdrawals were not reported for treatment versus control groups. Therefore, evidence was insufficient to determine the harms of psychological interventions. However, due to the noninvasive nature of CBT-I, adverse effects are likely to be mild.

Pharmacologic Treatment

Harms were insufficiently reported in many of the included RCTs, which most often provided data only on study withdrawals. In addition to evidence from the systematic review on study withdrawals and adverse effects, specific adverse effects associated with the various pharmacologic treatments are summarized in Appendix Tables 4 and 5.

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Data from observational studies suggest that serious adverse effects, such as dementia and fractures, may be associated with hypnotic drugs (74, 75). Product labels from the FDA warn patients about cognitive and behavioral changes, such as possible driving impairment and motor vehicle accidents, as well as other adverse effects. The FDA also recommends lower doses of benzodiazepine and nonbenzodiazepine hypnotics in women and in older or debilitated adults. In addition, the FDA recommends short-term use of these drugs, although many patients may continue their use for extended periods.

Comparative Safety of Pharmacologic Treatments

Evidence was generally insufficient to determine the comparative safety of various pharmacologic treatments.

The Figure summarizes the recommendations and clinical considerations.

RECOMMENDATIONS

Recommendation 1: ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. (Grade: strong recommendation, moderate-quality evidence)

Cognitive behavioral therapy for insomnia consists of a combination of treatments that include cognitive therapy around sleep, behavioral interventions (such as sleep restriction and stimulus control), and education (such as sleep hygiene). It can be performed in primary care (18, 19). There are various delivery methods for CBT-I, such as individual or group therapy, telephone- or Web-based modules, or self-help books. Most studies focused on in-person CBT-I; however, the data suggest that other delivery methods are also effective.

Cognitive behavioral therapy for insomnia should be considered first-line treatment for adults with chronic insomnia disorder. Although the current evidence is insufficient to show the harms associated with behavioral interventions, any such harms are likely to be mild. Moderate-quality evidence showed that CBT-I improved global outcomes in the general population, including increased remission and treatment response and reduced ISI and PSQI scores compared with controls. Moderate-quality evidence showed that CBT-I also improved sleep outcomes in the general population, including reduced sleep onset latency and wake after sleep onset and improved sleep efficiency and sleep quality. Low- to moderate-quality evidence showed that CBT-I also improved global and sleep outcomes in older adults, including improved PSQI and ISI scores, reduced sleep onset latency, and improved sleep efficiency. Moderate-quality evidence showed that CBT-I reduced wake after sleep onset in older adults.

Recommendation 2: ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful. (Grade: weak recommendation, low-quality evidence)

Benefits of pharmacologic treatment include improved sleep outcomes, such as sleep onset latency and total sleep time, and in some cases improved global outcomes in the general population and in older adults. Most studies have examined newer medications, whereas commonly used older and generic medications, such as diphenhydramine and trazodone, have not been studied. Low-quality evidence showed that both eszopiclone and zolpidem improved global outcomes in the general population, and low- to moderate-quality evidence showed that eszopiclone, zolpidem, and doxepin improved sleep outcomes, such as sleep onset latency, total sleep time, and wake after sleep onset. Moderate-quality evidence showed that suvorexant, an orexin antagonist recently approved by the FDA, improved treatment response and sleep outcomes in mixed general and adult populations. Low-quality evidence showed no statistically significant difference between ramelteon and placebo for sleep outcomes in the general population.

In older adults, low-quality evidence showed that eszopiclone improved global and sleep outcomes and both zolpidem and ramelteon decreased sleep onset latency. Moderate-quality evidence showed that doxepin improved ISI scores, and low- to moderate-quality evidence showed that it improved sleep outcomes.

Evidence was insufficient for melatonin in the general population and in older adults. Benzodiazepines, although widely used, were not addressed in this guideline because few studies met the inclusion criteria of the systematic review (insufficient evidence).

Evidence on harms was limited from RCTs that met the inclusion criteria for the review, which mostly reported on study withdrawals. However, observational studies have shown that hypnotic drugs may be associated with infrequent but serious adverse effects, such as dementia, serious injury, and fractures (74, 75, 76, 77). In addition, FDA labels warn of daytime impairment, "sleep driving," behavioral abnormalities, and worsening depression. The FDA suggests dosages lower than those used in many of the included studies, especially for older adults.

