Effective Health Care Program

Comparative Effectiveness Review
Number 159

Management of Insomnia Disorder

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This report is based on research conducted by the Minnesota Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2012-00016-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Management of Insomnia Disorder

Structured Abstract

Objective. To assess the efficacy, comparative effectiveness, and harms of treatments for insomnia disorder in the general adult population and older adults.

Data sources. Ovid MEDLINE®, the Cochrane Central Register of Controlled Trials, Embase®, and PsycINFO® bibliographic databases; hand searches of references of relevant studies.

Review methods. Two investigators screened abstracts and full-text articles of identified references for eligibility. Eligible studies included systematic reviews, randomized controlled trials (RCTs), and long-term observational pharmacologic studies enrolling participants with insomnia disorder. We analyzed data for global outcomes (measures that assess both sleep and daytime functioning associated with sleep), sleep parameters, and harms. We assessed risk of bias for RCTs, extracted data, assessed quality of relevant systematic reviews, and evaluated strength of evidence for comparisons and outcomes. Pooled estimates were analyzed to assess the efficacy and comparative effectiveness of treatments.

Results. We searched bibliographic databases through January 2015 for studies evaluating psychological, pharmacologic, and complementary and alternative medicine interventions for insomnia disorder. We synthesized evidence from 181 unique studies (data from 128 unique RCTs and 3 systematic reviews that synthesize data from 42 unique RCTs) and 12 observational studies. Sample sizes and enrollment criteria varied; most trials were short in duration. Outcome reporting and intervention effect sizes varied, and a large placebo response was often observed. Cognitive behavioral therapy for insomnia (CBT-I) improved global outcomes and nearly all sleep parameters in the general adult population, older adults, and adults with pain. We found insufficient evidence on adverse effects of these interventions. Evidence was less robust for psychological interventions other than CBT-I, but low-strength evidence shows that some interventions improve some sleep outcomes. Low- to moderate-strength evidence indicated that the nonbenzodiazepine hypnotics eszopiclone and zolpidem, and the orexin receptor antagonist suvorexant, improved short-term global and sleep outcomes in general adult populations. Doxepin improved sleep outcomes. The absolute mean effect was small. Evidence for benzodiazepine hypnotics, melatonin agonists, and antidepressants in general populations and for most pharmacologic interventions in older adults was generally insufficient. Evidence on adverse effects from RCT data was generally insufficient or low strength. Observational studies suggest that hypnotics may be associated with dementia, fractures, and major injury. Food and Drug Administration (FDA) labels warn about cognitive and behavioral changes, including driving impairment, and other harms, and advise lower doses for females and older/debilitated adults. Evidence on complementary and alternative medicine was insufficient. Evidence was insufficient to compare hypnotic medications within or across classes or versus CBT-I.

Conclusions. CBT-I or medical therapy with eszopiclone, zolpidem, and suvorexant improve global and sleep outcomes for insomnia disorder. Clinical significance, applicability, comparative effectiveness, and long-term efficacy, especially among older adults, are less well known. Effect sizes vary, and a large placebo response is sometimes observed. Observational

studies suggest an association of hypnotics with infrequent but serious harms. FDA labels provide specific warnings and precautions for drugs approved for insomnia.

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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]

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.

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]

Table A. Psychological/behavioral interventions for insomnia disorder (continued)

Psychological and Behavioral Treatments for Insomnia	Definition
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.

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 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. 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]

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

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]

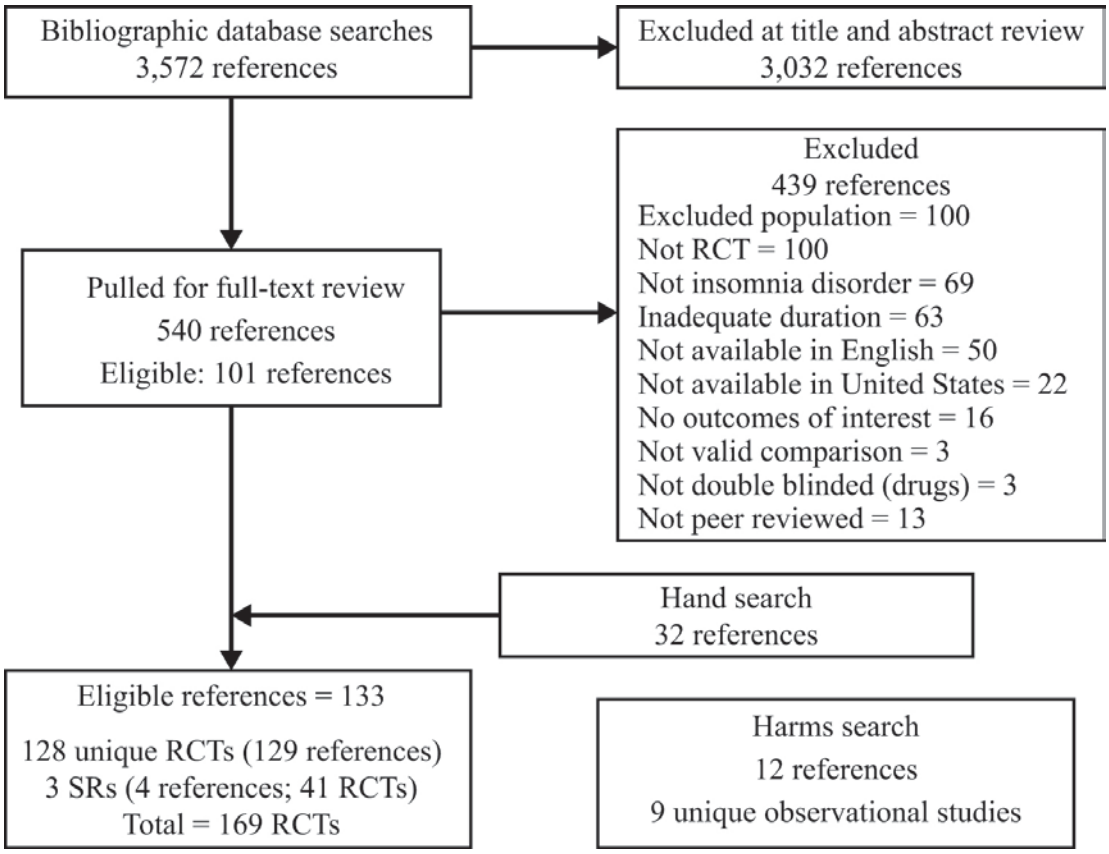
Specific factors that could modify the effect of treatment and affect the applicability of findings include diagnostic accuracy, insomnia severity, and specific patient characteristics such as age.

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.

Figure A. Literature flow diagram



RCT = randomized controlled trial; SR = systematic review

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 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 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.

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

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. 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.

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
Nonbenzo-diazepine 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
	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

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
Nonbenzo-diazepine Hypnotics (continued)	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
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	NR	NR	NR	NR	NR	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	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
	Zolpidem 5–10 mg vs. zolpidem and CBT-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

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)	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
Nonbenzo-diazepine 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.

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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Introduction

Background

Sleep problems are one of the most common complaints for adults in primary care.[1] They are associated with a decline in overall health status and perception of poor health and can have negative personal and social consequences.[2]

The term insomnia is variously defined and can 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 complaint(s): difficulty with sleep initiation, difficulty maintaining sleep, or early morning waking with inability to return to sleep.[3] Individuals with sleep problems also report higher levels of anxiety, physical pain and discomfort, and cognitive deficiencies.[4] Insomnia may be associated with long-term health consequences, including increased morbidity, respiratory disease, rheumatic disease, cardiovascular disease, cerebrovascular conditions, and diabetes.[2]

While insomnia is typically transient, some cases are persistent and can last for years.[5] 'Insomnia disorder' should be diagnosed using diagnostic criteria from the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) and/or the International Classification of Sleep Disorders (ICSD). Both have been recently updated. The fifth edition of the DSM (DSM-5)[3] is geared towards primary care and general mental health providers. Criteria for insomnia disorder require that sleep symptoms cause clinically significant distress or impairment(s) in functioning (social, occupational, educational, academic, behavioral, or other) and occur despite adequate opportunity for sleep on at least 3 nights per week for at least 3 months. Diagnosis also requires that symptoms not be primarily linked to other sleep disorders or occur exclusively during the course of another sleep-wake disorder (narcolepsy, breathing-related sleep disorder, circadian rhythm disorder); not be attributable to the physiological effects of a substance; and not be explained by coexisting mental disorders or medical conditions. Dysfunction associated with insomnia disorder includes fatigue, poor cognitive function, mood disturbance, and distress or interference with personal functioning.[1,6] Both criteria recognize sleep-related complaint(s) despite adequate opportunity for sleep combined with distress or dysfunction created by the sleep difficulty in their current and previous versions. Until recently, diagnostic criteria classified insomnia as primary or comorbid, depending on the absence or presence of other conditions. However, the DSM-5 now uses the term "insomnia disorder" and ICSD-III uses the term "insomnia;" both eliminate the distinction between primary and secondary insomnia.[3] The distinction had questionable relevance in clinical practice, and revisions reflect this understanding by suggesting a diagnosis of insomnia disorder for patients who meet diagnostic criteria, despite any coexisting conditions, unless the other condition explains the sleep problems.

Depending on how insomnia is defined, prevalence estimates range from nearly 33 percent in an international sample of primary care patients to 17 percent of U.S. adults reporting "regularly having insomnia or trouble sleeping in the past 12 months" to 6–10 percent of adults meeting established diagnostic criteria.[1,3,6,7] Insomnia disorder in the general population consists of difficulties getting to sleep and maintaining sleep.[8] Previous diagnostic criteria for insomnia did not specify a minimum timeframe for sleep difficulties; chronic insomnia was used to describe cases that lasted from weeks to months, and insomnia was considered chronic in 40 – 70 percent of cases.[6] When chronic, as with insomnia disorder, duration ranges from 1 to 20 years across longitudinal studies.[5]

Females are 1.4 times more likely than males to suffer from insomnia.[9] 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.[10] Older adults typically report difficulty maintaining sleep.[8] Many insomnia cases coexist with other conditions (especially psychiatric diagnoses and pain disorders);[11,12] however, current diagnostic criteria suggest that insomnia disorder includes sleep problems that cannot be explained by another mental or medical condition.

Insomnia disorder is associated with medical and psychiatric morbidity including hypertension and depression.[5] Insomnia disorder is also linked to reduced productivity, disability, and health care costs.[5] Annual cost estimates for insomnia in the United States range from $30 – $107 billion.[13] Direct costs of $12 – $14 billion cover expenses such as medical appointments, over-the-counter sleep aids, and prescription medication. The remainder includes indirect costs such as lost productivity due to absenteeism and presenteeism (attending work while sick, fatigued), reduced quality of life, accidents, and injuries. These costs and consequences highlight the importance of treating this condition. Treatment decisions would greatly benefit from an enhanced understanding about the efficacy and comparative effectiveness of the wide variety of treatments available.

Insomnia is often not diagnosed and may remain untreated.[5] Other individuals suffering from sleep problems tend to seek treatment when symptoms become bothersome (e.g., distress, fatigue, daytime functioning, cognitive impairment).[13] Once insomnia disorder is accurately diagnosed, many treatments are available (Table 1), 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.

Current guidelines also stress the importance of identifying and treating coexisting conditions. Various treatment options described in the guidelines include psychological and behavioral interventions, drugs, and combined approaches.[14] The American Academy of Sleep Medicine (AASM) practice parameters state that psychological and behavioral interventions are effective and recommended for primary chronic insomnia and secondary insomnia (ICSD-II criteria) in adults.[14,15] Support for short-term use of pharmacological interventions was based on consensus.[14] However, an updated review of evidence synthesis and recommendations on these interventions is underway.[16] Combined or stepped care interventions are also used in treatment. Combination therapy specifies the timing of certain intervention components.[17] The stepped care model has been described in terms of how limited cognitive behavioral therapies for insomnia (CBT-I) could be used.[18] These approaches are designed to maximize treatment benefits and minimize harms while assisting in efficient delivery of services at the level appropriate for the patient.

Psychological interventions include multicomponent interventions such as CBT-I or brief behavioral therapy (BBT) or single-component treatments such as stimulus control alone, progressive relaxation alone, or sleep restriction alone (Table 2).

