Comparative Effectiveness Review
Number 159

Effective Health Care Program

Management of Insomnia Disorder

Executive Summary

Introduction

Sleep problems are common concerns for adults.[1] Compromised sleep is associated with lower overall and sleep-related health status, which can lead to negative personal and social consequences.[2] Individuals with sleep problems report higher levels of anxiety, depressed mood, physical pain and discomfort, and cognitive deficiencies.[3] Insomnia may also be associated with long-term health consequences, including increased morbidity, respiratory disease, rheumatic disease, cardiovascular disease, cerebrovascular conditions, and diabetes.[2]

The term *insomnia* is variously defined to describe a symptom and/or a disorder. It involves dissatisfaction with sleep quantity or quality and is associated with one or more of the following subjective reports: difficulty initiating sleep, difficulty maintaining sleep, or early morning waking with inability to return to sleep.[4] Insomnia disorder should be diagnosed in accordance with criteria from the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) and/or the International Classification of Sleep Disorders. Both sets of criteria (in current and previous versions) define sleep-related reports despite adequate opportunity for sleep combined with distress or dysfunction created by the sleep difficulty. The DSM-5 defines insomnia disorder as occurring when sleep problems and associated distress/dysfunction last longer than 3 months.[4]

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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Effective Health Care

Between 6 and 10 percent of adults have insomnia that meets established diagnostic criteria.[1,4-6] Previous diagnostic criteria for insomnia did not specify a minimum timeframe for sleep difficulties; chronic insomnia (now called insomnia disorder) was used to describe cases that lasted from weeks to months, and insomnia was considered chronic in 40–70 percent of insomnia cases.[6]

Several factors are associated with insomnia. Females are 1.4 times as likely as males to have insomnia.[7] Older adults also have higher prevalence of insomnia; aging is often accompanied by changes in sleep patterns (disrupted sleep, frequent waking, early waking) that can lead to insomnia.[8] Older adults typically report difficulty maintaining sleep.[9] Additionally, about half of insomnia cases coexist with a psychiatric diagnosis.[10]

Many treatments are available, including over-the-counter medications and supplements, education on sleep hygiene and recommended lifestyle changes, behavioral and psychological interventions, prescription medications, and complementary and alternative medicine (CAM) treatments.

The American Academy of Sleep Medicine (AASM) practice parameters state that psychological and behavioral interventions are effective and recommended for adults.[11,12] Support for short-term use of pharmacologic interventions was based on consensus.[12] An updated AASM evidence synthesis and recommendations on pharmacologic interventions are underway.[13]

Examples of psychological interventions (Table A) include cognitive behavioral therapy for insomnia (CBT-I), brief behavioral therapy (BBT), and other behavioral interventions alone (i.e., stimulus control, relaxation training, sleep restriction).

Prescription drugs are often used to treat insomnia. The Food and Drug Administration (FDA) has approved several for use, typically for short-term use (doxepin, triazolam, estazolam, temazepam, flurazepam, quazepam, zaleplon, zolpidem, eszopiclone, ramelteon, suvorexant), for insomnia and to improve sleep parameters associated with insomnia. Other medications from various drug classes (e.g., antidepressants, antipsychotics) are used off label. Melatonin is a commonly used over-the-counter insomnia treatment.

Efficacy research has been conducted on a variety of CAM approaches (Chinese herbal medicine, acupuncture, reflexology, Suanzaoren decoction, etc.). Methodological limitations have prevented conclusive evidence synthesis for these treatments.[14-23]

Treatment goals include meaningful improvements in sleep and associated distress and/or dysfunction. Insomnia treatment may affect several outcomes. We categorized outcomes as global, specific sleep, or secondary. Global outcomes measure improvements in sleep and the accompanying daytime dysfunction or distress simultaneously. Two instruments that measure global outcomes are the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI). Sleep outcomes measure specific sleep parameters and sleep quality. Specific sleep parameters include sleep-onset latency, waking after sleep onset, total sleep time, and sleep efficiency (total sleep time/total time in bed). Improvements in specific sleep measures can be assessed objectively or subjectively. Sleep parameters can be objectively measured with polysomnography (measuring sleep continuity parameters—sleep time spent in each stage in a sleep lab) or actigraphy (measuring body movements). Subjective measures are generally believed to be more clinically valuable because they are patient centered. Sleep quality is also subjectively measured in a variety of ways. Functioning, mood, and quality-of-life outcomes that measure factors such as daytime fatigue or sleepiness, depression and anxiety, or quality of life reflect improvements associated with improved sleep.

Systematic reviews have assessed the efficacy and comparative effectiveness of insomnia treatment. Available reviews, however, do not incorporate the broad range of interventions (psychological, pharmacologic, CAM). This review uses previous systematic reviews and randomized controlled trials (RCTs) to provide a comprehensive up-to-date synthesis of the evidence on efficacy and comparative effectiveness of insomnia disorder treatments. Data from large long-term observational studies are included to further assess pharmacologic harms.

Scope and Key Questions

Our review addresses the following Key Questions and PICOTS (populations, interventions, comparators, outcomes, timing, and settings).

Key Questions

Key Question 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

Table A. Psychological/behavioral interventions for insomnia disorder	
Psychological and Behavioral Treatments for Insomnia	**Definition**
Sleep hygiene education	Behavioral intervention aiming to educate patients about health and environmental factors they can change to improve sleep. Educational materials describe avoiding caffeine and nicotine, limiting consumption of alcoholic beverages, maintaining a regular sleep schedule, avoiding napping, exercising regularly, and maintaining a quiet and dark bedroom.[6]
Stimulus control	Behavioral treatment that aims to change behaviors associated with bed and bedroom and establish consistency in sleep patterns. Techniques include restricting bedroom for sleep only; going to bed only when sleepy; avoiding reading, television, phone, etc., in the bedroom; leaving the bedroom when unable to sleep; regular sleep schedule; no snooze button.[6]
Sleep restriction	Behavioral intervention that limits time in bed to sleep time, gradually increasing time in bed as sleep efficiency improves. Techniques include setting strict bedtime and rising schedules, and keeping a set wakeup time, with modifications based on sleep efficiency after a certain duration of time.[6]
Relaxation training	Training to reduce somatic tension and control bedtime thought patterns that impair sleep. Techniques include progressive muscle relaxation, guided imagery, and paced breathing.[6]
Brief behavioral therapy	Combines core behavioral interventions of stimulus control and sleep restriction.[6]
Cognitive therapy	An intervention that aims to change how patients think about sleep by identifying, challenging, and replacing dysfunctional beliefs and attitudes. Dysfunctional beliefs create tension, impair sleep, and reinforce the beliefs. Techniques include challenging notions about requisite amounts of sleep, notions that sleep is out of their control, and fears about missed sleep; thought journaling; and behavioral experiments around sleep beliefs.[6]
Cognitive behavioral therapy	A multimodal combination of treatments that include cognitive therapy around sleep and behavioral interventions (sleep restriction, stimulus control) and education (sleep hygiene).[6]

Adapted from Morgenthaler, Kramer, Alessi, et al.[11] and Buysse.[6] See Buysse for more detailed description and specific techniques.

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?

Key Question 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?

PICOTS

Population(s)

- Adults age 18 and older with insomnia disorder (i.e., insomnia definitions that match insomnia disorder diagnostic criteria)
  - Specific subgroups:
    - Older adults (trials that exclusively enroll adults age 55 and older)
    - Adults with coexisting medical or mental health disorders (such as mild depression/anxiety)

Intervention categories

- Psychological
- Pharmaceutical (available in the United States)
- CAM

Comparators

- Drug and CAM supplement efficacy trials must be double-blind placebo-controlled studies. Psychological therapy efficacy trials can be controlled with placebo or sham treatment, usual care, attention control (i.e., sleep hygiene or sleep education), or wait-list controls. Comparative effectiveness trials can include any active therapy approved and available in the United States.

Outcomes

- Key Question 1
  - Global outcomes
    - Measures that assess improvements in both sleep symptoms and daytime functioning or distress associated with sleep symptoms.

      Measurement: Questionnaires that include items related to sleep problems and daytime functioning or distress—ISI,[12,24] PSQI,[11,24] Patient Global Impression scale.
  - Sleep outcomes, patient reported
    - Assessments derived from sleep diaries (sleep-onset latency, wake time after sleep onset, total sleep time, sleep efficiency [total sleep time/total time in bed], and sleep quality [variously defined]).
  - Functioning, mood/well-being, and quality of life
    - Assessments of outcomes related to sleep, such as daytime fatigue, mood, and quality of life.

      Measurement: Assessments derived from questionnaires—Beck Depression Inventory,[12,24] State-Trait Anxiety Inventory,[12,24] Short-Form Health Survey (SF-36),[12,24] World Health Organization Quality of Life,[24] Epworth Sleepiness Scale[12] or Fatigue Severity Scale (FSS).[12,24]
- Key Question 2
  - Adverse effects of intervention(s)
    - Any adverse effects (e.g., headache, somnolence, myalgia, poor taste, dependence, falls, abnormal sleep behaviors). Timing for adverse effects was similar to that for other outcomes. (See Timing.)

Timing

- Key Question 1: Outcomes measured at 4 weeks to 3 months after initiation of treatment were used to assess efficacy/comparative effectiveness.
- Key Question 1c. Followup measures beyond 3 months of treatment were used to evaluate long-term efficacy and comparative effectiveness.