Evidence is insufficient to evaluate the balance of the benefits and harms of long-term use of pharmacologic treatments in adults with chronic insomnia disorder. The FDA has approved pharmacologic therapy for short-term use (4 to 5 weeks), and patients should not continue using the drugs for extended periods. The FDA also recommends that patients with insomnia that does not remit within 7 to 10 days of treatment should be further evaluated.

There was insufficient evidence overall on the comparative effectiveness and safety of the various pharmacologic treatments. See Appendix Tables 4 and 5 for a summary of efficacy, adverse events, and costs for

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Figure. Summary of the American College of Physicians guideline on management of chronic insomnia disorder in adults.

Summary of the American College of Physicians Guideline on Management of Chronic Insomnia Disorder in Adults

Disease/Condition	Chronic insomnia disorder
Target Audience	Internists, family physicians, other clinicians
Target Patient Population	Adults with insomnia disorder
Interventions Evaluated	Psychological: CBT-I, BBT, multicomponent behavioral therapy, sleep restriction, stimulus control, relaxation therapy Pharmacologic: benzodiazepines (triazolam, estazolam, temazepam, flurazepam, quazepam), nonbenzodiazepines (eszopiclone, zaleplon, zolpidem, suvorexant, melatonin, ramelteon, antidepressants) Complementary and alternative treatments: acupuncture, Chinese herbal medicine
Outcomes Evaluated	Global outcomes: CGI, PSQI, Patient Global Impression Scale, ISI Sleep outcomes (patient-reported): SOL, number of awakenings, WASO, TST, sleep efficiency (total sleep time / total time in bed), sleep quality Adverse effects Study withdrawals
Benefits	General Population Psychological CBT-I: improved remission, treatment response, PSQI (2.1 points) and ISI (4.8 points) scores, SOL (11.6 min), WASO (21.4 min), sleep efficiency, sleep quality Stimulus control: improved SOL (31.2 min), TST (43.5 min) Pharmacologic Eszopiclone: improved remission, ISI scores (4.6 points), SOL (19.1 min), TST (44.8 min), WASO (10.8 min) Zolpidem: improved SOL (15 min), TST (23 min) Zolpidem "as needed": improved CGI, SOL (14.8 min), TST (48.1 min) Zolpidem extended-release: improved CGI, SOL (9 min), TST (25 min), WASO (16 min) Zolpidem sublingual: improved SOL (18 min) Suvorexant: improved treatment response, ISI score (1.2 points), SOL (6.0 min), TST (16.0 min), WASO (4.7 min) Doxepin: improved TST (11.9 min for 3 mg, 17.3 min for 6 mg), WASO (10.2 min for 3 mg, 14.2 min for 6 mg) Older Adults Psychological CBT-I: improved PSQI (3.0 points) and ISI (3.6 points) scores, SOL (8.2 min), WASO (37.6 min), sleep efficiency Multicomponent behavioral therapy/BBT: improved SOL (10.4 min), WASO (14.9 min), sleep efficiency, sleep quality Stimulus control: improved TST (40.4 min) Pharmacologic Eszopiclone: improved remission, ISI score (2.3 points), TST (30.0 min), WASO (21.6 min) Zolpidem: improved SOL (18.3 min) Ramelteon: improved SOL (10.1 min) Doxepin: improved ISI score (1.7 points), SOL (14.7 min), TST (23.9 min), WASO (17.0 min) Complementary and alternative Insufficient evidence