Table 1. Examples of treatments for insomnia in adults studied in the literature

Treatment Category	Treatment
Psychological	Sleep hygiene education Stimulus control Sleep restriction Relaxation training Paradoxical intention Biofeedback Imagery training Brief behavioral therapy (BBT) Cognitive behavioral therapy (CBT)
Complementary and Alternative Medicine (CAM)	Acupuncture Acupressure Cupping Homeopathy Hypnotherapy Reflexology Tai Chi Yoga Herbal/dietary supplements • Bach Flower • Isoflavones • L-tryptophan • Magnesium • Melatonin • Valerian
Miscellaneous	Aroma therapy Bright light Exercise Music therapy
Medications[b]	*Generic name*
Medications - antihistamines	Diphenhydramine Doxylamine
Medications - Prescription antidepressants	Amitriptyline Doxepin[a] Trazodone Mirtazapine
Medications – Prescription antipsychotics	Olanzapine Quetiapine
Medications –Prescription hypnotics	<u>Benzodiazepines</u> Alprazolam Clonazepam Estazolam[a] Flurazepam[a] Lorazepam Quazepam[a] Temazepam[a] Triazolam[a] <u>Nonbenzodiazepines</u> Eszopiclone[a] Zaleplon[a] Zolpidem[a]
Medications - melatonin receptor agonist	Melatonin Ramelteon[a]
Medications – Prescription antipsychotics	Gabapentin Pregabalin
Medications – Prescription orexin receptor antagonist	Suvorexant[a]

BBT = brief behavioral therapy; CBT = cognitive behavioral therapy

[a] FDA approved to treat insomnia

Table 2. Psychological/behavioral interventions for insomnia disorder[15,19]

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; regular exercise; maintaining a quiet and dark bedroom.
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
Sleep restriction	Behavioral intervention that limits time in bed to sleep time, gradually increasing as sleep efficiency improves. Techniques include setting strict bedtime and rising schedules; keeping a set wake-up time; with modifications based upon sleep efficiency after certain duration.
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.
Brief Behavioral Treatment	Combines core behavioral interventions of stimulus control and sleep restriction.
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, sleep is out of their control, and fears about missed sleep; thought journaling; behavioral experiments around sleep beliefs.
Cognitive behavior therapy	A multimodal combination of treatments that include cognitive therapy around sleep and behavioral interventions (sleep restriction, stimulus control) and education (sleep hygiene).

Adapted from Morgenthaler T, Kramer M, Alessi C, et al.[15] and Buysse.[19] See Buysse for more detailed description and specific techniques.

Despite recommendations to treat insomnia with psychological treatments, insomnia disorder is often treated with prescription medication. Several prescribed medications are FDA approved for the indication of 'insomnia.' However, approval appears to be for specific insomnia symptoms and label indications are not consistent with established diagnostic criteria. Medications of varying half-lives that are FDA approved for insomnia symptoms include doxepin, triazolam, estazolam, temazepam, flurazepam, quazepam, zaleplon, zolpidem, eszopiclone, ramelteon, and suvorexant. Newer drugs such as nonbenzodiazapine hypnotics and suvorexant typically have shorter half-lives than the benzodiazepine hypnotics. Additionally, drugs can be formulated to address specific problem (i.e., long acting to help with middle of the night awakening or short acting that can be taken in the middle of the night. The FDA specifically suggests 'short term use' in their approval for many of these medications including zolpidem products, zaleplon, triazolam, and temazepam and specifically states that 'prolonged use of hypnotics is usually not indicated.[20] The FDA has lowered recommended dosages in certain approved nonbenzodiazapines, especially for females. These and other prescription medications are used off-label for insomnia disorder.

Efficacy research has also been conducted on a variety of CAM approaches (Chinese herbal medicine, acupuncture, reflexology, Suanzaoren decoction, etc.). Unfortunately, methodological limitations have prevented conclusive evidence synthesis for these treatments.[21-30]

Insomnia treatment goals include meaningful improvements in sleep and associated distress and/or dysfunction. Insomnia treatment may affect several types of outcomes. Ideally,

improvements in both sleep and daytime functioning occur and distress associated with sleep problems is reduced. We call instruments (questionnaires) that simultaneously measure these constructs global outcomes. Sleep outcomes include measurements of specific elements of sleep. Better sleep should improve the specific elements of daytime functioning or distress associated with the sleep problems. Among these outcomes are functioning, mood, and quality of life.

Global outcomes are typically measured using questionnaires that contain items assessing sleep and daytime functioning and distress. Unfortunately, many currently available sleep outcome questionnaires were developed to identify poor sleepers and are not adequately sensitive to detect clinically meaningful treatment effects.[31] Two commonly used instruments that measure both constructs include the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI).

Sleep outcomes, the most frequently reported outcomes in insomnia disorder treatment literature, include sleep-onset latency, number of awakenings, wake time after sleep onset, and total sleep time, and sleep efficiency (total sleep time/total time in bed). Improvements in these specific sleep measures can be measured objectively or subjectively. Sleep parameters are objectively measured with polysomnography (measuring sleep continuity parameters, sleep time spent in each stage) or actigraphy (measuring body movements). Despite discrepancies between objective and subjective measures of sleep parameters, subjective measures are considered more valuable because they are considered patient-centered outcomes. Sleep quality, subjectively measured in a variety of ways, is also an important measure.

Many different instruments measuring function, mood, and quality of life outcomes have been used in insomnia efficacy and comparative effectiveness research. Among these are the Short-form Health Survey [SF-36];[14,32] Sickness Impact Profile Scale;[32] and World Health Organization Quality of Life (WHOQOL).[32]

Several systematic reviews have assessed the efficacy and comparative effectiveness of insomnia treatment. Available reviews, however, do not incorporate the broad range of interventions (psychological and behavioral, pharmacologic, CAM) or target guideline developers with the specific intention of improving the treatment of insomnia disorder in primary care and general mental health settings. This review identifies 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.

Scope and Key Questions

Preliminary Key Questions for this review were posted for public comment in October 2013. We received several comments useful in revising the Key Questions to better address stakeholder concerns in the most meaningful and efficient way.

Public comments suggested possible contamination by including studies that enroll patients with insomnia as well as other conditions. However, we believe that studies enrolling subjects with the wide variety of conditions (heart disease, diabetes, anxiety/depression, and other chronic medical or psychiatric conditions) accurately reflect the patient population; thus we included these. However, we excluded studies that strictly enroll subjects with a diagnosis that could explain the sleep problems, such as Parkinson's disease or post-traumatic stress disorder.

Public comments also expressed concern over the subjective nature of many outcomes and their associated measurement instruments. While patient-reported outcomes have disadvantages, they are considered patient-centered and thus the best way to assess improvements in response to treatment. By examining the marginal improvement over appropriate control conditions, we hope

to better capture the patient's perceived treatment effect. Additionally, because insomnia disorder is typically treated in primary care settings and polysomography is not recommended by the American Academy of Sleep Medicine in diagnosing insomnia disorder, polysomography data are not likely to translate to clinical practice. Polysomography and referral to sleep medicine is recommended as a last resort and to rule out other sleep disorders when suspected.

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 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

PICOTS (populations, interventions, comparators, outcomes, timing, and setting) are shown below.

Population(s)

- Adults, age 18 and above, 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

(Table 1 lists examples of specific interventions in each category.)

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

Comparators

- Drug and CAM supplement efficacy trials must be double-blind placebo controlled. 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

- KQ1
    - 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 [i.e., Insomnia Severity Index (ISI);[14,32] Pittsburgh Sleep Quality Index (PSQI);[15,32] Patient Global Impression (PGI) 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: [i.e., Beck Depression Inventory (BDI);[14,32] State-Trait Anxiety Inventory (STAI);[14,32] Short-form Health Survey (SF-36);[14,32] World Health Organization Quality of Life (WHOQOL);[32]]; Epworth sleepiness scale (ESS);[14] or Fatigue Severity Scale (FSS).[14,32]]
- KQ2
    - Adverse effects of intervention(s)
        - Any adverse effects (e.g., headache, somnolence, myalgia, poor taste, dependence, falls, abnormal sleep behaviors, etc.). Timing for adverse effects will be similar to that of other outcomes (see Timing).

Timing

- KQ1: Outcomes measured at 4 weeks to 3 months after initiation of treatment will be used to assess efficacy/comparative effectiveness.
- KQ1c. Followup measures beyond 3 months of treatment will be used to evaluate long-term efficacy and comparative effectiveness.

Settings

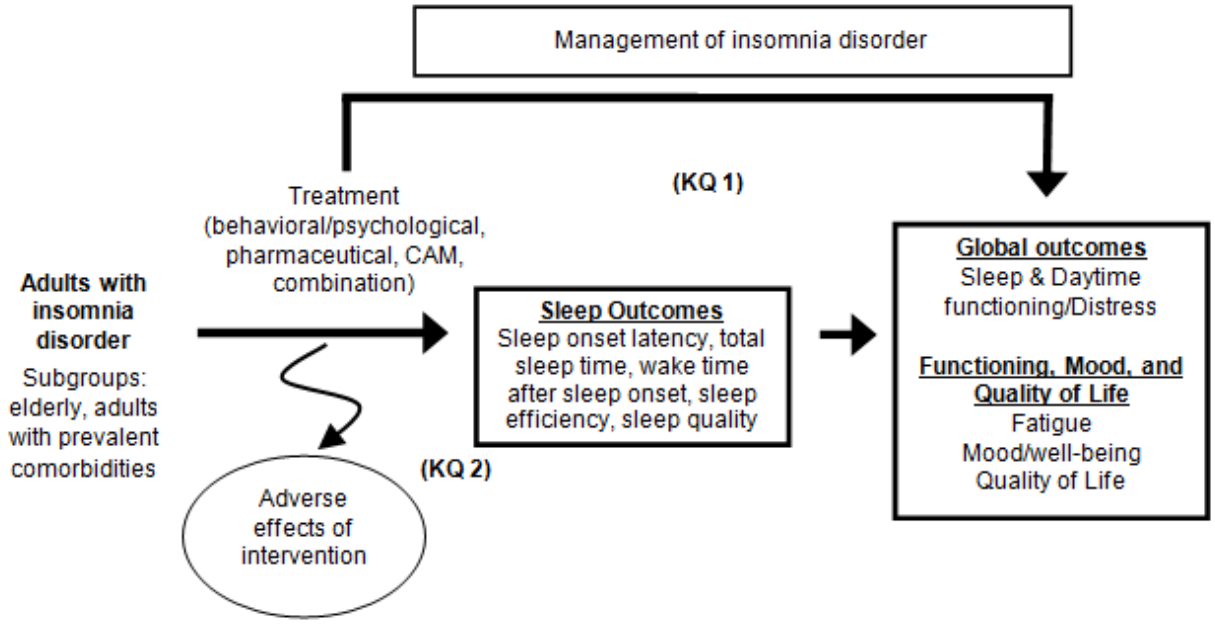
- Any outpatient setting

Methods

Analytic Framework

Figure 1 provides an analytic framework to illustrate the population, interventions, outcomes, and adverse effects that will guide the literature search and synthesis.

Figure 1. Analytic framework



CAM = complementary and alternative interventions; KQ = Key Question

Criteria for Inclusion/Exclusion of Studies in the Review

We included or excluded studies based on the PICOTS framework outlined above and the study-specific inclusion criteria described in Table 3. Treatments for insomnia disorder in primary care settings needed to address certain subpopulations such as the elderly. Coexisting diseases are common among patients with sleep problems, so we included studies that enrolled participants with comorbidities (sometimes called 'secondary insomnia') and trials enrolling pure subgroups of patients with certain conditions (i.e., anxiety, mild depression, noncancer pain). Other medical or mental health conditions (e.g., pregnancy, menopause, major depressive disorder, bipolar disorder, post-traumatic stress disorder, fibromyalgia, rheumatoid arthritis, Parkinson's disease, etc.) may explain insomnia symptoms, and therefore trials enrolling these subgroups were excluded; it is not clear that these patients meet diagnostic criteria for insomnia disorder. These conditions deserve the attention of a separate review and are considered outside the scope of this review. Insomnia disorder is a chronic condition, so a study duration of at least 4-weeks was required for eligibility. We included studies that reported subjective outcomes. Polysomography outcomes are not patient-centered and trials reporting only these outcomes were excluded. Providers use history and patient report to diagnose insomnia disorder and assess patient opinion regarding treatment. Providers are more likely to value a patients' perspective of improvement based upon their typical sleep routine. Sleep parameters obtained in a laboratory environment are not necessary or relevant to insomnia treatment.

Table 3. Study inclusion criteria

Category	Criteria for Inclusion
Study enrollment	• Adults with diagnoses consistent with insomnia disorder • Pure subgroups of adults (older adults, adults with anxiety, mild depression, noncancer pain)
Timing	• Efficacy/comparative effectiveness: 4 weeks to 3 months • Sustained efficacy/comparative effectiveness: over 3 months
Study design and quality	• Efficacy/comparative effectiveness: systematic reviews and RCTs • Adverse effects: systematic reviews and RCTs and large observational studies (sample size at least 100; study duration at least 6 months)
Outcomes	• Reports subjective global or sleep outcomes
Publication type	• Published in peer reviewed journals
Language of publication	• English

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

We searched Ovid Medline®, Ovid PsycInfo®, Ovid Embase®, and the Cochrane Library to identify previous systematic reviews and randomized controlled trials published and indexed in bibliographic databases from 2004 through January 2015 (Appendix A). We chose our beginning literature search date in 2004 because previous systematic reviews with ending search dates from 2003 to 2005 were available. We identified eligible studies published prior to 2004 through these systematic reviews. 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 randomized controlled trials (RCTs) and systematic reviews. Bibliographic database searches were supplemented with backward citation searches of highly relevant systematic reviews. We relied on previous systematic reviews to identify studies published prior to 2004. Studies that were rated low or moderate risk of bias and had study durations of 4 weeks or more were identified in the previous Agency for Healthcare Research and Quality (AHRQ) review.[33] This review is not an update of that review, but our Key Questions overlap with those of the previous AHRQ review. Other reviews were important to identify studies not included in the AHRQ review.[34-37]

Two independent investigators reviewed titles and abstracts of search results to identify systematic reviews and trials evaluating interventions for insomnia. 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 inclusion and exclusion status of citations undergoing full-text screening.