Settings

- Any outpatient setting

Methods

We searched Ovid Medline®, Ovid PsycINFO®, Ovid Embase®, and the Cochrane Library to identify previous systematic reviews and RCTs published and indexed in bibliographic databases from 2004 through January 2015. Our search strategy included relevant medical subject headings and natural language terms for the concept of insomnia. This concept was combined with filters to select RCTs and systematic reviews. We identified older eligible trials by citation searching previous systematic reviews. Bibliographic database searches were supplemented with backward citation searches of highly relevant systematic reviews (those that addressed similar KQs and PICOTS).

We included RCTs of pharmacologic therapies available in the United States and other interventions if they enrolled adults with insomnia disorder, provided at least 4 weeks of followup, and reported global or sleep outcomes. We included observational studies that reported harms if they (1) included adults with chronic insomnia without other major diagnoses, such as cancer or Parkinson's disease, or the hypnotics evaluated were FDA indicated for insomnia and likely administered for sleep disorders; (2) had a duration of at least 6 months; (3) reported on at least 100 individuals; and (4) reported harms by drug class.

Two independent investigators reviewed titles and abstracts of search results. Citations deemed eligible by either investigator underwent full-text screening. Two investigators independently screened full text to determine if inclusion criteria were met. Discrepancies in screening decisions were resolved by consultation between investigators and, if necessary, consultation with a third investigator. We documented the exclusion reason for studies excluded at the full-text screening stage.

We used data from relevant comparisons in previous systematic reviews to replace the de novo extraction process when the comparison was relevant, the methodology was fair or high quality according to an AMSTAR (A Measurement Tool to Assess Systematic Reviews) assessment, and a reliable strength-of-evidence assessment was conducted (or the information necessary to assess strength of evidence was available). We used AMSTAR criteria[25] to assess the quality of eligible systematic reviews. Quality assessment of systematic reviews included items such as a priori design, dual review, and individual study risk-of-bias assessment. Results of previous systematic reviews used in lieu of de novo extraction were updated with new data when additional relevant studies were identified.

Two investigators assessed the risk of bias of the remaining RCTs meeting inclusion criteria using forms developed using Agency for Healthcare Research and Quality (AHRQ) guidance. Domains included sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcomes data (i.e., whether incomplete outcomes data were adequately addressed), selective reporting, and other sources of bias (i.e., problems not covered by other domains). Each investigator summarized the overall risk of bias for each study and classified it as low, moderate, or high based on a subjective summary assessment of risk of bias across domains and confidence that the results were believable given the study's limitations. Studies that two investigators assessed as high risk of bias were excluded from analysis. Studies identified as eligible from citation searching of previous systematic reviews were assessed for risk of bias using our methodology. Studies that the previous AHRQ review assessed as poor quality were excluded from our review.[26]

One investigator extracted relevant study, population demographic, and outcomes data. Outcomes data used in analyses were confirmed by a second investigator.

We synthesized evidence for each unique population, comparison, and outcome combination. When a comparison was adequately addressed by a previous systematic review of acceptable quality according to AMSTAR criteria and no new studies were available, we reiterated the conclusions drawn from that review. Strength of evidence was assessed using AHRQ methodology. When new trials were available, previous systematic review data were synthesized with data from additional trials if possible.

We summarized study characteristics and outcomes in evidence tables. We assessed the clinical and methodological heterogeneity and variation in effect size to determine the appropriateness of pooling data.[27] Pooling was conducted when populations, interventions, and outcomes were sufficiently similar. Meta-analysis was performed using random-effects models (DerSimonian and Laird models using RevMan 5.2[28] software). We calculated risk ratios and absolute risk differences with the corresponding 95% confidence intervals (CIs) for binary primary outcomes. Weighted mean differences (WMDs) and/or standardized mean differences, with the corresponding 95% CIs, were calculated for continuous outcomes. We assessed statistical heterogeneity with Cochran's Q test and measured magnitude with the I^2 statistic.[27]

Global outcomes were most often measured using the ISI and the PSQI (Table B). We searched the literature to identify minimum important differences (MIDs) to facilitate interpretation of results for these outcomes. We identified one study estimating the MID for the ISI;[29] it used distribution- and anchor-based approaches. The anchor-based approach used 14 variables from three different instruments (the SF-36 Health Survey, the Work Limitations Questionnaire, and the FSS) and the SF-36 Vitality scale as the anchors in estimating the MID for the ISI. Anchor-based MIDs are considered superior to distribution-based methods, but distribution-based MIDs can be supplemental or used when anchor-based methods are not available.[30] MIDs can vary depending on estimation method and population studied.[31] They are also often closely related to baseline values.[32] Despite these complications, trials that conduct responder analysis based on the established MID offer simplistic interpretation.

Table B. Characteristics of instruments measuring global outcomes

Outcome	Measurement/Instrument Properties	MIDs Reported in Literature and Method of Derivation
Insomnia Severity Index	7 Likert items; range 0-28; demonstrated sensitivity to change[35] Score interpretation— 0–7: no clinically significant insomnia 8–14: subthreshold insomnia 15–21: clinical insomnia (moderate severity) 22–28: clinical insomnia (severe)	MID = 6: anchor based[29]
Pittsburgh Sleep Quality Index	7 components; 19 items; range 0–21, with lower scores indicating better sleep; demonstrated sensitivity to change[35]	No MID identified

MID = minimum important difference

Unfortunately, many trials did not conduct responder analysis and reported only mean scale scores or mean change in scale scores. It is not appropriate to apply the MID established based on changes from baseline for individuals to WMDs between groups.[31,33] We did not identify MIDs relevant to interpreting differences between groups. We therefore interpret the WMDs between groups in relation to the MID. WMDs between groups equal or above the MID suggest that many patients may gain important benefits from treatment; WMDs between 0.5(MID) and MID suggest that the treatment may benefit an appreciable number of people; and a WMD below 0.5(MID) suggests that it is less likely that that an appreciable number of patients will achieve important benefits from treatment.[34]

The overall strength of evidence for primary outcomes within each comparison was evaluated based on five required domains. Based on these factors, the overall strength of evidence for each outcome was judged as follows:[36]

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence; findings believed to be stable.
- **Moderate:** Moderately confident that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings are likely to be stable, but some doubt exists.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence is necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient:** No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

Strength-of-evidence assessments were made by one investigator and confirmed through team discussions.

Applicability of studies was determined according to the PICOTS framework. Study characteristics affecting applicability include, but are not limited to, the following:

- Population from which the study participants were enrolled. Studies enrolling participants from sleep medicine clinics may not produce results applicable to the general population of patients being treated for insomnia in primary care clinics.
- Narrow eligibility criteria.
- Patient and intervention characteristics different from those described by population studies of insomnia.[37]

Specific factors that could modify the effect of treatment and affect the applicability of findings include diagnostic accuracy, insomnia severity, and specific patient characteristics such as age.

Results

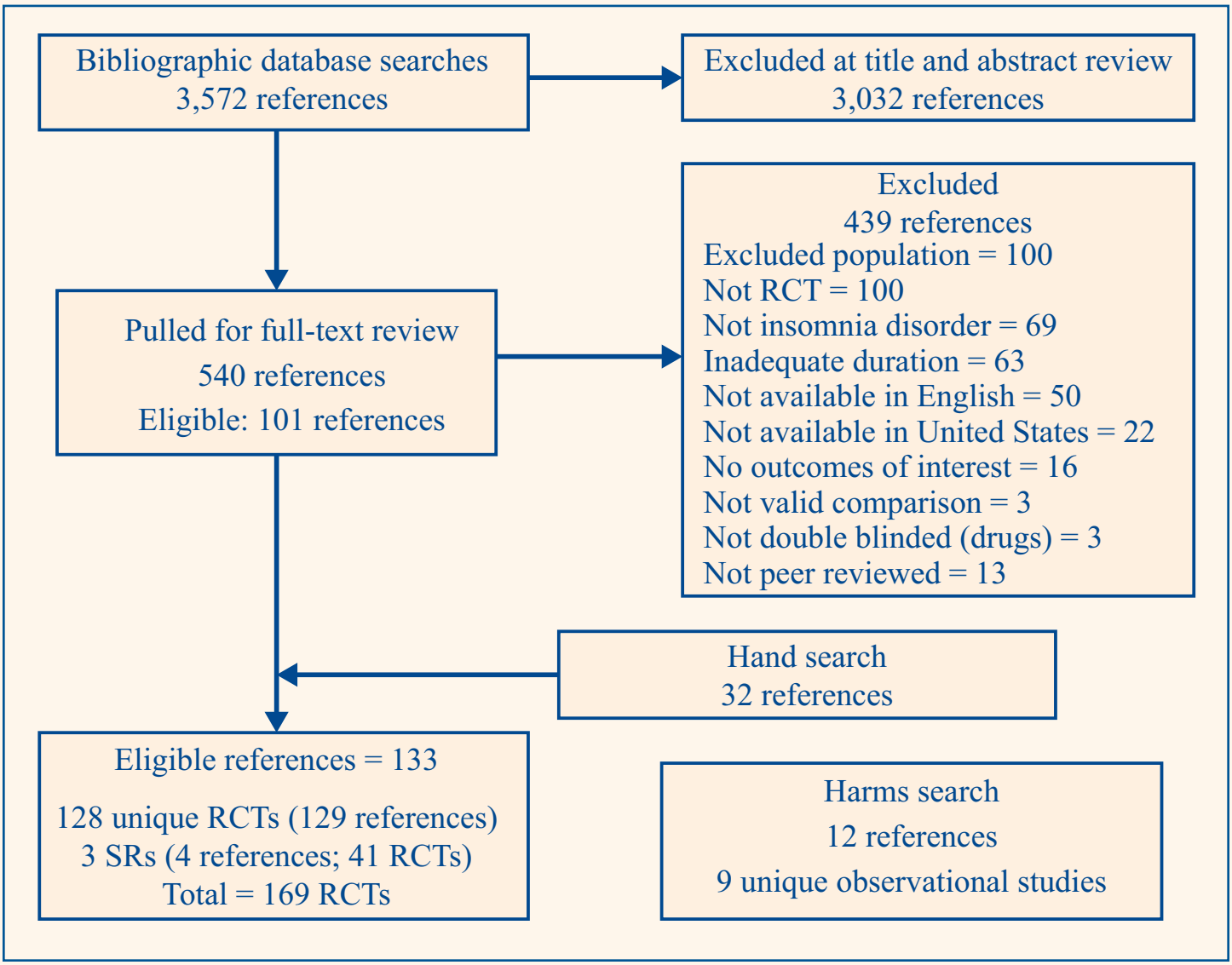
Our search identified 3,572 citations, of which 540 required full-text review after title and abstract screening (Figure A). Of the 540 full-text articles screened, we identified 133 eligible articles; we identified another 32 eligible references by hand searching, for a total of 133 publications on 128 unique RCTs and 3 unique systematic reviews. Systematic reviews included in our analysis synthesized evidence on 41 unique RCTs, primarily studying CAM interventions. The total number of RCTs reflected in this review is 169. We searched for observational studies to supplement our harms discussion. We identified 12 observational studies that met inclusion criteria.