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Figure–Continued

Harms	Psychological: sparsely reported but likely small because of noninvasive nature of therapy Pharmacologic: sparsely reported overall from the included RCTs Benzodiazepines Daytime drowsiness, dizziness or lightheadedness, dementia Increased risk for falls, hip fractures, and mobility problems in older adults Temazepam associated with an increase in incident cancer cases Nonbenzodiazepines Eszopiclone: somnolence, unpleasant taste, myalgia, memory impairment, psychiatric-related adverse effects, depression, anxiety, accidental injury Zaleplon: pain, somnolence or dizziness, gastrointestinal events, arrhythmia, hallucinations Zolpidem: anxiety, somnolence, mood alterations, hallucinations, depression, psychiatric-related adverse events, memory and driving impairment, risk for fractures or major head injury or fracture requiring hospitalization, increase in incident cancer cases Suvorexant: somnolence; cognitive and behavioral changes, such as amnesia, anxiety, hallucinations, and other neuropsychiatric symptoms; complex behaviors, such as "sleep-driving"; worsening of depression, including suicidal thinking in persons with depression; daytime impairments; sleep paralysis; hypnagogic/hypnopompic hallucinations Ramelteon: dizziness; somnolence (similar to placebo); fatigue; headache; unpleasant taste; nausea; new cognitive or behavioral abnormalities; complex behaviors, such as "sleep-driving"; exacerbation of depression and suicidal ideation in primarily depressed patients Doxepin: sedation, fatigue, weakness, lethargy, dry mouth, constipation, blurred vision, headache Infrequent but serious adverse events, such as fractures and dementia, have been reported for hypnotic drugs in observational studies. FDA label warnings include daytime impairment, "sleep driving," behavioral abnormalities, and worsening depression in depressed patients. Complementary and alternative treatments: none reported
Recommendations	*Recommendation 1: ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. (Grade: strong recommendation, moderate-quality evidence)* *Recommendation 2: ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful. (Grade: weak recommendation, low-quality evidence)*
Clinical Considerations	Medications should ideally be used for no longer than 4 to 5 wk, and the skills learned in CBT-I can manage insomnia over the longer term. Studies of chronic insomnia disorder typically excluded patients with insomnia due to another disorder. Before recommending that patients continue use of insomnia medications, clinicians should consider treatable secondary causes of insomnia, such as depression; pain; benign prostatic hypertrophy; substance abuse disorders; and other sleep disorders, such as sleep apnea and restless legs syndrome. If, after a trial of CBT-I, a shared decision is made to continue medications for longer than 4 to 5 wk, clinicians should revisit the need for medication continuation at periodic intervals. Chronic insomnia disorder itself may have deleterious health effects. However, whether medications decrease the harmful health effects of sleep deprivation is unknown, and evidence is insufficient to assess the balance of benefits and harms from long-term use of medications. Older adults more frequently report WASO than SOL. Older adults can be more sensitive to medications and their adverse effects and should be monitored closely when treated with pharmacologic agents.

BBT = brief behavioral therapy; CBT-I = cognitive behavioral therapy for insomnia; CGI = Clinical Global Impression Scale; FDA = U.S. Food and Drug Administration; ISI = Insomnia Severity Index; PSQI = Pittsburgh Sleep Quality Index; RCT = randomized, controlled trial; SOL = sleep onset latency; TST = total sleep time; WASO = wake after sleep onset.

pharmacologic treatments and the Figure for clinical considerations.

AREAS WITH INSUFFICIENT EVIDENCE

For nonpharmacologic therapy, evidence was insufficient to determine the effect of multicomponent behavioral interventions or BBT, sleep restriction, stimulus control, or relaxation therapy on global outcomes in the general population or in older adults with chronic insomnia disorder. There was also insufficient evidence to determine the effect of sleep restriction or relaxation therapy on sleep outcomes in these populations.

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For pharmacologic therapy, there was insufficient evidence on the effectiveness of benzodiazepine hypnotics (temazepam, triazolam, flurazepam, or quazepam), melatonin, or trazodone on global or sleep outcomes in the general population or in older adults with chronic insomnia disorder. Evidence was also insufficient for the effectiveness of complementary and alternative treatments.

There was insufficient evidence to determine the comparative safety or efficacy of pharmacologic or psychological treatments for insomnia disorder in the general population or in older adults. Trials comparing pharmacologic and nonpharmacologic therapies are lacking and would be useful. Evidence was insufficient for pharmacologic therapy or the choice of agent to treat patients with sleep maintenance insomnia if CBT-I alone was unsuccessful. There was insufficient evidence for the balance of the benefits and harms of long-term use of pharmacologic treatments in adults with chronic insomnia disorder.