We conducted grey literature searching to identify relevant completed and ongoing studies. Relevant grey literature resources include clinicaltrials.gov and the FDA drug database. We also

reviewed Scientific Information Packets (SIPs) sent by manufacturers of relevant drugs. Grey literature search results were used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias and inform future research needs.

Our study eligibility criteria including only RCTs identified few studies reporting rare or long-term harms associated with use of sleep medications for longer periods of time. We therefore supplemented our search with searches of bibliographic databases for large observational studies of individuals taking medications for insomnia. Studies had to have a sample size of 100 and a study duration of at least 6 months.

Data Abstraction and Data Management

We used data from relevant comparisons in previous systematic reviews to replace the *de novo* extraction process when the comparison was sufficiently relevant and the systematic review quality was assessed as fair or high (according to methods described below).

Remaining RCTs meeting inclusion criteria were distributed among investigators for risk of bias assessment and data extraction. For studies assessed as having low to moderate risk of bias (according to methods described below), one investigator extracted relevant study, population demographic, and outcomes data. Data fields extracted included author, year of publication; setting, subject inclusion and exclusion criteria, intervention and control characteristics (intervention components, timing, frequency, duration), followup duration, participant baseline demographics, comorbidities; insomnia definition, method of diagnosis and severity, descriptions and results of primary outcomes and adverse effects, and study funding source. Relevant data were extracted into Excel spreadsheets for descriptive analysis. Data were analyzed in RevMan 5.2[38] software. Data used in quantitative synthesis were checked for accuracy by a second investigator. Data appearing in final evidence tables are uploaded to the Systematic Review Data Repository.

Assessment of Methodological Risk of Bias of Individual Studies

Quality of systematic reviews meeting eligibility criteria was assessed using AMSTAR criteria.[39] Two investigators independently assessed risk of bias for eligible RCTs using an assessment tool developed for this project (Appendix B).[40] Investigators assess several types of bias including selection bias (method of randomization, group similarity at baseline, allocation concealment), performance bias (blinding of provider and recipient, intervention definition—theory based, manualized, fidelity to treatment), detection bias (outcome assessors blinded, instruments validated and reliable, clinical significance of outcomes, co-interventions avoided or similar, correction for multiple comparisons, power—if pooling not possible), attrition bias (extent of attrition, reasons for incomplete data provided, incomplete data handled appropriately), reporting bias (select group of outcomes reported, select analysis conducted), and other sources of bias. Certain items (such as adequacy of intervention definition and implementation) were especially necessary to adequately capture all potential risk of bias associated with psychological interventions. Each investigator summarized overall risk of bias for each study classifying it as low, moderate, or high based upon the collective risk of bias inherent in each domain and their confidence that the results were believable given the study's limitations. Both investigators' summary Risk of Bias assessments were aggregated. Studies that two investigators rated as high risk of bias were excluded from analysis.

Data Synthesis

When a comparison was adequately addressed by a previous systematic review of acceptable quality and no new studies were available, we reiterated the conclusions drawn from that review. When new trials were available, previous systematic review data were synthesized with data from additional trials by rerunning pooled analysis.

We summarized study characteristics and outcomes of RCTs not included in previous eligible systematic reviews in evidence tables. We grouped studies by population, intervention, and comparison. Studies that included adults of any age were classified as general adult population; studies that included only older adults (age cutoffs varied among studies) were classified as older adults. We assessed the clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.[41] 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[38] software). We calculated risk ratios (RR) and absolute risk differences (RD) with the corresponding 95% confidence intervals (CI) for binary primary outcomes. Weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95% CIs were calculated for continuous outcomes. We assessed statistical heterogeneity with Cochran's Q test and measured magnitude with I^2 statistic.[41] An I^2 score of 50 percent suggests moderate heterogeneity and 75 percent or greater indicates substantial heterogeneity among studies.

Global outcomes were most often measured using the ISI and the PSQI (Table 4). We searched the literature to identify minimum important differences to facilitate interpretation of results for these outcomes. We identified one study estimating minimum important difference (MID) for the ISI.[42] Distribution- and anchor-based approaches were used. The anchor-based approach used 14 variables from three different instruments (the SF-36 Health Survey, the Work Limitations Questionnaire, and the Fatigue Severity Scale) 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 when anchor-based methods are not available.[43] MIDs can vary depending on estimation method and population studied.[44] MIDs are also often closely related to baseline values.[45] Despite these complications, trials that conduct responder analysis based upon established MID offer simplistic interpretation. Unfortunately, many trials did not conduct responder analysis and report only mean scale scores or mean change in scale scores. It is not appropriate to apply the MID established based upon changes from baseline for individuals to WMDs between groups.[44,46] 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 MID suggests 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 individuals; and if the weighted mean difference falls below 0.5 (MID) suggests that it is less likely that that an appreciable number of patients will achieve important benefits from treatment.[47]

Table 4. Characteristics of instruments measuring global outcomes

Global Outcome	Measurement/Instrument Properties	MIDs Reported in Literature Method of Derivation
Insomnia Severity Index	7 Likert items; range 0-28; demonstrated sensitivity to change[48] 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[42]
Pittsburgh Sleep Quality Index	7 components; 19 items; range 0-21 with lower scores indicating better sleep; demonstrated sensitivity to change[48]	No MID identified
Athens Insomnia Scale	8 components; range 0-24 with lower scores indicating better sleep; score ≥6 indicates insomnia	No MID identified

MID = minimum important difference

Grading the Strength of Evidence for Individual Comparisons and Outcomes

The overall strength of evidence for primary outcomes within each comparison was evaluated based on five required domains: (1) study limitations (risk of bias); (2) directness (single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size); (4) precision (degree of certainty around an estimate); and (5) reporting bias.[49] Evidence from previous systematic reviews was reassessed based upon the information provided (evidence quality or attributes of the data and included studies) by the systematic review. Based on study design and conduct of the individual studies making up the body of evidence for a particular comparison, study limitations were rated low, medium, or high based upon the number and magnitude of limitations detected during risk of bias assessments. Consistency was rated as consistent, inconsistent, or unknown (e.g., single study) after comparing the direction and size of the effect across studies. Directness was rated direct or indirect depending upon whether the outcome measured had a direct link to patient wellbeing and if comparisons were direct. Precision was rated precise or imprecise based upon whether confidence intervals contain or exceed clinical differences. Reporting bias was rated as undetected or suspected after assessing the presence of publication bias, selective outcome reporting bias, and selective analysis bias. Reporting bias was assessed by comparing the methods section with results to identify outcomes or analysis not planned or reported. Other factors considered in assessing strength of evidence included dose-response relationship, the presence of confounders, and strength of association. These factors were used to upgrade or downgrade strength of evidence assessments arising from the five required domains. A strong association was suggested when the total number of trials, total number of participants, and effect size demonstrate a robust outcome. Based on these factors, the overall strength of evidence for each outcome was rated as:[49]

- **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 likely to be stable, but some doubt.

- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence 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.

Assessing Applicability

Applicability of studies was determined according to the PICOTS framework. Study characteristics affecting applicability include, but are not limited to, the population from which the study participants were enrolled (i.e., 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, and patient and intervention characteristics different from those described by population studies of insomnia.[50] Specific factors that could modify the effect of treatment and affect applicability of findings include diagnostic accuracy, insomnia severity, and specific patient characteristics such as age.

Results

Literature Search and Screening

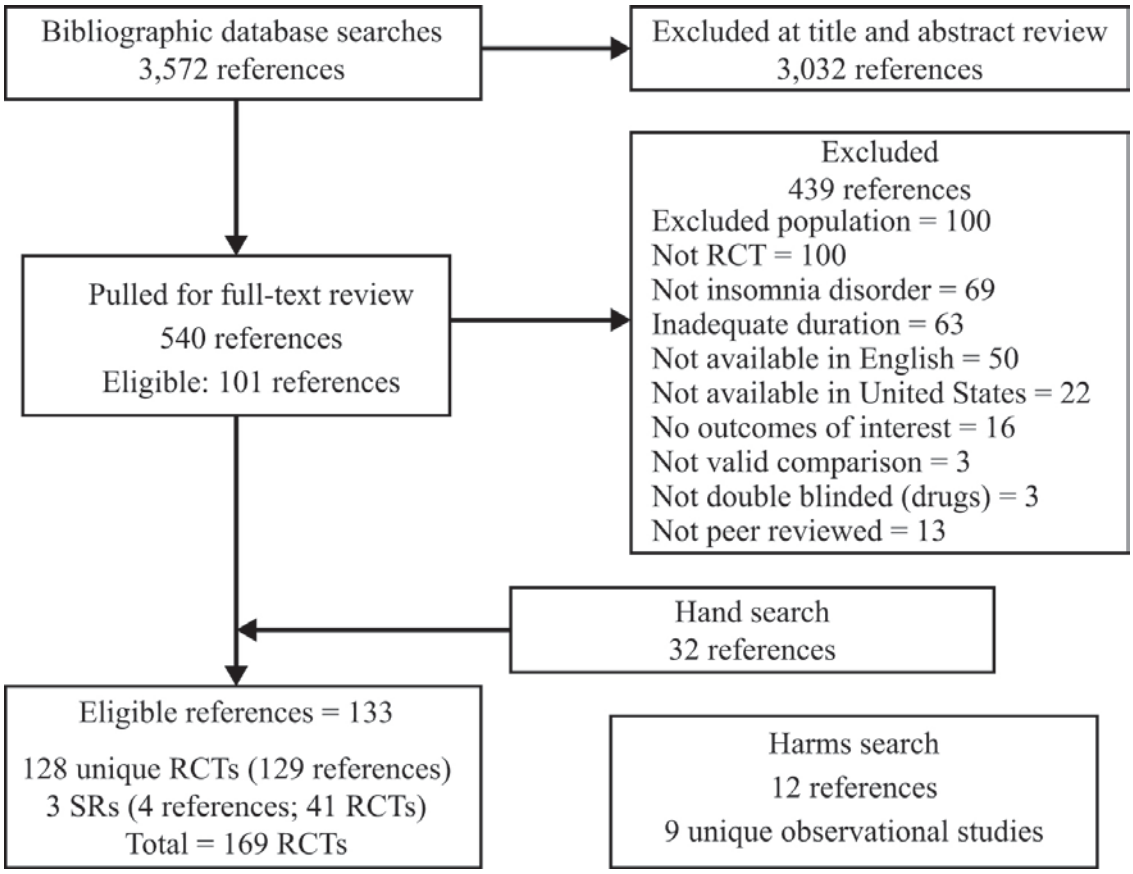
Key Points

- Global outcomes were less often measured than sleep outcomes, especially in the drug studies; recent research was more likely to assess global outcomes.
- Minimum important differences were identified for some instruments used to assess global outcomes, but these were not frequently used nor is it clear whether they are well established. We did not identify established minimum important differences for most sleep outcomes. Remission defined using sleep onset latency and sleep efficiency were the exceptions.
- A large body of literature tests a wide variety of treatments for insomnia disorder. Strength of evidence suffers because of limited studies with similar comparisons. In addition, sample sizes were typically small and studies often contained multiple arms. Older studies often did not provide data sufficient for analysis.

Our search identified 3572 citations, of which 540 required full text review after title and abstract screening (Figure 2). Of the 540 full text articles screened, we identified 102 eligible references; we identified another 32 eligible references by hand searching for a total of 133 publications of 128 unique RCTs and 3 unique systematic reviews. Systematic reviews included in our analysis synthesized evidence on 41 unique RCTs. Studies excluded after full text review are listed in Appendix C along with exclusion reasons. The most frequent exclusion reasons included a lack of randomization, inadequate study duration, drugs not approved for use in the United States, insomnia not clinically diagnosed, and not available in English. Studies not available in English were often complementary and alternative medicine (CAM) treatments published only in Chinese. We captured results of many of these studies by including systematic reviews (that did not have language restrictions) in lieu of de novo extraction. We also searched for observational studies to supplement our harms discussion, and identified nine observational studies (for medication adverse effects) that met inclusion criteria.

Evidence tables including study characteristics and outcomes for all included studies are available upon request and will be uploaded to the Systematic Review Data Repository after the final version of this report is posted. AMSTAR ratings, risk of bias assessments, and strength of evidence assessments appear in Appendix D for psychological interventions; Appendix E for pharmacologic interventions; Appendix F for CAM interventions; and Appendix G for combination or comparative effectiveness of interventions across intervention types.

Figure 2. Literature flow diagram



RCT = randomized controlled trial; SR = systematic review

Efficacy and Comparative Effectiveness of Psychological Interventions

Key Points

- 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 improves several sleep outcomes (sleep onset latency, wake time after sleep onset, and sleep efficiency) in 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.