Efficacy, Comparative Effectiveness, and Adverse Effects of Psychological Interventions

Key points regarding psychological interventions are as follows:

- CBT-I across several delivery modes improves global and sleep outcomes compared with passive control in the general adult population (moderate-strength evidence). Evidence was insufficient to assess adverse effects of CBT-I.
- CBT-I across several delivery modes improves global and several sleep outcomes (sleep onset latency, wake time after sleep onset, and sleep efficiency) compared with passive control among older adults with insomnia disorder (low- to moderate-strength evidence). Sleep outcomes remain improved long term (low-strength evidence).
- CBT-I across several delivery modes improves global and several sleep outcomes (sleep onset latency, total sleep time, wake time after sleep onset, and sleep efficiency) compared with passive control among adults with pain conditions and insomnia disorder (low-strength evidence)
- Multicomponent behavioral therapy and/or BBT improve several sleep outcomes (sleep onset latency, wake time after sleep onset, and sleep efficiency) in

Figure A. Literature flow diagram



RCT = randomized controlled trial; SR = systematic review

older adults with insomnia disorder (low-strength evidence).

- Data on the efficacy of specific cognitive or behavioral interventions alone (stimulus control, sleep restriction, relaxation techniques) were limited and evidence was insufficient to draw conclusions.
- Evidence was insufficient to assess adverse effects of any psychological treatments.

We identified 59 unique RCTs with acceptable risk of bias studying psychological interventions for insomnia disorder. Trials enrolled adults with insomnia from three overlapping populations (the general adult population [adults of any age], older adults, and adults with pain conditions). Within each population, we grouped trials based on intervention type and comparison. Enrollment criteria varied across studies. Trials were required to use insomnia symptoms consistent with a clinical diagnosis to be included in our review, but specific criteria varied across trials. Several studies required a minimum symptom duration ranging from 4 weeks to 6 months. Insomnia duration ranged from 6 months to 19 years in trials reporting insomnia duration. Duration was greater than 10 years in most trials reporting duration. Several trials required sleep disturbances totaling at least 30 minutes, and a few required total sleep time below 6.5 hours. Other trials required specific thresholds on particular diagnostic questionnaires. Interventions that had both cognitive and behavioral components were grouped into a CBT-I category. Interventions with multiple behavioral

components without a cognitive component, such as BBT, were grouped with multicomponent behavioral therapy. The more commonly studied single-therapy interventions were sleep restriction, stimulus control, and progressive relaxation. Studies of psychological interventions typically enrolled adults with insomnia disorder lasting years. Participants often had comorbidities. Table C lists global and sleep outcomes for all psychological interventions, as shown for the general adult population in Table C, for older adults in Table D, and for adults with pain conditions in Table E.

We identified 20 trials on the efficacy of CBT-I with acceptable risk of bias. The mean age of participants was typically in the mid-40s, participants were predominantly female, and most were white (in the trials that reported race). Baseline ISI scores were just over 17 and baseline sleep onset latency was over 45 minutes. Evidence from 18 of these RCTs (n = 1,842) provided data sufficient for pooling on one or more outcomes. Passive controls most often included attention control, treatment as usual, or wait-list; six trials had sham treatment or placebo passive controls. Moderate-strength evidence demonstrates that CBT-I improves global and sleep outcomes in the general adult population.[38] Effectiveness was demonstrated across modes of delivery (individual in person, in-person group, telephone, Web based, based on self-help book) and across passive control for both global and sleep outcomes. Moderate-strength evidence from four small RCTs (n = 179) showed that CBT-I resulted in a nearly threefold rate of "remission" versus passive control. Further supporting efficacy are differences in mean ISI and PSQI scores. CBT-I decreased ISI scores from baseline by more than 7 points, or 40 percent, compared with 2 points, or a 10-percent reduction, with passive control, for a WMD between groups of -5.15 (95% CI, -7.13 to -3.16). The WMD and entire CI are more than 0.5(MID), suggesting that an appreciable number of people will gain important benefits. CBT-I efficacy trials demonstrated improvements across all sleep outcomes, according to data pooled from 11 to 16 studies per outcome representing 945 to 1,369 participants. Pooled estimates showed that compared with passive control, CBT-I reduced sleep onset latency by 12 minutes (95% CI, 7 to 18 minutes), increased total sleep time by 14 minutes (95% CI, 4 to 26 minutes), reduced wake time after sleep onset by 22 minutes (95% CI, 8 to 37 minutes), improved sleep efficiency by nearly 7 percentage points (95% CI, 5 to 9 percentage points), and modestly improved sleep quality. Adverse effects of CBT-I were not often reported. Withdrawals were reported in some studies, but data were insufficient to assess differences in adverse effects by group. Many of these outcomes were maintained when outcomes were measured at timepoints beyond 6 months of treatment initiation.

Low-strength evidence from two small RCTs (n = 68) showed that, compared with passive control, stimulus control decreased sleep onset latency by over 30 minutes (95% CI, -45.26 to 17.22) and increased total sleep time by over 40 minutes (95% CI, 12.67 to 74.42) in the general adult population. Evidence was insufficient to draw conclusions about global outcomes and adverse effects.

Other comparisons were studied in the general adult population. Similar comparisons and the volume of adequately reported data necessary for pooling limited the amount of analysis that could be conducted with these data. Evidence regarding the efficacy of multicomponent behavioral therapy and sleep restriction, and regarding the comparative effectiveness of various psychological interventions was insufficient to draw conclusions for any outcomes.

Four RCTs (n = 220) studied the efficacy of CBT-I in older adults. Low-strength evidence showed that, compared with passive control, CBT-I improved global outcomes, with a pooled WMD in PSQI scores from two trials (n = 162) of -2.98 (95% CI, -4.01 to 1.95). Another trial compared mean change in PSQI and showed consistent results. Clinical significance is unclear because we did not find an established MID for the PSQI. PSQI scores decreased by over 35 percent from baseline with CBT-I and by less than 10 percent with passive control. Moderate-strength evidence showed that, compared with passive control, CBT-I improved wake time after sleep onset by 27 minutes (95% CI, 18 to 36 minutes). Low-strength evidence showed that, compared with passive control, CBT-I decreased sleep onset latency by 10 minutes (95% CI, 4 to 16 minutes) and improved sleep efficiency by over 9 points (95% CI, 6 to 13 points). Low-strength evidence showed that CBT-I had a similar effect on mean total sleep time as passive control. All improvements in sleep outcomes were maintained long term. Evidence was insufficient to assess adverse effects.