HIGH-VALUE CARE

Cognitive behavioral therapy for insomnia is an effective therapy for chronic insomnia disorder and can be performed and prescribed in the primary care setting. Evidence showed that CBT-I was effective in treating the general population of adults as well as older adults with chronic insomnia disorder. There is insufficient evidence to directly compare CBT-I and pharmacologic treatment. However, because CBT-I is noninvasive, it is likely to have fewer harms, whereas pharmacologic therapy can be associated with serious adverse events. Thus, CBT-I provides better overall value than pharmacologic treatment. As indicated on FDA labeling, pharmacologic treatments for insomnia are intended for short-term use, and patients should be discouraged from using these drugs for extended periods. Because few studies evaluated the use of the medications for more than 4 weeks, long-term adverse effects are unknown.

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Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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Appendix: Detailed Methods

The evidence review was conducted by the Minnesota Evidence-based Practice Center to address the following key questions:

1. What are the efficacy and comparative effectiveness of treatments for insomnia disorder in adults?

a. What are the efficacy and comparative effectiveness of treatments for insomnia disorder in specific subgroups of adults?

b. What are the efficacy and comparative effectiveness of combined treatments (e.g., cognitive behavioral therapy and drug therapy) for the treatment of insomnia disorder in adults?

c. What are the long-term efficacy and comparative effectiveness of treatments for insomnia disorder in adults?

2. What are the harms of treatments for insomnia disorder in adults?

a. What are the harms of treatments for insomnia disorder in specific subgroups of adults?

b. What are the harms of combined treatments (e.g., cognitive behavioral therapy and drug therapy) for insomnia disorder in adults?

c. What are the long-term harms of treatments for insomnia disorder in adults?

Search Strategy

The systematic literature search included English-language RCTs published from 2004 through September 2015 (nonpharmacologic interventions), identified using MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and PsycINFO bibliographic databases as well as hand-searches of references of relevant studies. Studies were limited to RCTs of at least 4 weeks' duration that enrolled participants with insomnia disorder and reported global or sleep outcomes. Studies focused on patient-reported outcomes rather than sleep measures obtained by actigraphy and polysomnography. Large observational studies on pharmacologic hypnotics in adults with insomnia were included for consideration of harms data.

Quality Assessment

The quality of studies was assessed using the Cochrane Risk of Bias tool and the AHRQ handbook (78, 79), and the quality of systematic reviews was assessed using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) criteria (80). Additional information, including inclusion and exclusion criteria, is in the full evidence report (13) and the accompanying articles (11, 12). This guideline rates the evidence and recommendations by using the ACP guideline grading system (Table).

Population Studied

Studies were limited to adults older than 18 years with chronic insomnia disorder (that is, insomnia definitions that matched diagnostic criteria for insomnia disorder). "Older adults" were those older than 55 years. Patients who use alcohol to treat their insomnia disorder and those who misuse or abuse alcohol were outside the scope of this guideline.

Interventions Evaluated

Psychological therapy included CBT-I, multicomponent behavioral therapy or BBT for insomnia, stimulus control, relaxation strategies, and sleep restriction. Pharmacologic therapy included doxepin, triazolam, estazolam, temazepam, flurazepam, quazepam, zaleplon, zolpidem, eszopiclone, ramelteon, and suvorexant; off-label use of drugs, such as antidepressants and antipsychotics; and melatonin. Complementary and alternative approaches included acupuncture and Chinese herbal medicine.

Comparators

Psychological interventions were compared with usual care, wait-list controls (patients who have not yet received the intervention but are on a wait list to receive it), or other insomnia treatments. Efficacy or effectiveness of pharmacologic interventions and complementary and alternative approaches were compared with those of placebo or another agent in the same or another drug class.

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Outcomes

The goal of insomnia treatment is meaningful improvement in sleep and associated distress and/or dysfunction. Outcomes evaluated included 1) global outcomes, which measure improvements in sleep and related daytime dysfunction or distress and were assessed by the ISI and the PSQI; 2) sleep outcomes, which can be objective or patient-reported from sleep diaries and include sleep onset latency, wake after sleep onset, total sleep time, the intermediate sleep measures of sleep efficiency (total sleep time divided by the total time in bed) and sleep quality, function, mood, and quality of life; and 3) harms of treatment, such as adverse effects and study withdrawals.

Target Audience

The target audience for this guideline includes all clinicians, patients, health system leaders, and policymakers.

Target Patient Population

The target patient population includes all adults with chronic insomnia disorder.

Limitations

Sample sizes were small in most of the included RCTs, which were also of short duration. Minimally important differences were often not established or used in the studies. A large placebo response was observed for pharmacologic treatments.