Efficacy of Cognitive Behavioral Therapy in the General Adult Population

Overview of Studies

We included studies as efficacy of CBT-I if they had an active CBT-I arm and passive control arm (sham treatment/placebo, wait-list control, no treatment, or sleep hygiene/sleep education). We identified 20 RCTs with acceptable risk of bias assessing the efficacy of CBT-I to treat insomnia disorder in the general adult population.[51-72] Trials were conducted in the United States,[51,54-56,60,67] Sweden,[53,61,62,68] Canada,[64,66,71] the Netherlands,[63,69,70] the United Kingdom,[58,59,65] Norway,[52] Scotland,[57] and China.[72] Studies differed in how CBT-I was delivered. Six studied individual in-person CBT-I,[54-56,60,62,65] five studied group CBT-I,[53,57,59,61,72] one studied phone-delivered CBT-I,[51] and ten studied self-help CBT-I using either books or handouts or electronic resources.[52,58,63,64,66-71] Comparison groups also varied across trials. Some trials attempted to have a placebo control group that received similar therapy hours (i.e., quasi-desensitization or stress management).[54-56,58,60,72] Enrollment criteria varied across trials, most relied on the DSM-IV criteria for enrollment. The mean age was typically in the mid-40s; participants were predominantly female, and most were white (in the trials that reported race). Insomnia duration ranged from an average of 6 months to nearly 2 decades with most trials reporting mean duration of several years. Baseline ISI scores were just over 17 and baseline sleep onset latency was over 45 minutes. Interventions were typically once a week for 1 hour or less and lasted from 4 to 6 weeks. Eighteen of these RCTs (n=1842) provided data sufficient for pooling on one or more outcomes (Table 5). Risk of bias of included trials was predominantly medium.

Table 5. Overview and strength of evidence: efficacy of CBT-I in the general adult population

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Individual CBT vs. passive control (18 RCTs; N=1,842)	Global Outcomes	Remission	4 (179)	61% (58/95)	18% (15/84)	Favors CBT RR = 2.95 [1.78 to 4.87] ARR = 43% NNT = 2.32	Moderate (moderate study limitations)
		Responder	2 (123)	55% (37/67)	18% (10/56)	NS RR = 2.59 [0.45 to 14.99]	Insufficient (moderate study limitations, imprecise)
		CGI="very much improved"	1 (60)	35% (13/37)	4% (1/23)	Favors CBT RR = 8.08 [1.13 to 57.73] ARR = 31% NNT = 2.0	Low (moderate study limitations)
		ISI score	5 (345)			Favors CBT WMD = -5.15 [-7.13 to -3.16]	Moderate (moderate study limitations)
		PSQI score	6 (580)			Favors CBT WMD = -2.10 [-2.87 to -1.34]	Moderate (moderate study limitations)
		PSQI score (> 6 months followup)	2 (241)			Favors CBT WMD = -2.71 [-3.67 to -1.75]	Low (moderate study limitations)
	Sleep Outcomes	Sleep onset latency, self-report, minutes	15 (1246)			Favors CBT-I WMD = -12.70 [-18.23 to -7.18]	Moderate (moderate study limitations)
		Sleep onset latency, self-report, minutes (>6 months followup)	4 (413)			NS WMD = -15.69 [-32.67 to 1.29]	Insufficient (moderate study limitations, inconsistent, imprecise)
		Total sleep time, self-report, minutes	15 (1233)			Favors CBT-I WMD = 14.24 [2.08 to 26.39]	Moderate (moderate risk study limitations, reporting bias detected)
		Total sleep time, self-report, minutes (>6 months followup)	4 (413)			NS WMD = 17.30 [-4.28 to 38.87]	Insufficient (moderate study limitations, inconsistent, imprecise)

Table 5. Overview and strength of evidence: efficacy of CBT-I in the general adult population (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Individual CBT vs. passive control (18 RCTs; N=1,842) (continued)	Sleep Outcomes (continued)	Wake time after sleep onset, self-report, minutes	11 (832)			Favors CBT-I WMD = -22.33 [-37.44 to -7.21]	Moderate (moderate study limitations)
		Wake time after sleep onset, self-report, minutes (>6 months followup)	3 (377)			Favors CBT-I WMD = -15.20 [-26.28 to -4.12]	Low (moderate study limitations)
		Sleep efficiency	15 (1230)			Favors CBT-I WMD = 7.20 [4.57 to 9.82]	Moderate (moderate study limitations, reporting bias detected)
		Sleep efficiency (>6 months followup)	4 (413)			Favors CBT-I WMD = 5.00 [1.71 to 8.29]	Low (moderate study limitations)
		Sleep quality	10 (809)			Favors CBT-I SMD = 0.40 [0.18 to 0.595]	Moderate (moderate study limitations, reporting bias detected)
		Sleep quality (>6 months followup)	1 (136)			Favors CBT-I MD = 0.54 [0.20 to 0.89]	Low (moderate study limitations)

ARR = absolute risk reduction; CBT = cognitive behavioral therapy; CGI = Clinician's global impression scale; CI = confidence intervals; NNT = number needed to treat; RR = risk ratio; SMD = standardized mean difference; WMD = weighted mean difference

Global Outcomes

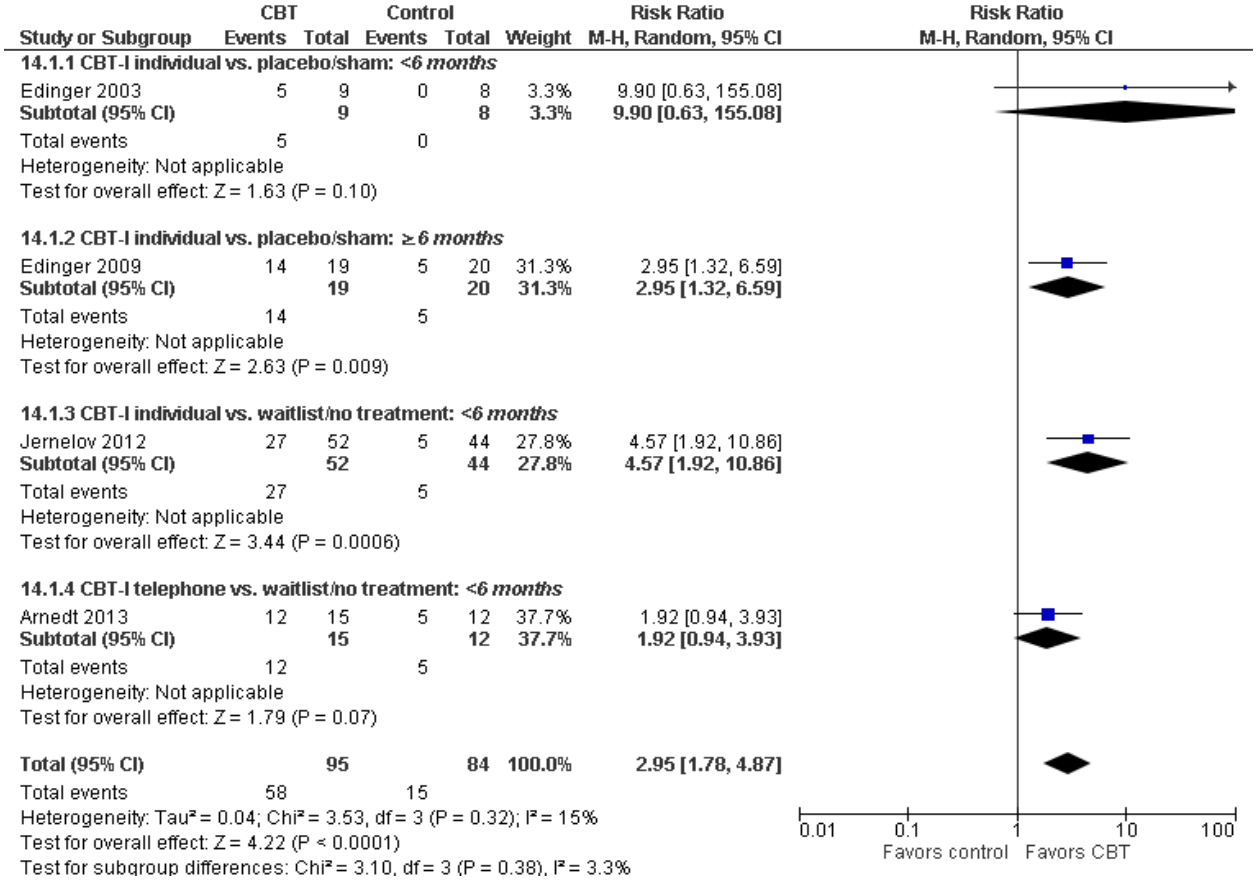
Four small trial assessed insomnia remitters (achieving an ISI score ≤7 or PSQI score ≤5 at followup) (Figure 3).[51,54,56,62] Two small studies used the "ISI score ≤7" definition of remission. Edinger compared individual CBT-I to placebo.[54,56] Jernelov et al. compared self-help CBT-I with therapist support to waitlist controls[62] and Arnedt et al. compared CBT-I delivered by phone with a control group who received sleep hygiene information.[51] Both Arnedt and Edinger had small sample sizes and failed to reach statistical significance. Pooled results show that CBT-I participants are nearly three times more likely to achieve remission than passive controls; 43 percent more CBT-I participants achieved remission compared with passive controls; and just over two individuals with insomnia would need to be treated to see one achieve remission. Two trials assessed 'responders' to treatment according to established thresholds (Figure 4).[51,62] The pooled result was not statistically significant.

Six of the CBT-I efficacy trials across four delivery methods reported mean ISI scores (Figure 5).[51,53,62,66,67,71] Only one trial achieved a weighted mean change in ISI scores equal or greater than the minimum important difference of seven.[67] The pooled estimate shows that CBT-I across delivery methods achieves a 5.15 point reduction in ISI scores suggesting that many patients will realize important benefits from CBT-I... Studies across four delivery methods reported mean PSQI scores (Figure 6).[51,52,56,59,64,66] The pooled estimate showed that CBT-I across delivery methods achieved a 2-point reduction in PSQI scores. We did not identify literature suggesting a minimum important difference, so it is unclear how this change should be interpreted.

One last global outcome was evaluated in CBT-I efficacy trials, clinical global impression (CGI). Vincent, et al., showed that clinicians reported that participants enrolled in web-based CBT-I were at eight times higher odds of being "much or very much improved" compared with passive controls.[71]

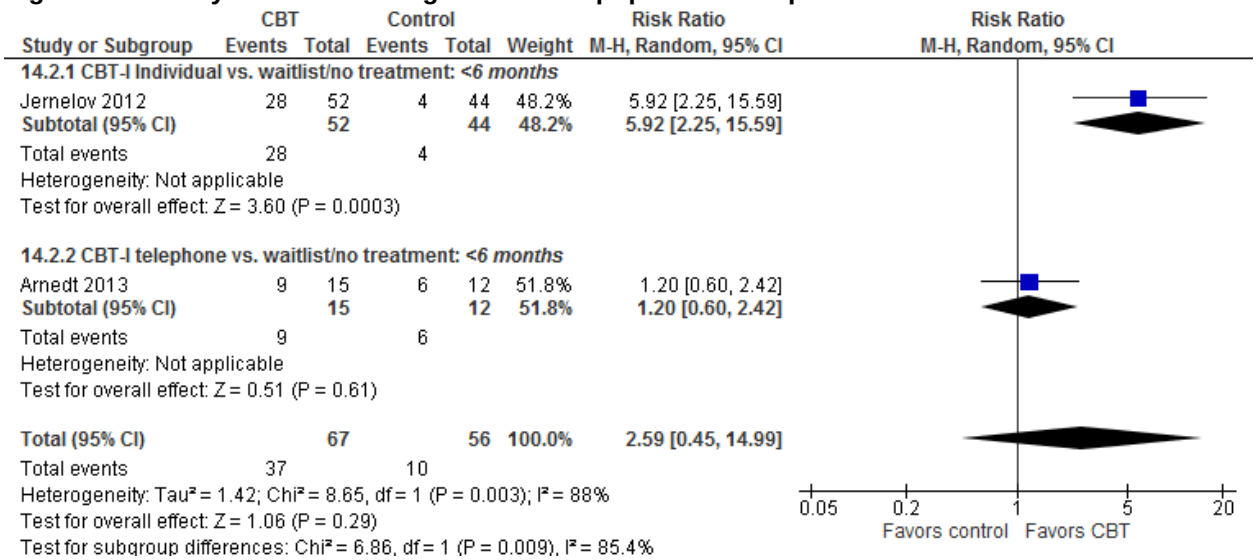
One trial provided evidence that global outcomes remain improved at 6 month after treatment initiation.