Three RCTs (n = 146) studied the efficacy of multicomponent behavioral therapy in older adults. The mean age was around 70, the majority of participants were female, and mean insomnia duration was 15.3 years in the two trials reporting duration. All trials were conducted in the United States.[39-42] Low-strength evidence showed that, compared with passive control, CBT-I decreased sleep onset latency by over 10 minutes (95% CI, 5 to 16 minutes), decreased wake time after sleep onset by 15 minutes (95% CI, 7 to 23 minutes), and improved sleep

Table C. Efficacy of psychological interventions for insomnia disorder in the general adult population									
	Psychological Intervention; Total Number of Trials (Total Enrolled)	**Global Outcomes (Remission/ Response) [95% CI] SOE**	**Global Outcomes (Continuous) [95% CI] SOE**	**Sleep Onset Latency WMD in Minutes [95% CI] SOE**	**Total Sleep Time WMD in Minutes [95% CI] SOE**	**Wake After Sleep Onset WMD in Minutes [95% CI] SOE**	**Sleep Efficiency WMD in Percentage Points [95% CI] SOE**	**Sleep Quality SMD [95% CI] SOE**	**Adverse Effects SOE**
Efficacy	CBT-I; 18 (1,842)	Favors CBT-I. Remitters:61% vs. 18%; RR, 2.95 [1.78 to 4.87]; k = 4 (179). Responders: 55% vs. 18%; RR, 2.59 [0.45 to 14.99]; k = 2 (123). Very much improved: 35% vs. 4%; RR, 8.08 [1.13 to 57.73]; k = 1 (60). Moderate	Favors CBT-I. ISI: WMD = -5.15 [-7.13 to -3.16]; k = 5 (345). PSQI: WMD = -2.10 [-2.87 to -1.34]; k = 6 (580). Moderate	Favors CBT-I. -12.70 [-18.23 to -7.18]; k =15 (1,246). Moderate	Favors CBT-I. 14.24 [2.08 to 26.39]; k = 15 (1,233). Moderate	Favors CBT-I. -22.33 [-37.44 to -7.21]; k = 12 (832). Moderate	Favors CBT-I. 7.20 [4.57 to 9.82]; k = 15 (1,230). Moderate	Favors CBT-I. 0.40 [0.18 to 0.59]; k = 110 (809). Moderate	Insufficient
	Stimulus control; 2 (68)	NR	Insufficient	Favors SC. -31.24 [-45.26 to -17.22]; k = 2 (68). Low	Favors SC. 43.54 [12.67 to 74.42]; k=2 (68). Low	Insufficient	Insufficient	NR	Insufficient
	Relaxation; 2 (77)	NR	NR	Insufficient	Insufficient	NR	NR	NR	NR
Long-Term Efficacy	CBT-I; 4 (413)	NR	Favors CBT-I. WMD = -2.71 [-3.67 to -1.75]; k = 2 (241). Low	NS. WMD = -15.69 [-32.67 to 1.29]; k = 4 (413). Insufficient	NS. WMD = 17.30 [-4.28 to 38.87]; k = 4 (413). Insufficient	Favors CBT-I. WMD = 15.20 [-26.28 to -4.12]; k = 3 (377). Low	Favors CBT-I. 5.00 [1.71 to 8.29]; k = 4 (413). Moderate	Favors CBT-I. MD = 0.54 [0.20 to 0.89]. Low	NR

CBT-I = cognitive behavioral therapy for insomnia; CI = confidence interval; ISI = Insomnia Severity Index; k = number of studies; MD = mean difference; NR = not reported; NS = no statistical difference between groups; PSQI = Pittsburgh Sleep Quality Index; RR = risk ratio; SC = stimulus control; SMD = standardized mean difference; SOE = strength of evidence; WMD = weighted mean difference

Table D. Efficacy of psychological interventions for insomnia disorder in older adults								
Psychological Intervention; Total Number of Trials (Total Enrolled)	**Global Outcomes (Remission/ Response) [95% CI] SOE**	**Global Outcomes (Continuous) [95% CI] SOE**	**Sleep Onset Latency WMD in Minutes [95% CI] SOE**	**Total Sleep Time WMD in Minutes [95% CI] SOE**	**Wake After Sleep Onset WMD in Minutes [95% CI] SOE**	**Sleep Efficiency WMD in Percentage Points [95% CI] SOE**	**Sleep Quality SMD [95% CI] SOE**	**Adverse Effects SOE**
CBT-I; 4 (220)	Insufficient	Favors CBT-I. PSQI: WMD = 2.98 [-4.01 to -1.95]. AIS: MD = -2.20 [-4.13 to -0.27]. PSQI change: MD = -2.20 [-3.39 to -1.01]. ISI change: MD = -3.60 [-2.13 to -5.07]; k = 3 (287). Low	Favors CBT-I. -9.98 [-16.48 to -3.48]; k = 3 (191). Low	NS. Low	Favors CBT-I. -26.96 [-35.73 to -18.19]; k = 4 (220). Moderate	Favors CBT-I. 9.18 [5.76 to 12.62]; k = 4 (220). Low	NR	Insufficient
Multicomponent behavioral therapy or BBT; 3 (146)	Insufficient	Insufficient	Favors MBT/ BBT. -10.43 [-16.31 to -4.55]; k = 3 (146). Low	Insufficient	Favors MBT/ BBT. -14.90 [-22.66 to -7.14]; k = 3 (146). Low	Favors MBT/ BBT. 6.33 [3.38 to 9.29]; k = 3 (146). Low	NR	NR
Sleep restriction; 1 (94)	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Stimulus control; 1 (94)	Insufficient	Insufficient	Insufficient	Favors SC. 40.37 [23.47 to 57.27]; k = 2 (113). Low	Insufficient	Insufficient	Insufficient	Insufficient

AIS = Athens Insomnia Scale; BBT = brief behavioral therapy; CBT-I = cognitive behavioral therapy for insomnia; CI = confidence interval; ISI = Insomnia Severity Index; k = number of studies; MBT = multicomponent behavioral therapies; MD = mean difference; NR = not reported; NS = no statistical difference between groups; PSQI = Pittsburgh Sleep Quality Index; SC = stimulus control; SMD = standardized mean difference; SOE = strength of evidence; WMD = weighted mean difference

Table E. Efficacy of psychological interventions for insomnia disorder in adults with pain								
Psychological Intervention	**Global Outcomes (Remission/ Response) SOE**	**Global Outcomes (Continuous) [95% CI] SOE**	**Sleep Onset Latency WMD in Minutes [95% CI] SOE**	**Total Sleep Time WMD in Minutes [95% CI] SOE**	**Wake After Sleep Onset WMD in Minutes [95% CI] SOE**	**Sleep Efficiency WMD in Percentage Points [95% CI] SOE**	**Sleep Quality SMD [95% CI] SOE**	**Adverse Effects SOE**
CBT-I	NR	Favors CBT-I. ISI: WMD = -7.10 [-12.87 to -1.32]; k = 4 (130). Low	Favors CBT-I. WMD = -26.50 [-43.25 to -9.75]. Low	NS Insufficient	Favors CBT-I. WMD = -38.18 [-65.57 to -10.78]. Low	Favors CBT-I. WMD = 13.22 [5.07 to 21.38]. Low	Insufficient	Insufficient

CBT-I = cognitive behavioral therapy for insomnia; CI = confidence interval; ISI = Insomnia Severity Index; k = number of studies; NR = not reported; SMD = standardized mean difference; SOE = strength of evidence; WMD = weighted mean difference

efficiency by over 6 percentage points (95% CI, 3 to 9 percentage points). Evidence for global outcomes, total sleep time and adverse effects was insufficient to draw conclusions.

Two RCTs (n = 141) studied the efficacy of sleep restriction in older adults. The mean age across two studies reporting age was close to 70, the majority of study participants were female, and almost all were white (in the trial that reported race).[43] Evidence was insufficient to draw conclusions for global or sleep outcomes or adverse effects.

Two RCTs (n = 113) studied the efficacy of stimulus control in older adults. Low-strength evidence showed that total sleep time improved 40 minutes more with stimulus control than with passive control.

Four RCTs (n = 132) studied the efficacy of CBT-I in adults with pain. Low-strength evidence showed that global outcomes were better in the CBT-I participants than passive controls, as indicated by a 7-point lower mean ISI score (95% CI, -12.87 to -1.32), showing that many patients will gain important benefits from treatment. Low-strength evidence showed that CBT-I decreased sleep onset latency by over 26 minutes (95% CI, -43.25 to -9.75), decreased wake time after sleep onset by over 38 minutes (95% CI, -65.57 to -10.78), and improved sleep efficiency by over 13 points (95% CI, 5.07 to 21.38 percentage points). Low-strength evidence showed that CBT-I and passive treatment were similar in improving total sleep time in adults with pain.

Many other comparisons were studied in remaining trials. Similar comparisons and the volume of adequately reported data necessary for pooling limited the amount of analysis that could be conducted with these data.

Efficacy, Comparative Effectiveness, and Adverse Effects of Pharmacologic Interventions

Key points regarding pharmacologic interventions are as follows:

- Most RCTs were small and of short duration. MIDs were often not established or used. We found no eligible trials for many insomnia treatments, and some insomnia pharmacologic treatments are not specifically approved for insomnia disorders.
- Evidence from RCTs indicated that some pharmacologic interventions improve short-term global and sleep outcomes in selected populations without evidence of serious short-term adverse effects. Effect sizes varied and a large placebo response was observed. Applicability, comparative effectiveness, and long-term efficacy and adverse effects, especially among older adults, are less well known.
- Nonbenzodiazepine hypnotics have low- to moderate-strength evidence for efficacy on global and some sleep outcomes in the general adult population. Improvements over placebo in sleep outcomes were higher with eszopiclone and zolpidem than zaleplon. Results for adverse effects were mixed, with few differences compared with placebo.
- Low-strength evidence shows that eszopiclone improved one global outcome by a MID and improved several sleep outcomes, but not sleep onset latency, in older adults. Evidence on adverse effects was insufficient. Low-strength evidence showed that zolpidem improved sleep onset latency in older adults. Evidence on other outcomes was insufficient.
- Ramelteon, a melatonin agonist, did not improve global or sleep outcomes in a clinically meaningful way in the general population when compared with placebo. Withdrawals were higher with ramelteon (low-strength evidence), but withdrawals for adverse effects and number of patients with more than one adverse effect were similar in both groups (low- and moderate-strength evidence, respectively).
- Very few benzodiazepine trials met eligibility criteria. Data were insufficient to assess any global, sleep, or adverse effect outcomes in the general adult or older adult populations.
- In older adults, improvement in ISI scores favored doxepin 1–6 mg compared with placebo. There was low- to moderate-strength evidence that doxepin improved sleep outcomes.
- Data on long-term adverse effects, derived from observational studies, suggest that use of hypnotics may be associated with dementia. The effect on mortality was inconsistent. Zolpidem, but not benzodiazepines, may be associated with fractures. Withdrawal due to any reason was common, especially with ramelteon.
- Suvorexant, an orexin receptor antagonist, improved global and sleep outcomes versus placebo (moderate-strength evidence). Adverse effects did not differ between groups.
- Four small trials compared CBT-I versus nonbenzodiazepine hypnotics or benzodiazepines. Results were mixed and evidence was insufficient.