Grading the Evidence and Developing Recommendations

This guideline was developed by the ACP Clinical Guidelines Committee according to the ACP guideline development process, details of which can be found in the ACP methods paper (14). The Clinical Guidelines Committee used the evidence tables in the accompanying systematic review and full report (11–13) when reporting the evidence and graded the recommendations by using the ACP guideline grading system (Table).

Peer Review

The AHRQ evidence review was sent to invited peer reviewers and posted on the AHRQ Web site for public comments. The guideline underwent a peer review process through the journal and was posted online for comments from ACP Regents and Governors, who represent physician members at the national level.

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Appendix Table 1. Psychological Interventions for Insomnia Disorder*

Treatment	Description
Stimulus control	Behavioral treatment that aims to establish consistency in sleep patterns and maintain an association of sleep with the bed and bedroom (e.g., only go to sleep when tired)
Sleep restriction	Behavioral intervention that limits time in bed to sleep time, gradually increasing the time spent in bed as sleep efficiency improves
Relaxation training	Training to reduce somatic tension and control bedtime thought patterns that impair sleep
Cognitive behavioral therapy for insomnia	Combination treatments that include cognitive and behavioral components, including stimulus control, sleep restriction, and sometimes relaxation training
Multicomponent therapy or brief behavioral therapy for insomnia	Multicomponent behavioral therapies without cognitive therapy

* Adapted from reference 13.

Appendix Table 2. Efficacy and Safety of Psychological Treatments for Chronic Insomnia Disorder in All Adults*

Outcome	Direction of Effect	Quality of Evidence	Data
CBT-I vs. inactive control			
Remission	Improved	Moderate	RR, 2.89 (95% CI, 2.02 to 4.15)
Response to treatment	Improved	Moderate	RR, 2.31 (CI, 1.06 to 5.03)
ISI score	Improved	Moderate	WMD, −4.78 (CI, −6.45 to −3.11)
PSQI score	Improved	Moderate	WMD, −2.10 (CI, −2.87 to −1.34)
Sleep onset latency	Improved	Moderate	WMD, −11.63 (CI, −16.55 to −6.71)
Wake after sleep onset	Improved	Moderate	WMD, −21.39 (CI, −35.78 to −7.00)
Sleep efficiency	Improved	Moderate	WMD, 6.86 (CI, 4.55 to 9.16)
Sleep quality	Improved	Moderate	WMD, 0.39 (CI, 0.20 to 0.57)
Stimulus control vs. inactive control			
Sleep onset latency	Improved	Low	WMD, −31.24 (CI, −45.26 to −17.22)
Total sleep time	Improved	Low	WMD, 43.54 (CI, 12.67 to 74.42)

CBT-I = cognitive behavioral therapy for insomnia; ISI = Insomnia Severity Index; PSQI = Pittsburgh Sleep Quality Index; RR = relative risk; WMD = weighted mean difference.
* Evidence was insufficient to determine global or sleep outcomes or adverse events for sleep restriction or relaxation therapy in the general population with chronic insomnia disorder.

Appendix Table 3. Efficacy and Safety of Psychological Treatments for Chronic Insomnia Disorder in Older Adults*

Outcome	Direction of Effect	Quality of Evidence	Data
CBT-I vs. inactive control			
ISI mean change	Improved	Moderate	MD, −3.60 (95% CI, −2.13 to −5.07)
PSQI score	Improved	Moderate	WMD, −2.98 (CI, −4.01 to −1.95)
PSQI mean change	Improved	Moderate	MD, −2.60 (CI, −1.54 to −3.66)
Sleep onset latency	Improved	Low	WMD, −8.21 (CI, −13.43 to −2.99)
Total sleep time	NS	Low	–
Wake after sleep onset	Improved	Moderate	WMD, −37.59 (CI, −55.83 to −19.35)
Sleep efficiency	Improved	Low	WMD, 9.53 (CI, 6.54 to 12.52)
Multicomponent behavioral therapy or brief behavioral therapy for insomnia vs. inactive control			
Sleep onset latency	Improved	Moderate	WMD, −10.43 (CI, −16.31 to −4.55)
Wake after sleep onset	Improved	Low	WMD, −14.90 (CI, −22.66 to −7.14)
Sleep efficiency	Improved	Low	WMD, 6.33 (CI, 3.38 to 9.29)
Sleep quality	Improved	Low	SMD, 0.56 (CI, 0.20 to 0.92)
Stimulus control vs. inactive control			
Total sleep time	Improved	Low	WMD, 40.37 (CI, 23.47 to 57.27)