Figure 3. Efficacy of CBT-I in the general adult population: remitters



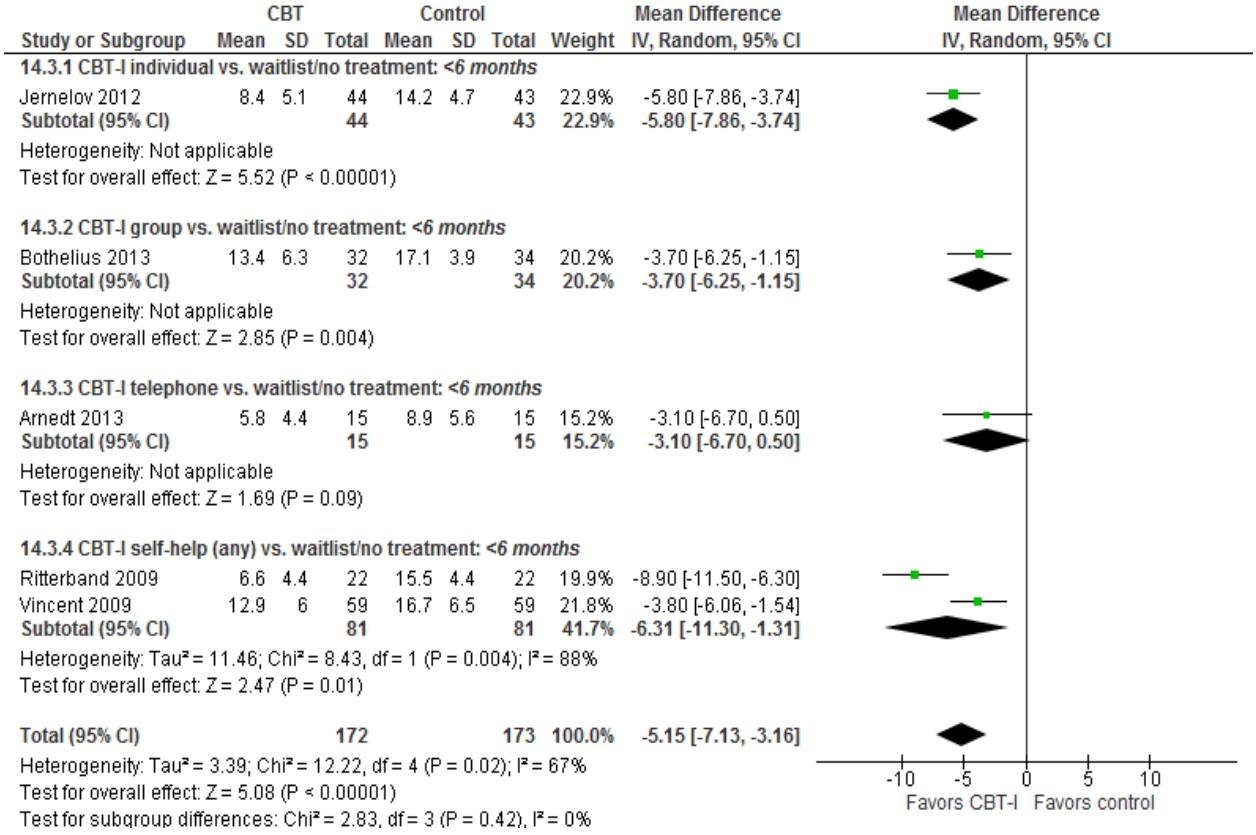
CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; M-H = Mantel-Haenszel

Figure 4. Efficacy of CBT-I in the general adult population: responders



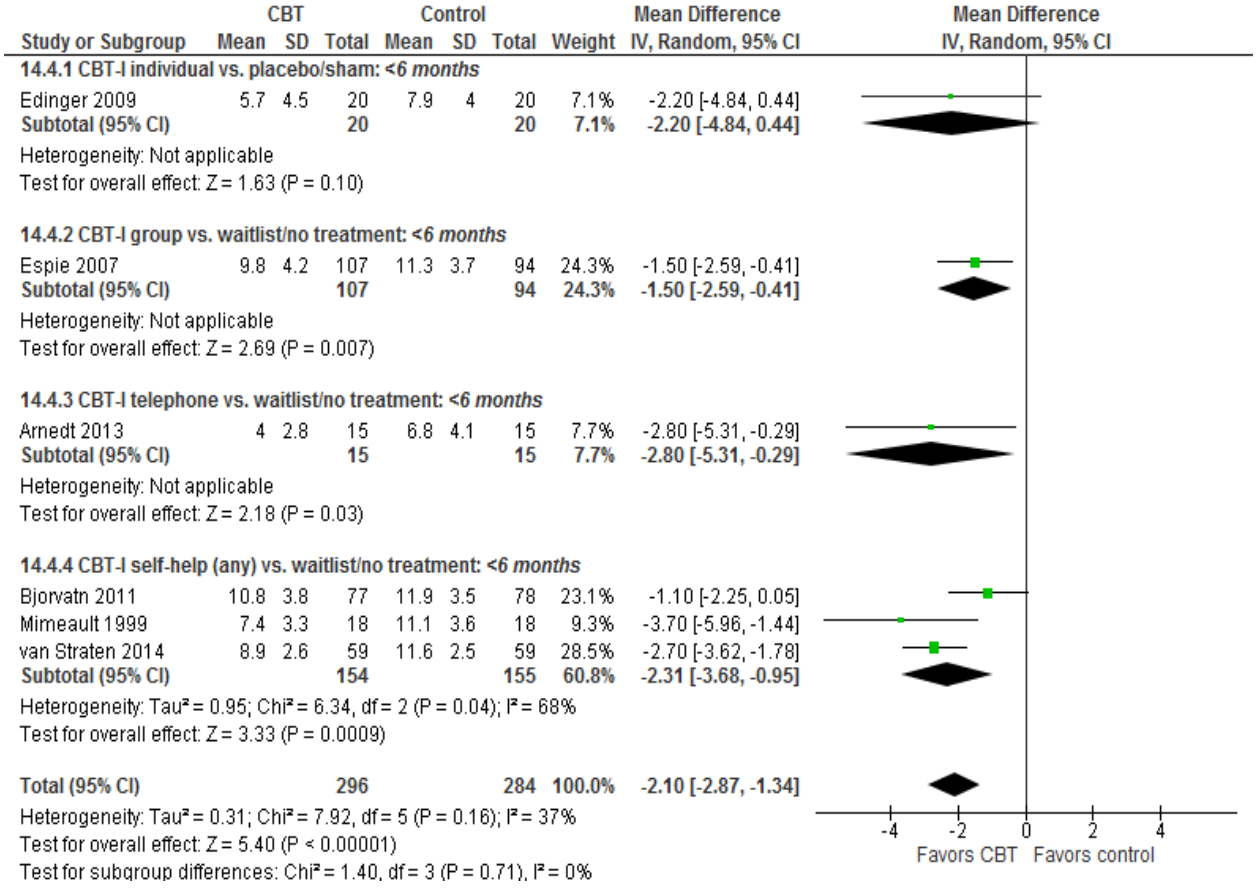
CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; M-H = Mantel-Haenszel

Figure 5. Efficacy of CBT-I in the general adult population: ISI mean score



CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; ISI = Insomnia Severity Index; IV = inverse variance; SD = standard deviation

Figure 6. Efficacy of CBT-I in the general adult population: PSQI scores



CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; PSQI = Pittsburgh Sleep Quality Index; IV = inverse variance; SD = standard deviation

Sleep Outcomes

Most CBT-I efficacy trials reported patient-reported sleep outcomes (Figures 7-9). Improvements in sleep onset latency differed significantly from passive control in only six of the 16 trials that reported poolable data (Figure 7). Pooled data show that the largest improvements in sleep onset latency occurred with CBT-I group compared with self-help CBT-I. However, this was due to a very large effect in two trials reporting mean decrease in sleep onset latency of over 30 minutes.[58,72] The pooled estimate across all delivery methods shows that CBT-I participants reduced their sleep onset latency by nearly 12 minutes compared with passive controls. However, trials that had sham treatment placebo controls were less likely to show a significant improvement over placebo. Pooled estimates show that CBT-I participants gained a mean of 15 minutes of total sleep time. Reductions in wake time after sleep onset were demonstrated in five of 12 trials reporting this outcome across four delivery methods. The pooled estimate shows that CBT-I participants decreased their mean awake time after sleep onset by nearly 22 minutes.

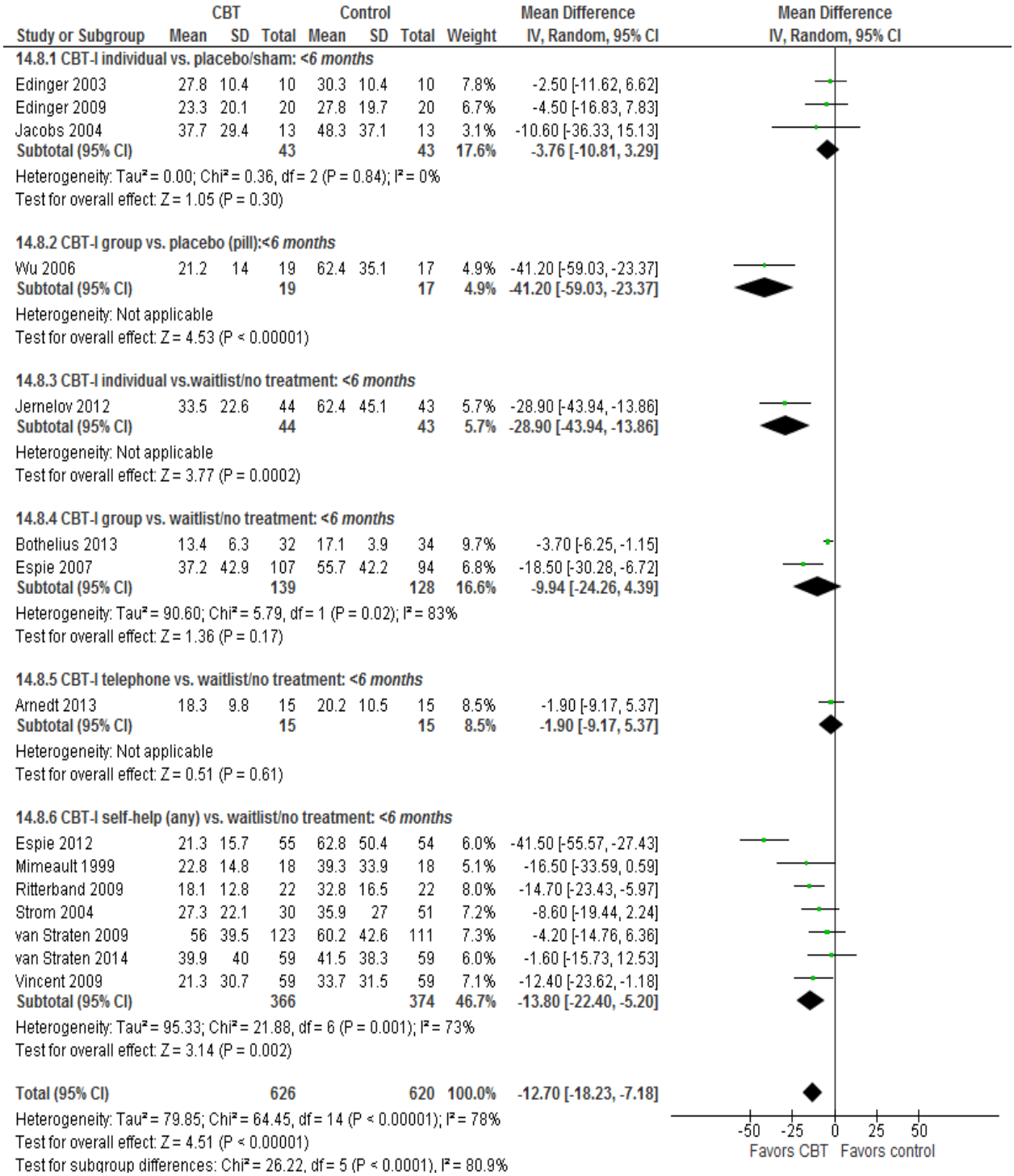
Post-intervention sleep efficiency improved with CBT-I in 9 of 16 trials. Mean sleep efficiency at endpoint ranged from 72 to 88 among CBT-I participants and from 64 to 85 among passive controls across the nine trials. The pooled estimate shows that sleep efficiency improved by over six percentage points in CBT-I participants compared with passive controls across six delivery methods.

This measure should increase with CBT-I compliance, which often suggests that participants get out of bed if they can't get to sleep, so may reflect compliance as well as efficacy.

Sleep quality improved in 6 of 11 trials reporting sleep quality. In-person CBT-I appears to have larger responses. Several self-help CBT-I trials failed to show efficacy. The pooled estimate of the standardized mean difference suggests that CBT-I creates a moderately sized improvement on sleep quality across delivery methods.