We identified 38 RCTs that evaluated pharmacologic treatments for insomnia disorder in the general adult population (Table F) and in older adults (Table G). We found the most data on the newer FDA-approved drugs.

Nonbenzodiazepine hypnotics have the strongest evidence of efficacy in the general adult population. Fourteen RCTs studied nonbenzodiazepine hypnotics in the general adult population: eszopiclone (3 RCTs; n = 1,929); zaleplon (2 RCTs; n = 973); zolpidem (6 RCTs; n = 844); zolpidem "as needed" (3 RCTs; n = 607); zolpidem sublingual (SL) (1 RCT; n = 295); and zolpidem extended release (ER) (1 RCT; n = 1,018). Global outcomes were reported only for eszopiclone, zolpidem "as needed," and zolpidem ER. Eszopiclone and zolpidem improved global outcomes, and eszopiclone and zolpidem "as needed" led to decreases in wake time after sleep onset and increases in total sleep time. Zolpidem and zaleplon improved sleep quality (moderate-strength evidence). However, only zolpidem improved sleep onset latency and total sleep time (moderate-strength evidence). Results for adverse effects varied across the different drugs and typically were not different from placebo. Adverse effects reported did not appear to be serious and included somnolence, unpleasant taste, and myalgia with eszopiclone, and somnolence with zolpidem.

Fewer trials assessed nonbenzodiazepine hypnotics in older adults with insomnia (Table G). Those that enrolled only older adults randomized participants to low doses of the drug. One study (n = 388) found low-strength evidence that eszopiclone 2 mg increased the percentage of patients having a MID in global outcomes versus placebo (37% vs. 24%). Evidence was insufficient to assess zolpidem.

Three RCTs (n = 2,811) studied the newly approved medication for insomnia suvorexant (Belsomra®). Fifty-five percent of participants were considered responders to 15 mg or 20 mg doses of suvorexant, compared with 42 percent taking placebo. All sleep outcomes were improved as well. Withdrawals due to adverse effects (3% with suvorexant; 5% with placebo) and the number of participants experiencing more than one adverse effect (46% with suvorexant; 47% with placebo) were similar in treatment and placebo groups. Somnolence was the most frequently reported adverse effect. Serious adverse effects were rare and not statistically different from placebo.

Six RCTs studied melatonin and melatonin agonists in the general adult population. One studied melatonin prolonged release (n = 711) and five studied ramelteon (n = 3,124). Global outcomes were not reported and evidence was insufficient on sleep outcomes for melatonin. Ramelteon did not improve sleep outcomes in clinically meaningful ways.

One RCT (n = 829) studied the efficacy of ramelteon in older adults. No global outcomes were reported. Sleep onset latency improved by a mean of 10 minutes, but there were no differences over placebo in total sleep time or sleep quality. Data were insufficient for adverse effects.

Few benzodiazepine or antidepressant trials met eligibility criteria, primarily because of short treatment durations. Evidence on temazepam was insufficient for global, sleep, and adverse effect outcomes in the general and older adult populations. Low-strength evidence from one trial (n = 221) found that doxepin 3 and 6 mg improved total sleep time and wake time after sleep onset in the general adult population. In older adults, improvement in ISI scores favored doxepin 1–6 mg compared with placebo. The mean difference in ISI scores was small (-1.7 points [95% CI, -2.6 to -0.9]) (moderate-strength evidence). There was low- to moderate-strength evidence that doxepin improved sleep parameters. There were no differences in overall study withdrawals or participants reporting at least one adverse event between the doxepin and placebo groups. Few eligible trials studied the comparative effectiveness of different drugs in treating insomnia. One study comparing zolpidem with temazepam provided insufficient evidence for all global, sleep, and adverse effect outcomes. Zolpidem and zaleplon achieved similar levels of sleep quality (moderate strength of evidence) and had similar levels of adverse effects (low strength of evidence).

Four moderate risk-of-bias trials compared CBT-I with a commonly used sleep medication—zolpidem (k [number of studies] = 2) or temazepam (k = 2)—or combined psychological and pharmacologic treatment versus either drug alone.[44-47] Only one study (zolpidem combined with CBT-I vs. CBT-I alone; n = 163) reported the percent of responders or remitters based on global outcomes. Evidence was insufficient for global outcomes and sleep outcomes, although differences were generally small and not significant.

Somnolence, unpleasant taste and myalgias, as well as any serious adverse effects, were higher with eszopiclone than placebo. Adverse effects, including study withdrawals, did not differ between zaleplon and placebo. Withdrawals due to adverse effects, but not any specific adverse effect or overall withdrawals, were greater with zolpidem than placebo (6% vs. 3%). Some specific adverse effects were noted with greater frequency in trials evaluating "as needed," SL, or ER zolpidem compared with placebo.

Table F. Pharmacologic interventions for insomnia disorder in the general adult population								
Pharmacologic Treatment Category	**Pharmacologic Intervention; Total Number of Trials (Total Enrolled)**	**Responders or Remitters Based on Global Scores, RR [95% CI], SOE**	**Global Symptom Scores, Mean Difference Between Groups [95% CI], SOE**	**Sleep Onset Latency WMD in Minutes [95% CI], SOE**	**Total Sleep Time WMD in Minutes [95% CI], SOE**	**Wake After Sleep Onset WMD in Minutes [95% CI], SOE**	**Total Withdrawals [95 % CI], SOE**	**Adverse Effects (≥1 AE per Participant) [95 % CI], SOE**
Nonbenzodiaze-pine Hypnotics	Eszopiclone 2 or 3 mg; 3 (1,929)	Remitters:[a] 50% vs. 19%; RR, 2.7 [2.1 to 3.4]; k = 1 (825). Low	ISI: -4.6 [-5.3 to -3.9]; k = 1 (828). Low	-19.1 [-24.1 to -14.1]; k = 3 (1,820). Moderate	44.8 [35.4 to 54.2]; k = 3. Moderate	-10.8 [-19.8 to -1.70]; k = 3. Low	Lower. 33% vs. 41%; RR, 0.8 [0.7 to 1.0]; k = 3. Low	Higher. 79% vs. 64%; RR, 1.2 [1.1 to 1.4]; k = 2 (1,616). Moderate
	Zaleplon 5-20 mg; 2 (973)	NR	NR	5 mg: 2.5 [-9.3 to 14.3]; k = 1[b] (208) 10 mg: -9.9 [-19.5 to -0.4]; k = 1 (209). Insufficient	NS in both trials (results not pooled). Low	NR	NS. 12% vs. 8%;[c] RR, 1.4 [0.9 to 2.3]; k = 2 (971). Low	NS. 71% vs. 73%;[c] RR, 0.96 [0.9 to 1.1]; k = 2 (965). Moderate
	Zolpidem 10 or 15 mg; 6 (844)	NR	NR	-15.0 [-22.1 to -7.8]; k = 4[d] (373). Moderate	23.0 [2.0 to 43.9]; k =3 (167). Moderate	NR	NS. 15% vs. 12%; RR, 1.2 [0.8 to 1.7]; k = 6. Low	NS. 68% vs. 67%; RR, 1.05 [0.9 to 1.2]; k = 4 (698). Moderate
	Zolpidem 10 mg as needed; 3 (607)	"Much/ very much improved":[e] 54% vs. 24%; RR, 2.2 [1.6 to 3.2]; k = 1 (243). Low	NA	-14.8 [-23.4 to -6.2]; k = 2 (355). Moderate	48.1 [34.8 to 61.5]; k = 2 (355). Moderate	NS (results not pooled). k = 2 (437). Low	NS. 13% vs. 13%; RR, 1.0 [0.5 to 2.0]; k = 3. Low	NS. 19% vs. 15%; RR, 1.3 [0.7 to 2.2]; k = 1 (245). Insufficient

Table F. Pharmacologic interventions for insomnia disorder in the general adult population (continued)