CBT-I = cognitive behavioral therapy for insomnia; ISI = Insomnia Severity Index; MD = mean difference; NS = not statistically significant; PSQI = Pittsburgh Sleep Quality Index; SMD = standardized mean difference; WMD = weighted mean difference.
* Evidence was insufficient to determine global or sleep outcomes or adverse events for sleep restriction or relaxation therapy in older adults (those aged >55 y) with chronic insomnia disorder.

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Appendix Table 4. Efficacy and Safety of Pharmacologic Treatments for Insomnia Disorder in All Adults*

Outcome	Direction of Effect	Quality of Evidence	Data	AEs	Cost of Medication (30-d Supply)
Eszopiclone (2-3 mg) vs. placebo					
Remission	Improved	Low	RR, 2.7 (95% CI, 2.1 to 3.4)	Somnolence, unpleasant taste, myalgia, memory impairment, psychiatric-related AEs, depression, anxiety, accidental injury	Brand (3 mg, Lunesta): $340 Generic: $24
ISI score	Improved	Low	MD, −4.6 (CI, −5.3 to −3.9)		
Sleep onset latency	Improved	Moderate	WMD, −19.1 (CI, −24.1 to −14.1)		
Total sleep time	Improved	Moderate	WMD, 44.8 (CI, 35.4 to 54.2)		
Wake after sleep onset	Improved	Low	WMD, −10.8 (CI, −19.8 to −1.70)		
Study withdrawals	Higher with placebo	Low	RR, 0.8 (CI, 0.7 to 1.0)		
Withdrawal due to AE	NS	Low	RR, 1.4 (CI, 0.97 to 2.0)		
>1 AE	Higher with eszopiclone	Moderate	RR, 1.2 (CI, 1.1 to 1.4)		
Zaleplon (5-20 mg) vs. placebo					
Total sleep time	NS	Low	Results not pooled	Headache, dizziness, nausea, abdominal pain, weakness, dysmenorrhea, eye pain, amnesia, paresthesia, tremor	Brand (10 mg, Sonata): $184.50 Generic: $19
Study withdrawals	NS	Low	RR, 1.4 (CI, 0.9 to 2.3)		
>1 AE	NS	Moderate	RR, 0.96 (CI, 0.9 to 1.1)		
Zolpidem (5-15 mg) vs. placebo					
Sleep onset latency	Improved	Moderate	WMD, −15.0 (CI, −22.1 to −7.8)	Dizziness, headache, drowsiness, allergy, hallucinations, myalgia, sinusitis, memory disorder, visual disturbance, pharyngitis, lightheadedness, palpitation, rash, constipation, depression, drowsiness, asthenia, diarrhea, dry mouth, flu-like symptoms	Brand (10 mg, Ambien): $364 Generic: $9
Total sleep time	Improved	Moderate	WMD, 23.0 (CI, 2.0 to 43.9)		
Study withdrawals	NS	Low	RR, 1.2 (CI, 0.8 to 1.7)		
Withdrawal due to AE	Higher with zolpidem	Moderate	RR, 2.8 (CI, 1.2 to 6.4)		
>1 AE	NS	Moderate	RR, 1.05 (CI, 0.9 to 1.2)		
Zolpidem "as needed" (10 mg) vs. placebo					
Clinical Global Impression	Improved	Low	RR, 2.2 (CI, 1.6 to 3.2)	Somnolence, mood alterations, hallucinations, depression	Brand (10 mg, Ambien): $364 Generic: $9
Sleep onset latency	Improved	Moderate	WMD, −14.8 (CI, −23.4 to −6.2)		
Total sleep time	Improved	Moderate	WMD, 48.1 (CI, 34.8 to 61.5)		
Study withdrawals	NS	Low	RR, 1.0 (CI, 0.5 to 2.0)		
Zolpidem ER (12.5 mg) vs. placebo					
Clinical Global Impression	Improved	Low	RR, 1.8 (CI, 1.6 to 2.0)	Somnolence, anxiety, disturbance in attention	NA
Sleep onset latency	Improved	Low	Greater by approximately 9 min		
Total sleep time	Improved	Low	Greater by approximately 25 min		
Wake after sleep onset	Improved	Low	Greater by approximately 16 min		
Study withdrawals	Higher with placebo	Low	RR, 0.7 (CI, 0.6 to 0.9)		
Withdrawal due to AE	Higher with zolpidem ER	Low	RR, 1.8 (CI, 1.0 to 3.1)		
>1 AE	Higher with zolpidem ER	Low	RR, 1.2 (CI, 1.1 to 1.4)		
Zolpidem sublingual (3.5 mg) vs. placebo					
Sleep onset latency (minutes after awakening in middle of night)	Improved	Low	38 vs. 56; −18 (CI NR)	NA	–
Ramelteon (4-16 mg) vs. placebo					
Sleep onset latency	NS	Low	WMD, −3.1 (CI, −7.4 to 1.2)	Dizziness, somnolence (similar to placebo), fatigue, headache, unpleasant taste, nausea, new cognitive or behavioral abnormalities, complex behaviors (such as "sleep-driving"), exacerbation of depression and suicidal ideation in primarily depressed patients	Brand (8 mg, Rozerem): $254 Generic: NA
Total sleep time	NS	Low	WMD, 0.1 (CI, −10.0 to 10.0)		
Wake after sleep onset	NS	Low	WMD, −5.9 (CI, −6.1 to 17.9)		
Study withdrawals	Higher with ramelteon	Low	RR, 1.5 (CI, 1.1 to 1.9)		
Withdrawal due to AE	NS	Low	RR, 1.2 (CI, 0.5 to 3.3)		
>1 AE	NS	Moderate	RR, 1.0 (CI, 0.9 to 1.1)		