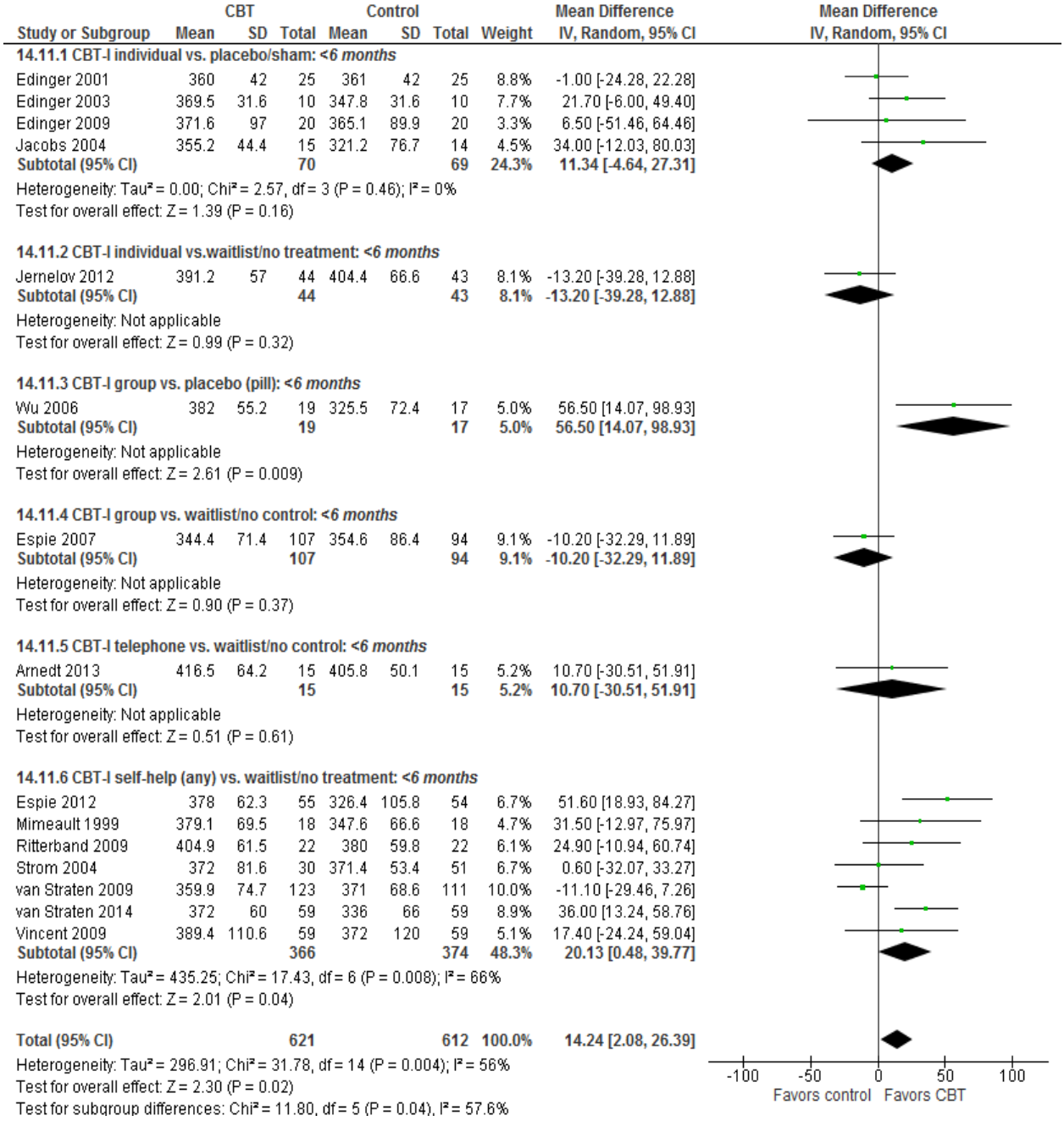
Four trials provided evidence that sleep onset latency and wake after sleep onset remain improved at time periods beyond 6 months from treatment initiation.

Figure 7. Efficacy of CBT-I in the general adult population: sleep onset latency



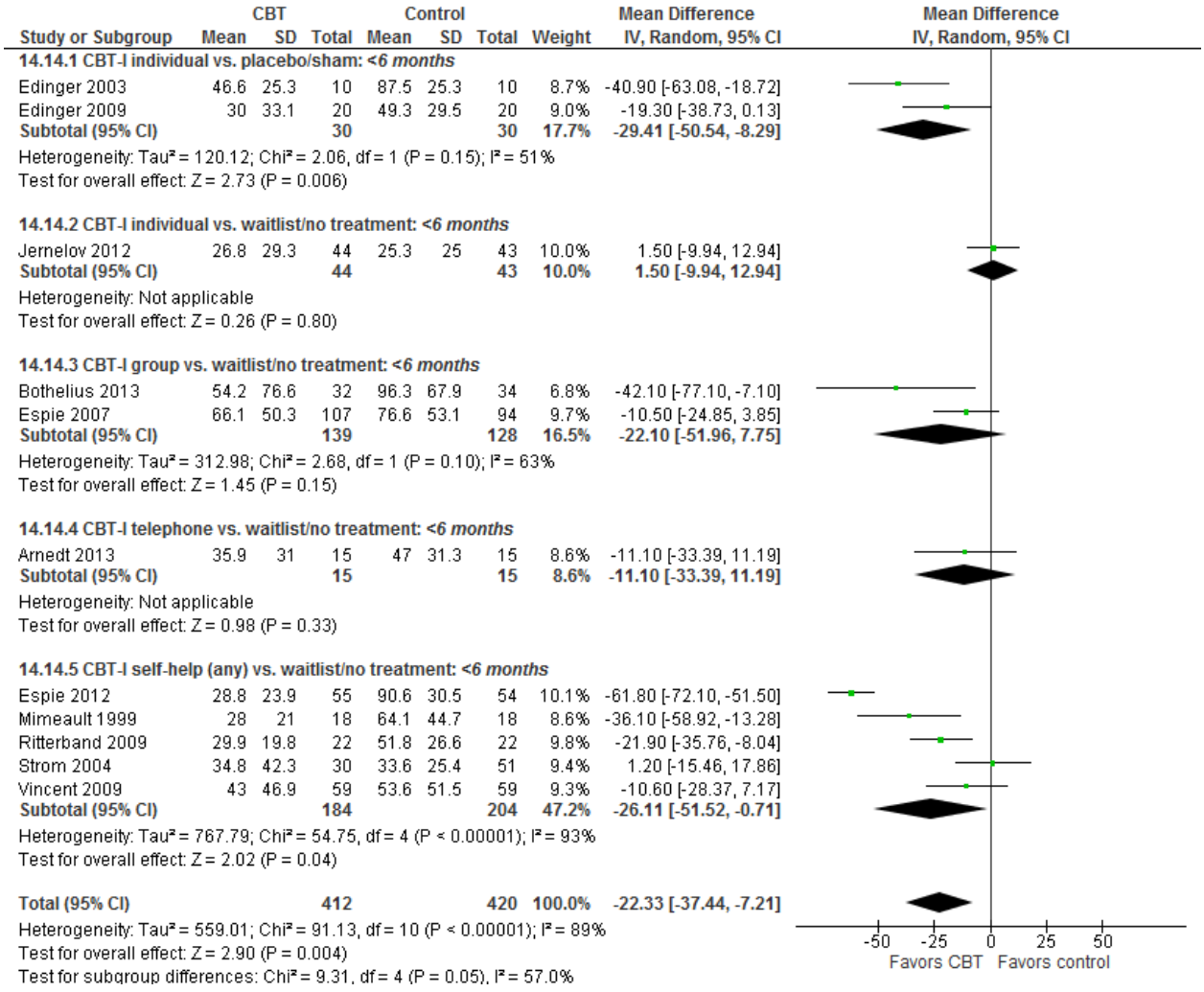
CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 8. Efficacy of CBT-I in the general adult population: total sleep time



CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 9. Efficacy of CBT-I in the general adult population: wake time after sleep onset



CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

Several trials mentioned functioning, mood, and quality of life using several different instruments. Most studies were small and few studies used similar instruments.

Adverse Effects

Specific adverse effects were not reported. Most trials reported withdrawals or loss to followup. Two studies did not report withdrawals or loss to followup by treatment group.[57,61] No statistically significant differences were found across groups in the rates of withdrawals or loss to followup.

Efficacy of Cognitive Behavioral Therapy in Older Adults

Overview of Studies

We included studies as efficacy of cognitive behavioral therapy (CBT) if they had an active CBT-I arm and a passive control arm (placebo, wait-list control, no treatment, or sleep hygiene/sleep education). We analyzed studies that enrolled older adults separately from those enrolling adults of all ages. We identified six trials that compared CBT-I with passive control in older adults.[73-77] Risk of bias for included studies was predominantly moderate. We pooled evidence on common outcomes when possible (Table 6).

Table 6. Overview and strength of evidence: efficacy of CBT-I in older adults

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Individual CBT vs. passive control (4 RCTs; N=220)	Global Outcomes	PSQI score (up to 6 months)	2 (162)			Favors CBT WMD = -2.98 [-4.01 to -1.95]	Low (moderate study limitations)
		PSQI score (16 months)	1 (75)			Favors CBT MD = -2.60 [-4.17 to -1.03]	Low (moderate study limitations)
		Athens Insomnia Scale (up to 6 months)	1 (75)			Favors CBT MD = -2.20 [-4.13 to -0.27]	Low (moderate study limitations)
		Athens Insomnia Scale (16 months)	1 (75)			Favors CBT MD = -2.60 [-4.17 to -1.03]	Low (moderate study limitations)
		PSQI mean change	1 (113)			Favors CBT MD = -2.20 [-3.39 to -1.01]	Low (moderate study limitations)
		ISI mean change	1 (125)			Favors CBT MD = -2.10 [-0.55 to -3.65]	Low (moderate study limitations)
	Sleep Outcomes	Sleep onset latency, self-report, minutes (up to 6 months)	3 (191)			Favors CBT WMD = -9.98 [-16.48 to -3.48]	Low (moderate risk of bias)
		Sleep onset latency, self-report, minutes (at 16 months)	1 (75)			NS WMD= -6.30 [-13.23 to 0.63]	Insufficient (moderate risk of bias, imprecise, unknown consistency)
		Total sleep time, self-report, minutes (up to 6 months)	4 (220)	-	-	NS WMD = 3.14 [-15.90 to 22.18]	Low (moderate risk of bias, imprecise)
		Total sleep time, self-report, minutes (at 1 year)	1 (23)	-	-	NS WMD = 55.60 [-9.32 to 120.52]	Low (moderate risk of bias)
		Total sleep time, self-report, minutes (at 16 months to 2 years)	2 (98)			NS WMD = 25.48 [-14.45 to 65.42]	Low (moderate risk of bias)
		Wake time after sleep onset, self-report, minutes (up to 6 months)	4 (220)			Favors CBT-I WMD = -26.96 [-35.73 to -18.19]	Moderate (moderate risk of bias)

Table 6. Overview and strength of evidence: efficacy of CBT-I in older adults (continued)

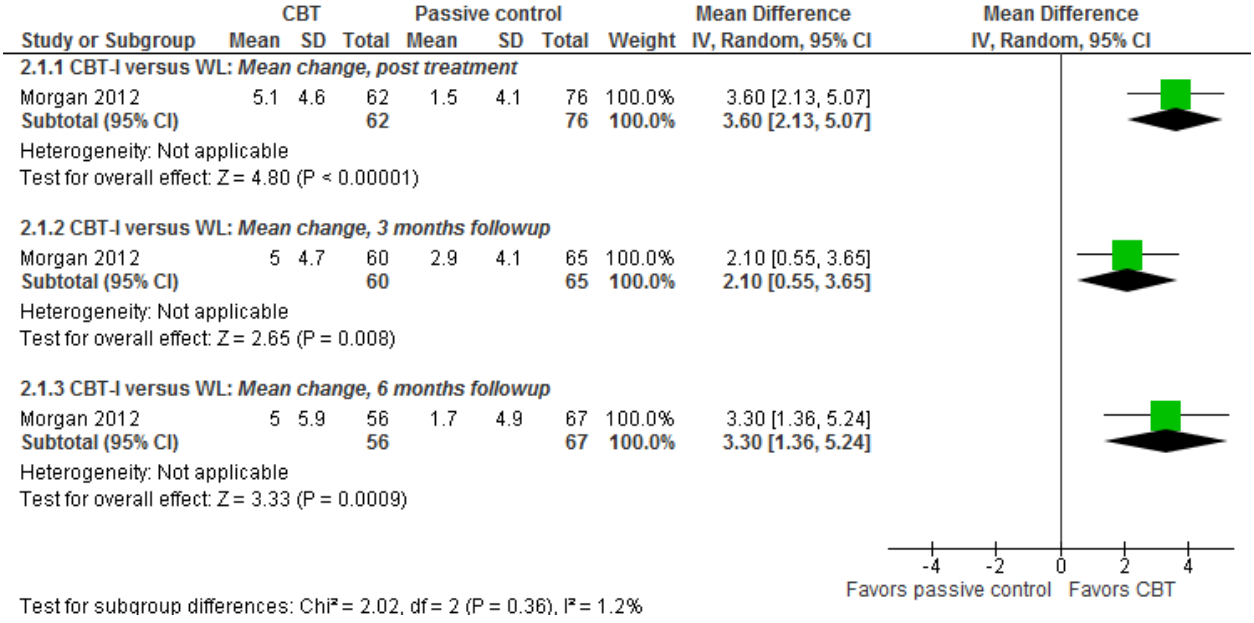
Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Individual CBT vs. passive control (4 RCTs; N=220) (continued)	Sleep Outcomes (continued)	Wake time after sleep onset, self-report, minutes (at 1 year)	1 (23)			Favors CBT-I WMD = -42.00 [-68.53 to -15.47]	Low (moderate study limitations, large effect size)
		Wake time after sleep onset, self-report, minutes (at 16 months to 2 years)	2 (98)			Favors CBT-I WMD = -19.13 [-37.26 to -1.01]	Low (moderate risk of bias, Precise)
		Sleep efficiency, mean change (up to 6 months)	4 (220)			Favors CBT-I WMD = 9.18 [5.76 to 12.62]	Low (moderate study limitations)
		Sleep efficiency, mean change (at 1 year)	1 (23)			Favors CBT-I MD = 18.00 [5.87 to 30.13]	Low (moderate study limitations, large effect size)
		Sleep efficiency, mean change (at 16 months to 2 years)	2 (98)			Favors CBT-I WMD = 7.75 [1.49 to 14.01]	Low (moderate study limitations)
	Adverse Effects	Withdrawals	2 (126)	13% (4/62)	11% (5/64)	NS	Insufficient (moderate study limitations, imprecise)