Pharmacologic Treatment Category	Pharmacologic Intervention; Total Number of Trials (Total Enrolled)	Responders or Remitters Based on Global Scores, RR [95% CI], SOE	Global Symptom Scores, Mean Difference Between Groups [95% CI], SOE	Sleep Onset Latency WMD in Minutes [95% CI], SOE	Total Sleep Time WMD in Minutes [95% CI], SOE	Wake After Sleep Onset WMD in Minutes [95% CI], SOE	Total Withdrawals [95 % CI], SOE	Adverse Effects (≥1 AE per Participant) [95 % CI], SOE
Nonbenzodiazepine Hypnotics (contniued)	Zolpidem 3.5 mg SL; 1 (295)	NR	NR	-18 [CI NR] after middle-of-the-night awakening. Low	NR	Insufficient (results NR).	NS. 8% vs. 6%; RR, 1.4 [0.6 to 3.4]. Insufficient	NR
	Zolpidem 12.5 mg ER; 1 (1,018)	"Much/ very much improved":[e] 85% vs. 48%; RR, 1.8 [1.6 to 2.0] (1,016). Low	NA	Approximately 9 minutes [CI NR]. Low	Approximately 25 minutes [CI NR]. Low	Approximately 16 minutes [CI NR]. Low	Lower. 36% vs. 48%; RR, 0.7 [0.6 to 0.9]. Low	Higher. 63% vs. 51%; RR 1.2 [1.1 to 1.4]. Low
Orexin Receptor Antagonist	Suvorexant 15 or 20 mg; 2 (1,260)	Responders:[f] 55% vs. 42%; RR, 1.3 [1.2 to 1.5]. Moderate	ISI -1.2 [-1.8 to -0.6]. Moderate	-6.0 [-10.0 to -1.9]. Moderate	16.0 [4.7 to 27.2]. Moderate	-4.7 [-8.9 to -0.5]. Moderate	NS. 12% vs. 12%; RR, 0.95 [0.7 to 1.3]. Low	NS. 46% vs. 47%; RR, 1.0 [0.9 to 1.1]. Moderate
Melatonin Agonists	Melatonin prolonged release 2 mg; 1 (711)	NR	PSQI -0.4 [-0.7 to -0.1]. Insufficient	-6 [-10 to -2.1]. Insufficient	NR	NR	NS. 21% vs. 24%; 0.9 [0.6 to 1.2]. Insufficient	NS. 74% vs. 77%; 0.96 [0.9 to 1.1]. Insufficient
	Ramelteon 4 to 16 mg; 5 (3,124)	NR	NR	-3.1 [-7.4 to 1.2]; k = 5 (2,972). Low	0.1 [-10.0 to 10.1]; k = 5 (2,781). Low	5.9 [-6.1 to 17.9]; k =2 (721). Low	Higher. 12% vs. 10%; RR, 1.5 [1.1 to 1.9]; k = 2 (1,594). Low	NS. 46% vs. 46%; RR, 1.0 [0.9 to 1.1]; k = 3 (1,999). Moderate
Benzodiazepine Hypnotic	Temazepam 7.5 up to 30 mg; 1 (39)	NR	NR	-30.9 [-50.4 to -11.4]. Insufficient	93.5 [47.6 to 139.4]. Insufficient	NR	NS. 1.4 [0.3 to 7.6]. Insufficient	NS. 6.7 [0.4 to 121.1]. Insufficient

Table F. Pharmacologic interventions for insomnia disorder in the general adult population (continued)								
Pharmacologic Treatment Category	**Pharmacologic Intervention; Total Number of Trials (Total Enrolled)**	**Responders or Remitters Based on Global Scores, RR [95% CI], SOE**	**Global Symptom Scores, Mean Difference Between Groups [95% CI], SOE**	**Sleep Onset Latency WMD in Minutes [95% CI], SOE**	**Total Sleep Time WMD in Minutes [95% CI], SOE**	**Wake After Sleep Onset WMD in Minutes [95% CI], SOE**	**Total Withdrawals [95 % CI], SOE**	**Adverse Effects (≥1 AE per Participant) [95 % CI], SOE**
Antidepressants	Doxepin 3 mg or 6 mg; 1 (229)	NR	NR	NR	3 mg: 12 [CI NR]. 6 mg: 17 [CI NR]. Low	3 mg: -10 [CI NR]. 6 mg: -14 [CI NR]. Low	NS. 12% vs. 12% (both trials included); RR, 1.0 [0.5 to 2.0]. Insufficient	NS. 42% vs. 43% (both trials included); RR, 1.1 [0.96 to 1.3]. Low
	Doxepin 25 up to 50 mg; 1 (47)	NR	NA	NR	NR	NR	NR	NR
Comparative Effectiveness	Zolpidem 10 mg vs. temazapam 20 mg; 1 (223)	"Much/very much improved": 22% vs. 33%; RR, 0.7 [0.4 to 1.3]. Insufficient	NA	0.0 [-10.4 to 10.4]. Insufficient	27.0 [2.1 to 51.9]. Low	1.0 [-10.5 to 12.5]. Insufficient	NR	NR
	Zolpidem 10 mg vs. CBT-I; 1 (30)	NR	NR	24.6 [-3.1 to 52.3]. Insufficient	17.7 [-33.4 to 68.8]. Insufficient	NR	NS. 13% vs. 7%; RR, 2.0 [0.2 to 19.8]. Insufficient	NR
	Temazepam 7.5–30 mg vs. CBT-I; 1 (39)	NR	NR	-12.0 [-20.9 to -3.1] favors temazepam. Insufficient	42.6 [6.3 to 79.0] favors temazepam. Insufficient	5.1 [-2.3 to 12.5]. Insufficient	NS. 15% vs. 0%; RR, 6.7 [0.4 to 121.1]. Insufficient	NR

Table F. Pharmacologic interventions for insomnia disorder in the general adult population (continued)

Pharmacologic Treatment Category	Pharmacologic Intervention; Total Number of Trials (Total Enrolled)	Responders or Remitters Based on Global Scores, RR [95% CI], SOE	Global Symptom Scores, Mean Difference Between Groups [95% CI], SOE	Sleep Onset Latency WMD in Minutes [95% CI], SOE	Total Sleep Time WMD in Minutes [95% CI], SOE	Wake After Sleep Onset WMD in Minutes [95% CI], SOE	Total Withdrawals [95 % CI], SOE	Adverse Effects (≥1 AE per Participant) [95 % CI], SOE
Comparative Effectiveness (continued)	Zolpidem 5–10 mg vs. zolpidem and BT-I; 1 (33)	NR	NR	20.2 [-17.0 to 57.4]. Insufficient	6.0 [-57.1 to 69.1]. Insufficient	NR	NS. 13% vs. 28%; RR, 0.5 [0.1 to 2.1]. Insufficient	NR
	Temazepam 7.5–30 mg vs. temazepam and CBT-I; 1 (39)	NR	NR	2.3 [-5.1 to 9.7]. Insufficient	9.4 [-30.0 to 49.3]. Insufficient	NR	NS. 15% vs. 5%; RR, 2.9 [0.3 to 25.1]. Insufficient	NR
	Combined zolpidem and CBT-I vs. CBT-I; 2 (193)	Remitters:[g] 45% vs. 39%; RR, 1.2 [0.8 to 1.7]; k =1 (149). Insufficient	ISI -0.5 [-1.6 to 0.6]; k = 1 (160). Insufficient	7.1 [-1.4 to 15.6]. Low	4.5 [-30.5 to 39.4]. Insufficient	-14.2 [-25.1 to -3.4] ↑ combined; k = 1 (160). Low	NS. 11% vs. 6%; RR, 1.7 [0.7 to 4.6]. Insufficient	NR
	Combined temazepam and CBT-I vs. CBT-I; 1 (38)	NR	NR	-14.3 [-23.5 to -5.1] ↑ combined. Insufficient	33.2 [-3.1 to 69.5]. Insufficient	NR	NS. 5% vs. 0%; RR, 3.0 [0.1 to 69.3]. Insufficient	NR

AE = adverse effect; CBT-I = cognitive behavioral therapy for insomnia; CI = confidence interval; ER = extended release; ISI = Insomnia Severity Index; k = number of studies; NA = not applicable; NR = not reported; NS = no statistical difference between groups; PSQI = Pittsburgh Sleep Quality Index; RR = risk ratio; SL = sublingual; SOE = strength of evidence; WMD = weighted mean difference

[a]Indicated by an ISI score <7 at endpoint.

[b]One trial could not be pooled (lower median sleep time with 10 mg dose but not 5 mg dose at week 4).

[c]Includes doses other than 5 or 10 mg.

[d]Two other trials could not be pooled. (One trial reported improvement vs. placebo and one reported no difference between groups.)

[e]Clinical Global Impression.

[f]Indicated by a ≥6 point improvement from baseline in the ISI score.

[g]Indicated by an ISI score <8 at endpoint.