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Appendix Table 4–Continued

Outcome	Direction of Effect	Quality of Evidence	Data	AEs	Cost of Medication (30-d Supply)
Doxepin (1–3 or 6 mg) vs. placebo					
Total sleep time (3 mg)	Improved	Low	MD, 11.9 (CI NR) (P = 0.05)	Sedation, fatigue, weakness, lethargy, dry mouth, constipation, blurred vision, headache, agitation, insomnia, anxiety, nausea, vomiting, sweating, confusion, extrapyramidal symptoms, dizziness, paresthesia, orthostatic hypotension, electrocardiographic changes, tachycardia, increased liver function tests, tinnitus, sexual dysfunction, rash, seizure, agranulocytosis, thrombocytopenia, eosinophilia, leukopenia, SIADH	Generic (10 mg): $6.33
Total sleep time (6 mg)	Improved	Low	MD, 17.3 (CI NR) (P = 0.004)		
Wake after sleep onset (3 mg)	Improved	Low	MD, −10.2, (CI NR) (P = 0.02)		
Wake after sleep onset (6 mg)	Improved	Low	MD, −14.2 (CI NR) (P = 0.001)		
>1 AE	NS	Low	RR, 1.1 (CI, 0.96 to 1.3)		
Suvorexant (15 or 20 mg) vs. placebo†					
Response to treatment	Improved	Moderate	RR, 1.3 (CI, 1.2 to 1.5)	Somnolence, cognitive and behavioral changes (such as amnesia, anxiety, hallucinations, and other neuropsychiatric symptoms), complex behaviors (such as "sleep-driving"), worsening of depression (including suicidal thinking in persons with depression), daytime impairments, sleep paralysis, hypnagogic/hypnopompic hallucinations	Brand (10 mg, Belsomra): $277 Generic: NA
ISI score mean change	Improved	Moderate	MD, −1.2 (CI, −1.8 to −0.6)		
Sleep onset latency	Improved	Moderate	WMD, −6.0 (CI, −10.0 to −1.9)		
Total sleep time	Improved	Moderate	WMD, 16.0 (CI, 4.7 to 27.2)		
Wake after sleep onset	Improved	Moderate	WMD, 4.7 (CI, −8.9 to −0.5)		
Study withdrawals	NS	Low	RR, 0.95 (CI, 0.7 to 1.3)		
Withdrawal due to AE	NS	Low	RR, 0.6 (CI, 0.3 to 1.3)		
>1 AE	NS	Moderate	RR, 1.0 (CI, 0.9 to 1.1)		
Comparative effectiveness					
Zolpidem (5–10 mg) vs. temazepam (15–20 mg)					
Total sleep time	Improved	Low	MD, 27.0 (CI, 2.1 to 51.9)	NA	NA
Zaleplon (5–20 mg) vs. zolpidem (10 mg)					
Study withdrawals	NS	Low	RR, 1.0 (CI, 0.7 to 1.5)	NA	NA
>1 AE	NS	Moderate	RR, 0.95 (CI, 0.9 to 1.03)		