CBT = cognitive behavioral therapy; CI = confidence intervals; MD = mean difference; NS = no significant difference; WMD = weighted mean difference

Global Outcomes

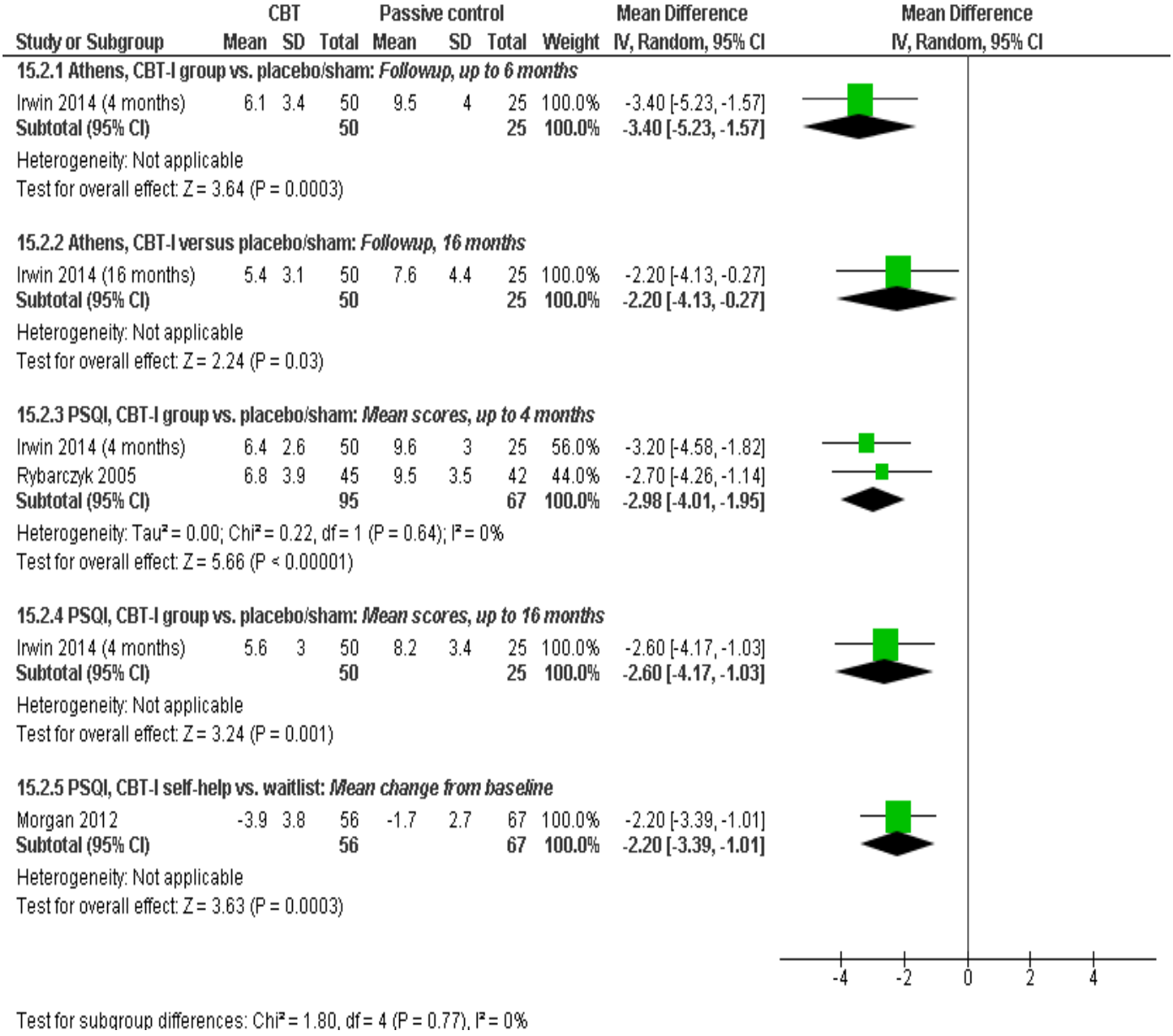
Three studies reported global outcomes (Figures 10 and 11).[73,76,77] All trials did not report the same instrument scores measured the same way. For instance, all three reported PSQI, but Rybarczyk et al. and Irwin et al. reported total scores and Morgan et al. reported mean changes in scores, so data could not be pooled. All trials showed statistically significant changes in global outcomes. Morgan et al. found statistically significant difference between the mean change on the ISI and the mean change on the PSQI at three time points.[73] Global outcomes were improved after CBT-I in older adults and improvements are sustained at 3 and 6 month followup. However mean difference in change between groups or mean change from baseline for the ISI did not achieve the minimum clinical difference of seven points (Figure 10). Similar improvements were demonstrated with the PSQI and the Athens Insomnia Scale; however, clinical significance of the difference in mean change is unclear (Figure 11).

Figure 10. Efficacy of CBT-I in older adults: ISI



CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; ISI = insomnia severity index; IV = inverse variance; SD = standard deviation

Figure 11. Efficacy of CBT-I in older adults: Athens Insomnia Index and PSQI



CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; PSQI = Pittsburgh Sleep Quality Index; IV = inverse variance; SD = standard deviation

Sleep Outcomes

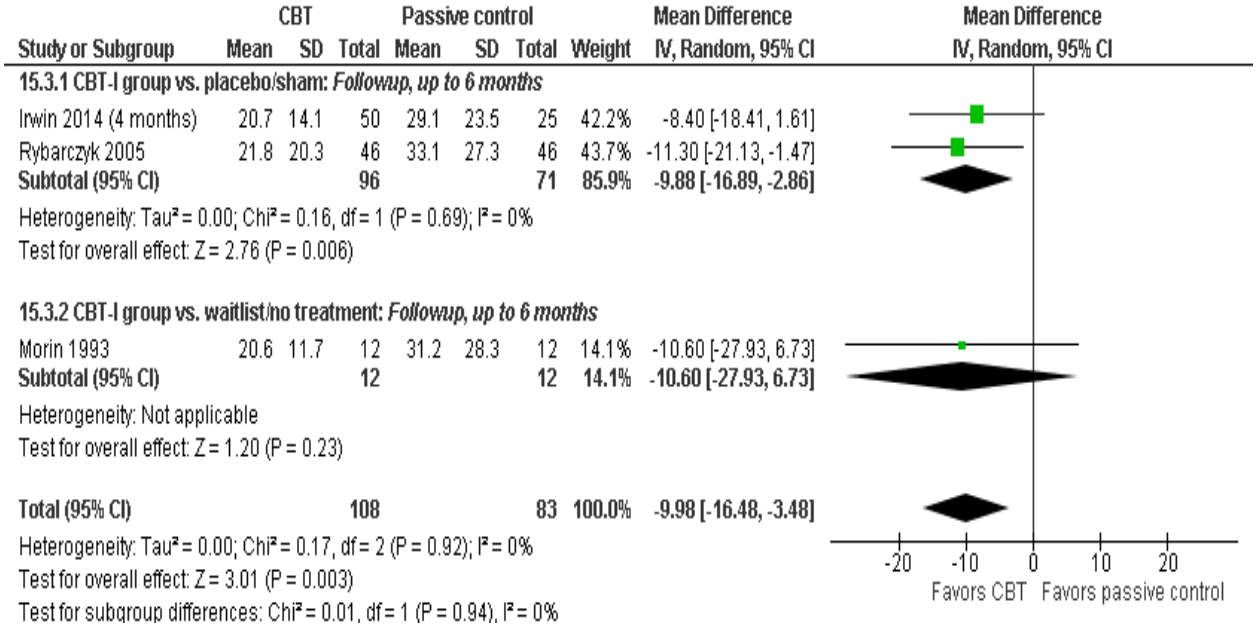
Sleep outcomes were reported in all CBT-I efficacy trials among older adult participants (Figures 12 and 13). One trial attempted to measure the proportion of participants who achieved clinically significant improvement in sleep.[78] It defined clinically significant improvement as the attainment of sleep efficacy equal to or greater than the mean in a group of patients without insomnia. More CBT-I participants achieved clinical improvement than passive controls

Sleep onset latency was reported in three trials.[75-77] Differences between groups were significant in only one individual trial and in the pooled analysis. CBT-I led to a decrease of 10

minutes in sleep onset latency. Only one trial reported sleep onset latency at a followup point over 6 months showing no statistical difference between the CBT-I group and passive control group.

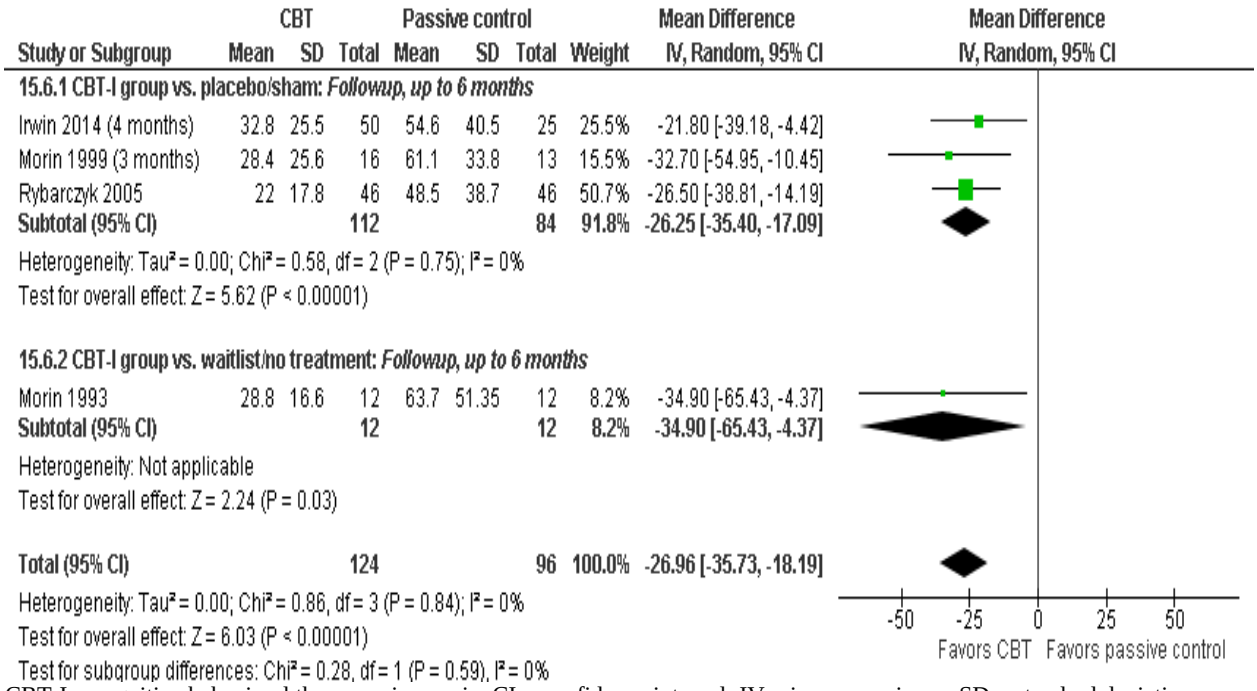
No differences were reported in any of the three trials reporting total sleep time at followup.[74-77] Pooled analysis was also insignificant post-treatment and at 1- and 2-year followup. Results for two other sleep outcomes were more promising. Wake time after sleep onset was reported in four trials.[74-77] Statistically significant reductions were shown in each individual study as well as with the pooled result. CBT-I participants reduced their wake time after sleep onset by nearly 27 minutes. One study showed that this result was maintained at 1-year and not 2-year followup. A similar pattern was demonstrated with sleep efficiency. The pooled analysis demonstrates that the CBT-I group increased their sleep efficiency by about 9 percentage points at followup. In Morin et al. sleep efficiency increased by 18 percentage points at 1-year followup, pooled results showed that sleep efficiency was nearly 8 percentage points higher at 2 years.