Table G. Pharmacologic interventions for insomnia disorder in older adults								
Pharmacologic Treatment Category	**Pharmacologic Intervention; Total Number of Trials (Total Enrolled)**	**Responders or Remitters Based on Global Scores, RR [95% CI], SOE**	**Global Symptom Scores, Mean Difference Between Groups [95% CI], SOE**	**Sleep Onset Latency WMD in Minutes [95% CI], SOE**	**Total Sleep Time WMD in Minutes [95% CI], SOE**	**Wake After Sleep Onset WMD in Minutes [95% CI], SOE**	**Total Withdrawals [95 % CI], SOE**	**Adverse Effects (≥1 AE per Participant) [95 % CI], SOE**
Nonbenzodiaze-pine Hypnotics	Eszopiclone 2 mg; 1 (388)	Remitters:[a] 37% vs. 24%; RR, 1.5 [1.1 to 2.1]. Low	ISI -2.3 [-3.3 to -1.3]. Low	-4.7 [-14.1 to 4.7]. Insufficient	30.0 [19.7 to 40.3]. Low	-21.6 [-29.6 to -13.6]. Low	NS. 24% vs. 24%; RR, 1.0 [0.7 to 1.5]. Insufficient	NS. 59% vs. 51%; RR, 1.2 [0.98 to 1.4]. Insufficient
	Zolpidem 5 mg; 1 (166)	NR	NR	-18.3 [-31.5 to -5.4]. Low	18.2 [-3.2 to 39.6]. Insufficient	NR	NS. 7% vs. 12%; RR, 0.6 [0.2 to 1.6]. Insufficient	NS. 63% vs. 56%; RR, 1.1 [0.9 to 1.5]. Insufficient
Melatonin Agonist	Ramelteon 4–8 mg; 1 (829)	NR	NR	-10.1 [-15.6 to -4.6]. Low	5.9 [-2 to 13.8]. Insufficient	NR	NS. 15% vs. 17%; RR, 0.9 [0.6 to 1.2]. Insufficient	NS. 56% vs. 51%; RR, 1.1 [0.96 to 1.3]. Insufficient
Benzodiazepine Hypnotic	Temazepam; 1 (40)	NR	NR	NR	33.2 [-7.1 to 73.5]. Insufficient	-22.3 [-36.3 to -8.3]. Insufficient	NS. 15% vs. 10%; RR, 1.5 [0.3 to 8.0]. Insufficient	NR
Antidepressant	Doxepin 1–6 mg; 2 (495)	NR	ISI -1.7 [-2.6 to -0.9]. k = 2 (494) Moderate	-14.7 [-24.0 to -5.4]. k = 1 (240) Low	23.9 [12.0 to 35.7]. k = 2 (494) Moderate	-17.0 [-29.3 to -4.7]. k =1 (254) Low	NS. 7% vs. 11%; RR, 0.6 [0.4 to 1.1]. k = 2 (495) Low	NS. 32% vs. 34; RR, 0.9 [06 to 1.3]. k = 2 (495) Low

Table G. Pharmacologic interventions for insomnia disorder in older adults (continued)								
Pharmacologic Treatment Category	**Pharmacologic Intervention; Total Number of Trials (Total Enrolled)**	**Responders or Remitters Based on Global Scores, RR [95% CI], SOE**	**Global Symptom Scores, Mean Difference Between Groups [95% CI], SOE**	**Sleep Onset Latency WMD in Minutes [95% CI], SOE**	**Total Sleep Time WMD in Minutes [95% CI], SOE**	**Wake After Sleep Onset WMD in Minutes [95% CI], SOE**	**Total Withdrawals [95 % CI], SOE**	**Adverse Effects (≥1 AE per Participant) [95 % CI], SOE**
Comparative Effectiveness	Temazepam 7.5–30 mg as needed vs. CBT-I; 1 (38)	NR	NR	NR	31.9 [-4.4 to 68.2]. Insufficient	7.2 [-5.0 to 19.3]. Insufficient	NS. 15% vs. 0%; RR, 6.7 [0.4 to 115.0]. Insufficient	NR
	Temazepam 7.5–30 mg as needed vs. temazepam and CBT-I; 1 (40)	NR	NR	NR	52.0 [12.1 to 91.9]; Favors temazepam. Insufficient	8.7 [-4.3 to 21.7]; Favors temazepam. Insufficient	NS. 15% vs. 0%; RR, 3.0 [0.3 to 26.5]. Insufficient	NR
	Combined temazepam and CBT-I vs. CBT-I; 1 (38)	NR	NR	NR	-20.1 [-58.2 to 18.0]. Insufficient	-1.5 [-24.6 to 21.6]. Insufficient	NS. 5% vs. 0%; RR, 2.7 [0.1 to 62.7]. Insufficient	NR

AE = adverse effect; CBT-I = cognitive behavioral therapy for insomnia; CI = confidence interval; ISI = Insomnia Severity Index; k = number of studies; NR = not reported; NS = no statistical difference between groups; RR = risk ratio; SOE = strength of evidence; WMD = weighted mean difference

[a]Indicated by an ISI score <7 at endpoint.

However, differences were small and not considered serious. Withdrawal for any reason and withdrawals due to adverse effects did not significantly differ between suvorexant 20/15 mg and placebo short term.[48] Moderate-strength evidence was found of no difference between groups in the proportion of participants reporting at least one adverse effect. The specific adverse effect most associated with suvorexant was somnolence (7% vs. 3% for placebo). There were no differences between melatonin or ramelteon and placebo in the type or frequency of adverse effects, including withdrawals due to adverse effects. Overall withdrawals were slightly greater with ramelteon than placebo. There were no significant differences in adverse effects or study withdrawals between participants receiving doxepin versus placebo. Strength of evidence for all adverse effects was considered insufficient to low.

We included 12 observational studies for long-term harms of pharmacologic treatments of insomnia. Study limitations included possible unmeasured or unknown confounders. However, hypnotic drugs were associated with dementia (hazard ratio [HR], 2.34 [95% CI, 1.92 to 2.85]) and fractures (adjusted odds ratio, 1.72 [95% CI, 1.37 to 2.16]). The effect on mortality was inconsistent based on two studies. Zolpidem was associated with risk of major head injury or fracture requiring hospitalization (adjusted HR, 1.67 [95% CI, 1.19 to 2.34]). Both zolpidem and temazepam were associated with incident cancers. The adverse effects most frequently associated with study withdrawal from zaleplon among older adults were pain (5%), somnolence or dizziness (4%), gastrointestinal events (2%), and arrhythmias (1%). In an open-label extension of an RCT evaluating eszopiclone, serious adverse effects leading to study withdrawal occurred in 2 percent of individuals. One open-label extension study evaluated zolpidem 20 mg and noted that 19 percent of patients withdrew from the study with adverse effects. Two open-label studies (n = 1,403) reported longer term harms related to ramelteon compared with placebo. Adverse effects with ramelteon were common, but rarely severe or requiring study withdrawal. Study withdrawal for any reason occurred in 58 percent of older adults.

FDA product labels for drugs approved to treat insomnia incorporate harms data from studies that we did not include. FDA labels provide warnings about cognitive and behavioral changes, including possible driving impairment and motor vehicle accidents, and other adverse effects. Labels advise lower doses of benzodiazepine and nonbenzodiazepine hypnotics for females and older/debilitated adults. FDA recommended doses are lower than those used in some studies we included.

Efficacy, Comparative Effectiveness, and Adverse Effects of Complementary and Alternative Interventions

Key points regarding CAM interventions are as follows:

- Evidence from three systematic reviews and five RCTs provided insufficient evidence to assess the efficacy or comparative effectiveness of acupuncture, homeopathy, valerian, or magnesium for insomnia.
- We identified three systematic reviews and nine RCTs evaluating CAM treatments for insomnia disorder. They evaluated acupuncture, homeopathy, and valerian. None of the remaining trials evaluated similar comparisons. The six remaining RCTs studied Wuling capsule, bright light therapy (2 trials), isoflavones, magnesium supplementation, and chamomile extract. Evidence was insufficient for all comparisons for all outcomes.

Comparative Effectiveness and Adverse Effects Across Intervention Types

Evidence was insufficient to draw conclusions regarding the comparative effectiveness of CBT-I versus hypnotic medication or the efficacy of combination therapy versus monotherapy.

We identified 10 RCTs evaluating comparative effectiveness between intervention types or between combinations of treatments across intervention types. Most trials were small, with several arms, and assessed efficacy in the general adult population. Evidence was insufficient for all comparisons and outcomes.

Discussion

We systematically searched for literature and synthesized evidence on a comprehensive set of interventions for insomnia disorder. We identified many trials meeting eligibility criteria. We found the strongest evidence for the efficacy of CBT-I, the nonbenzodiazepine hypnotics eszopiclone and zolpidem, and the orexin receptor antagonist suvorexant. Most trials assessed efficacy in the general adult population. Evidence to assess efficacy across a variety of outcomes for other psychological and pharmacologic interventions and for all CAM interventions was limited. Evidence was insufficient to draw conclusions about comparative effectiveness across intervention classes (i.e., psychological vs. pharmacologic) or combination interventions (i.e., psychological combined with pharmacologic).

The strongest evidence for efficacy is for CBT-I in the general adult population, older adults, and adults with pain

across a variety of delivery modes. Moderate-strength evidence shows that CBT-I improves global and sleep outcomes in the general adult population. Trials used a variety of passive (i.e., inactive) comparisons, including no treatment, attention control (i.e., sleep hygiene information/education), wait-list control, and placebo (sham treatments or pills). Risk ratios ranged from 2.95 to 8.95 across measures of remission and response. The rate of remission or response ranged from 50 to 80 percent in CBT-I groups and from 0 to 50 percent in passive control groups. Some trials showed a large placebo effect. The largest placebo effects were not reported for sham treatment controls but for wait-list controls. Trials for which we were unable to conduct remitter or responder analysis showed that an appreciable number of patients gain important benefits from treatment. CBT-I consistently improved nearly all sleep outcomes in the general adult population. Unfortunately, data were limited and evidence synthesis across CBT-I delivery modes was not warranted. The range of modes available should enhance access to CBT-I.

While the evidence was not as robust for older adults and adults with pain, it is clear that these populations also gain important benefits from CBT-I. Low-strength evidence showed that CBT-I improves global and several sleep outcomes in older adults. Moderate-strength evidence showed that wake time after sleep onset improves for older adults. This result is especially important, given that older adults frequently complain of this particular sleep problem.