AE = adverse effect; ER = extended-release; ISI = Insomnia Severity Index; MD = mean difference; NA = not applicable; NR = not reported; NS = not statistically significant; RR = relative risk; WMD = weighted mean difference; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

* Cost data were taken from the Healthcare Bluebook. Specific AEs associated with each drug were derived from the Evidence-based Practice Center report when available and from Medscape (limited to those with reported frequencies >1% where the frequencies were available [suvorexant, zaleplon, zolpidem]).

† Mixed population of general and older adults.

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Appendix Table 5. Efficacy and Safety of Pharmacologic Treatments for Insomnia Disorder in Older Adults*

Outcome	Direction of Effect	Quality of Evidence	Data	AEs	Cost of Medication (30-d Supply)
Eszopiclone (2 mg) vs. placebo					
Remission	Improved	Low	RR, 1.5 (95% CI, 1.1 to 2.1)	Somnolence, unpleasant taste, myalgia	Brand (3 mg, Lunesta): $340 Generic: $24
ISI score	Improved	Low	MD, −2.3 (CI, −3.3 to −1.3)		
Total sleep time	Improved	Low	MD, 30.0 (CI, 19.7 to 40.3)		
Wake after sleep onset	Improved	Low	MD, −21.6 (CI, −29.6 to −13.6)		
Zolpidem (5 mg) vs. placebo					
Sleep onset latency	Improved	Low	MD, −18.3 (CI, −31.5 to −5.4)	Dizziness, headache, drowsiness, allergy, hallucinations, myalgia, sinusitis, memory disorder, visual disturbance, pharyngitis, lightheadedness, palpitation, rash, constipation, depression, drowsiness, asthenia, diarrhea, dry mouth, flu-like symptoms	Brand (10 mg, Ambien): $364 Generic: $9
Ramelteon (4–8 mg) vs. placebo					
Sleep onset latency	Improved	Low	MD, −10.1 (CI, −15.6 to −4.6)	Dizziness, somnolence (similar to placebo), fatigue, headache, dysgeusia, nausea	Brand (8 mg, Rozerem): $254 Generic: NA
Doxepin (1–3 or 6 mg) vs. placebo					
ISI mean change	Improved	Moderate	WMD, −1.7 (CI, −2.6 to −0.9)	Sedation, fatigue, weakness, lethargy, dry mouth, constipation, blurred vision, headache, agitation, insomnia, anxiety, nausea, vomiting, sweating, confusion, extrapyramidal symptoms, dizziness, paresthesia, orthostatic hypotension, electrocardiographic changes, tachycardia, increased liver function tests, tinnitus, sexual dysfunction, rash, seizure, agranulocytosis, thrombocytopenia, eosinophilia, leukopenia, SIADH	
Sleep onset latency	Improved	Low	MD, −14.7 (CI, −24.0 to −5.4)		
Total sleep time	Improved	Moderate	WMD, 23.9 (CI, 12.0 to 35.7)		
Wake after sleep onset	Improved	Low	MD, −17.0 (CI, −29.3 to −4.7)		
Study withdrawals	NS	Low	RR, 0.6 (CI, 0.4 to 1.1)		
>1 AE	NS	Low	RR, 0.9 (CI, 0.6 to 1.3)		

AE = adverse effect; ISI = Insomnia Severity Index; MD = mean difference; NA = not applicable; NS = not statistically significant; RR = relative risk; WMD = weighted mean difference; SIADH = syndrome of inappropriate antidiuretic hormone secretion.
* Cost data were taken from the Healthcare Bluebook. Specific AEs associated with each drug were derived from the Evidence-based Practice Center report when available and from Medscape (limited to those with reported frequencies >1% where the frequencies were available [suvorexant, zaleplon, zolpidem]).

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