Low-strength evidence showed that CBT-I improves global and most sleep outcomes in adults with pain conditions. Adults in these trials had pain arising from osteoarthritis, congestive heart failure, chronic neck and back pain, and other nonmalignant pain conditions.

Evidence was limited for other psychological interventions. We identified fewer trials assessing specific interventions that had passive comparisons in similar populations, and sample sizes were typically small.

Evidence for functioning, mood, and quality-of-life outcomes was also limited. While many of the psychological intervention trials reported these outcomes, several different outcomes and many different instruments were used. Data for similar outcomes within similar comparisons were not common. Additionally, given the number of outcomes reported in some psychological intervention trials and the infrequent correction for multiple comparisons, statistical significance of one or more of these outcomes could be due to chance.

Psychological interventions are noninvasive and assumed to have low potential for physical harm to individuals, but few trials reported withdrawals, and they often reported withdrawals in the overall population as opposed to withdrawals by group. Withdrawals in psychological intervention trials may reflect intervention feasibility (i.e., the intervention requires too much time or it is inconvenient to attend weekly sessions) rather than physical or psychological harms, but reporting this information would improve understanding of these interventions in practice.

The nonbenzodiazepine hypnotics eszopiclone and zolpidem, and the orexin receptor antagonist suvorexant, improved short-term global and sleep outcomes in general adult populations. The risk ratio of remission or response with these drugs ranged from 1.3 for suvorexant to 2.7 for eszopiclone. Remitter or response rate ranged from 50 to 85 percent in the treatment groups and from 19 to 48 percent in the placebo groups, a variable and high placebo effect. Low-strength evidence shows that doxepin improved some sleep outcomes in the general adult population and in older adults. Evidence for benzodiazepine hypnotics, melatonin agonists in the general adult population, and most pharmacologic interventions in older adults was generally insufficient. Comparative effectiveness evidence was limited to a few small short-term studies, precluding meaningful comparisons between and across categories of pharmacologic agents as well as comparisons with CBT-I. Only six small studies specifically enrolled older adults. We found low-strength evidence that low doses of eszopiclone improved global and sleep outcomes in older adults.

Functioning, mood, and quality-of-life outcomes were infrequently reported in drug trials. When reported, results were mixed. When positive, the effect was typically small in magnitude.

Moderate-strength evidence shows that the proportion of trial participants with more than one adverse effect was higher with eszopiclone (2 or 3 mg) and zolpidem ER (12.5 mg) compared to placebo. High proportions of participants in treatment and placebo groups reported adverse effects. Low- to moderate-strength evidence shows that the proportion of participants with more than one adverse effect for zaleplon, zolpidem (10 or 15 mg), zolpidem (10 mg) as needed, suvorexant (15 or 20 mg), ramelteon (4 to 16 mg), and doxepin (3 to 50 mg) is similar to placebo. However, evidence on adverse effects

from randomized trials was limited and likely inadequate. Most included drug trials were 4 to 6 weeks in duration. If rare serious adverse effects are associated with these medications, it is possible that the relatively small number and short duration of the trials included in our review were not sufficient to capture them. Eligible observational studies suggested that hypnotic use is correlated with dementia, fractures, major injuries, and possibly cancer and death. FDA labels warn about cognitive and behavioral changes, including impaired driving, and other adverse effects that may be serious or life threatening. Lower doses are advised in female and older/debilitated adults, in part because data indicate that drugs remain in the system at levels high enough to interfere with morning driving in these populations.

Other researchers have also summarized adverse effects of drugs often used for insomnia using studies that were not eligible for our analysis because of study duration or other reasons. Using analyses of RCT data submitted to the FDA, Kripke found increased incidence of depression[49] and skin cancer[50] with nonbenzodiazepine hypnotics and ramelteon compared with placebo. Using pooled analyses of RCT data submitted to the FDA and published RCT data, Carson and colleagues[51] systematically assessed observational studies and case reports of nonbenzodiazepine hypnotics. They found that eszopiclone and zaleplon were associated with mild to moderate adverse effects, while zolpidem was associated with serious adverse effects, including amnesia, vertigo, confusion, and diplopia. A meta-analysis by Glass and colleagues showed that use of sedative-hypnotics compared with placebo in older patients with insomnia resulted in a fivefold increase in memory loss, confusion, and disorientation; a threefold increase in dizziness, loss of balance, and falls; and a fourfold increase in residual morning sedation, although absolute rates were low.[52] Weich and colleagues conducted a retrospective cohort study using data from the United Kingdom General Practice Research Database with mean followup of 7.6 years. Anxiolytic and hypnotic drugs were correlated with all-cause mortality.[53]

The applicability of the conclusions of this review to practice deserves discussion. Participants in trials of the general adult population were predominantly middle-aged, free of comorbid conditions, female, and white. Participants met specific diagnostic criteria for insomnia disorder (or chronic insomnia). In this respect, trial populations are likely similar to individuals in the general population with insomnia disorder, the caveat being that the individuals in the trials had insomnia disorder according to authoritative diagnostic criteria.

The drug doses used in efficacy trials may not be consistent with current prescribing practice. Drug trials for certain drugs often used doses that are no longer recommended by the FDA. For instance, the recommended dosage for zolpidem is now 5 mg. Eligible trials typically used 10 to 15 mg doses. Similarly, suvorexant's approved dose is 10 mg. Eligible trials used 15 to 20 mg doses. Therefore, it is difficult to say whether evidence from the trials in our analysis is applicable to the lower dosage of medications that will likely be prescribed. Additionally, many medications used for insomnia disorders have FDA label indications for short-term use. Other indications are for specific sleep problems, such as difficulty falling asleep.

Limitations

Current evidence has several limitations. First, data were limited for specific comparisons, despite the large number of eligible studies. RCTs of psychological interventions contained a wide variety of intervention and control conditions, limiting the data available to analyze similar comparisons. Older trials and drug trials were less likely to measure and report global outcomes.

We found limited research establishing MIDs for specific instruments commonly used to measure global outcomes. When established, few trials conducted responder analysis. This deficiency was more common in trials of psychological interventions than in drug trials. Diagnosis of insomnia disorder requires selected sleep symptoms accompanied by daytime dysfunction or distress. Most drug trials measured only sleep outcomes, which may not accurately reflect overall impact. This lack is especially important given the daytime symptoms that often accompany hypnotic drugs.

Sleep outcomes are commonly reported in insomnia efficacy and comparative effectiveness trials. However, the literature contains few established thresholds for use in assessing efficacy and effectiveness. Quantitative thresholds for changes in sleep outcomes indicating clinical improvement are not well established. When thresholds were used (e.g., 50% reduction in certain sleep outcomes,[54] achievement of sleep outcomes below specified value), it is not always clear how they were established, and remitter or responder analysis with regard to sleep parameters is not common.

Few drug trials reported baseline sleep onset latency, total sleep time, wake after sleep onset, or sleep efficiency. Thus the baseline severity of insomnia disorder or the percent change from baseline is unknown. These limitations further complicate the translation of reported changes

in sleep or global measures into clinically meaningful metrics, including percentage improvements.

Drug trials meeting our inclusion criteria were predominantly for drugs receiving more recent FDA approval. Few trials on benzodiazapines or antidepressants for insomnia disorder were identified, despite widespread use of these drugs for insomnia disorder. Many were excluded because study duration was less than 4 weeks.

Eligible drug trials rarely lasted longer than 6 weeks. We believe that excluding studies of very short duration was appropriate, given that insomnia disorder is a chronic condition often lasting years and the objective of this review was to synthesize the evidence on the treatment of insomnia disorder. Findings of safety in our review do not rule out the risk of serious adverse effects associated with long-term use or rare adverse effects.

Future Research Needs

Future research to improve our understanding of treatments for insomnia disorder should include—

- Conceptual research to establish MIDs for instruments measuring global outcomes and consensus development to identify clinically meaningful changes in sleep outcomes according to insomnia severity
- Increased use of global outcomes of insomnia treatment and responder analysis with established MIDs
- Additional trials of combined interventions with currently recommended medication dosages
- Improved documentation of study withdrawals and adverse effects
- Head-to-head comparisons of drugs, as well as comparison of drugs versus behavioral therapies
- Use of sham or placebo controls (vs. wait-list) for psychological therapies
- Greater understanding of the reason, effect, and role of placebo responses
- Pharmacologic and nonpharmacologic trials with treatment durations of 1 year or more to assess long-term efficacy, comparative effectiveness, adherence, and harms
- Systematic review of observational studies to evaluate harms associated with long-term use of interventions for insomnia disorder

Conclusions

Our review found a large number of trials and low to moderate strength evidence supporting several interventions for insomnia disorder. Our results are consistent with and strengthen previous reviews concluding the efficacy of CBT-I in both the general adult population and the older adult population. No other psychological interventions had evidence of efficacy across outcomes, largely due to the lack of a sufficient number of trials studying the same comparison. In older adults, multicomponent behavioral therapy as well as CBT-I has evidence of efficacy across several sleep outcomes.

Evidence shows the efficacy of nonbenzodiazapine hypnotics for treating insomnia disorder across several outcomes among the general adult population and older adults.

Overall, several options exist to treat insomnia disorder in adults and older adults. Psychological approaches may be more sustainable and are less likely to harm. Treatment offers global improvement as well as improved sleep to insomnia sufferers.

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