Figure 12. Efficacy of CBT-I in older adults: sleep onset latency



CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; IV = inverse variance; SD=standard deviation

Figure 13. Efficacy of CBT-I in older adults: wake time after sleep onset



CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

Morgan et al. reported Fatigue Severity Scores for both groups and found no statistically significant differences post-treatment, or at 3- or 6-month followup.[73]

Adverse Effects

Most trials reported withdrawals or adverse effects.[73,78,79] CBT-I participants were no more likely to withdraw from a study than participants of passive control groups.

Efficacy of Cognitive Behavioral Therapy in Adults With Pain

Overview of Studies

Seven trials reported in eight publications assessed CBT-I delivered to patients with pain and insomnia (Table 7). Four trials studied the general adult population with pain[80-84] and three assessed the efficacy of CBT-I in older adults with pain.[79,85,86] McCurry is a second publication of an earlier trial analyzing only a portion of the participants with pain.[85]

Table 7. Overview and strength of evidence: efficacy of CBT-I in the general adult population with pain

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Individual CBT vs. passive control (4 RCTs; N=132)	Global Outcomes	ISI score (up to 6 months)	4 (130)			Favors CBT-I WMD = -7.10 [-12.87 to -1.32]	Low (moderate study limitations, inconsistency)
		ISI score (at >6 months)	1 (74)			Favors CBT-I MD = -3.40 [-6.25 to -0.55]	Insufficient (moderate study limitations, unknown consistency)
	Sleep Outcomes	Sleep onset latency, self-report, minutes (up to 6 months)	3 (122)			Favors CBT WMD = -26.50 [-43.25 to -9.75]	Low (moderate risk of bias)
		Sleep onset latency, self-report, minutes (at >6 months)	1 (70)			NS WMD = -6.30 [-16.28 to 3.68]	Insufficient (moderate risk of bias, imprecise, unknown consistency)
		Total sleep time, self-report, minutes (up to 6 months)	4 (132)			NS WMD = 23.52 [-12.05 to 59.09]	Insufficient (moderate risk of bias, imprecision)
		Total sleep time, self-report, minutes (at >6 months)	1 (70)			NS WMD = -6.00 [-36.22 to 24.22]	Insufficient (moderate risk of bias, imprecise, unknown consistency)
		Wake time after sleep onset, self-report, minutes (up to 6 months)	3 (122)			Favors CBT-I WMD = -38.18 [-65.57 to -10.78]	Low (moderate risk of bias)
		Wake time after sleep onset, self-report, minutes (at >6 months)	1 (70)			NS WMD = -6.00 [-19.66 to 7.66]	Insufficient (moderate risk of bias, imprecise, unknown consistency)
		Sleep efficiency, mean change (up to 6 months)	4 (132)			Favors CBT-I WMD = 13.22 [5.07 to 21.38]	Low (moderate study limitations)
	Adverse Effects	Withdrawals	2 (126)	13% (4/62)	11% (5/64)	NS	Insufficient (moderate study limitations, imprecise)

CI = confidence intervals; CBT = cognitive behavioral therapy; MD = mean difference; NS = no significant difference; WMD = weighted mean difference

Global Outcomes

Four trials reported ISI scores. Three of the four trials show a statistical difference between groups (Table 7). Pooled analysis shows that ISI scores were 7.10 points lower with CBT-I (95% CI -12.87 to -1.27) (Figure 14) suggesting that most patients would see important benefits from treatment. Only one study assessed outcomes after 6 months and found ISI scores still better than passive controls, but the magnitude was smaller, with a mean difference of -3.40 (95% CI -6.25 to -0.55).

Sleep Outcomes

Three efficacy trials enrolling pain patients reported sleep onset latency (Figure 15). In all three trials, the CBT-I groups decreased sleep onset latency compared with passive control. Whether the control was a placebo or sham treatment or wait-list did not matter. Pooled estimate shows that sleep onset latency decreases by over 26 minutes. Four efficacy trials enrolling pain patients reported total sleep time. Total sleep time was similar across groups in all trials as well as the pooled result with CBT-I. The one trial measuring outcomes beyond 6 months found similar total sleep time with CBT-I and placebo. Three trials reported wake time after sleep onset (Figure 16). All trials showed a statistical improvement with CBT-I; pooled results show that CBT-I is associated with a decrease of nearly 40 minutes in wake time after sleep onset.

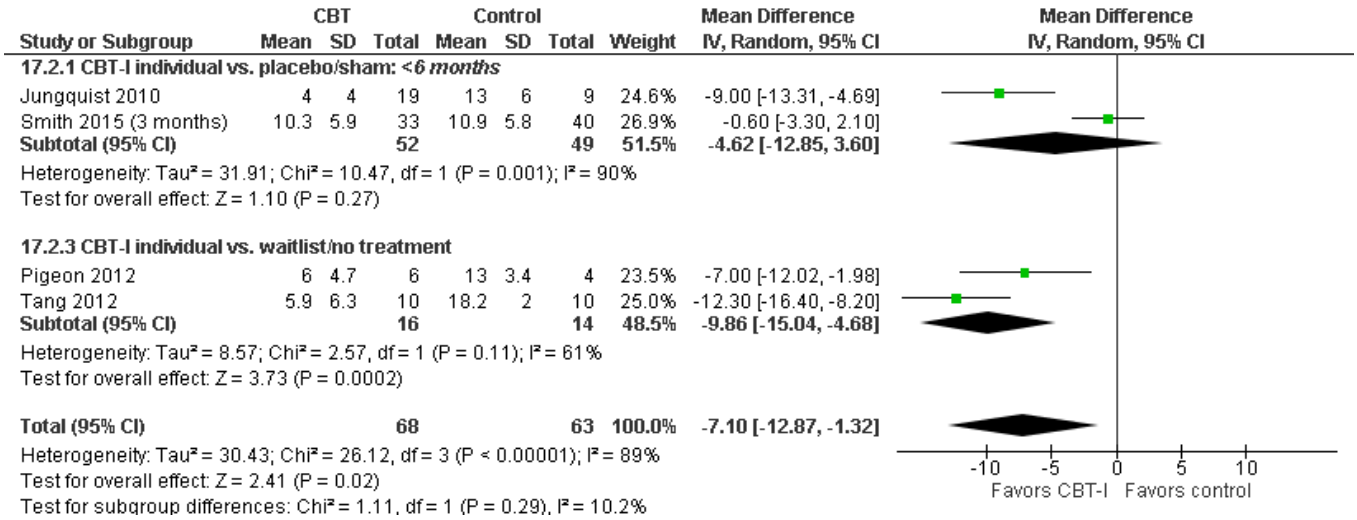
Functioning, Mood, and Quality of Life

Several trials reported functioning, mood, or quality of life outcomes.

Adverse Effects

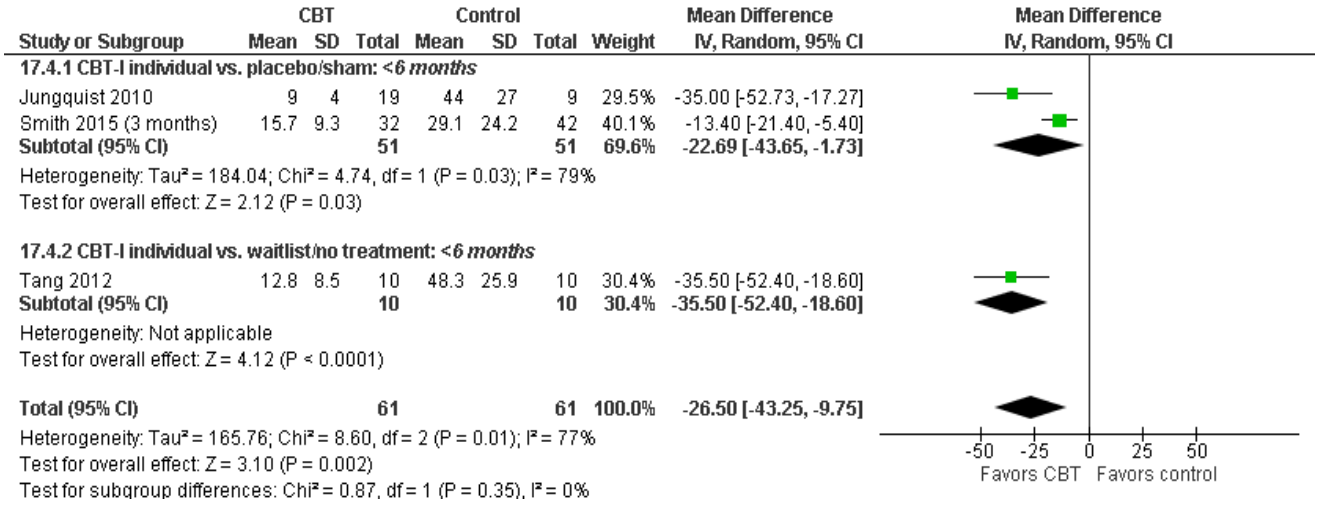
Most trials reported withdrawals or adverse effects.

Figure 14. Efficacy of CBT-I in adults with pain: ISI scores



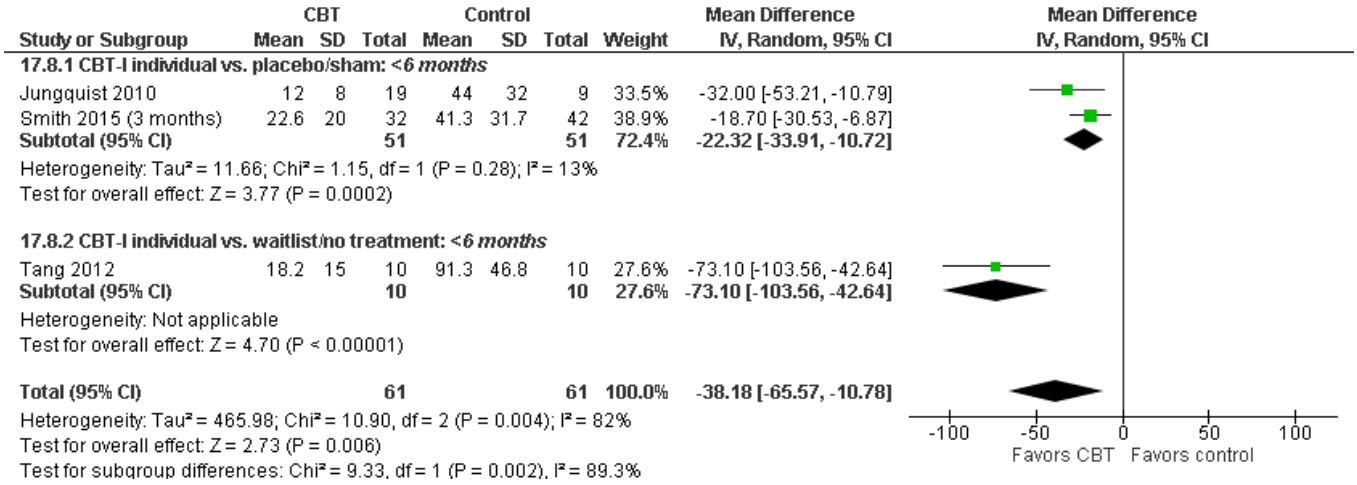
CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; ISI = Insomnia Severity Index; IV = inverse variance; SD = standard deviation

Figure 15. Efficacy of CBT-I in adults with pain: sleep onset latency



CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 16. Efficacy of CBT-I in adults with pain: wake time after sleep onset



CBT-I = cognitive behavioral therapy – insomnia; CI = confidence interval; IV = inverse variance; SD = standard deviation

Efficacy of Cognitive Behavioral Therapy in Other Special Populations

Overview of Studies

Two trials studied CBT-I in other special populations (college students and insomnia patients with hearing-impairment).[87,88] Because we have only one small trial with moderate study limitations in each of these special populations, evidence is insufficient to draw conclusions about the efficacy of CBT-I.

Efficacy of Multicomponent Behavioral Interventions in the General Adult Population

Overview of Studies

We identified one trial that assessed the efficacy of multicomponent behavioral interventions in the general adult population. Risk of bias was predominantly moderate.[89] Evidence from one small trial was insufficient to draw conclusions regarding the efficacy of multicomponent behavioral interventions in treating insomnia disorder in the general adult population.

Efficacy of Multicomponent Behavioral Interventions or Brief Behavioral Therapy in Older Adults

Overview of Studies

We identified three trials reported in four publications comparing multicomponent behavioral therapies (MBT) or BBT with passive control in older adults.[90-93] The trials randomized 146 participants, the mean age was around 70, and the majority of participants were female. In the two trials reporting, participants had mean insomnia duration of 15.3 years. All trials were conducted in the United States.[90-93] Two trials randomized participants to MBT/BBT or information control.[90-92] In the fourth trial, hypnotic-dependent adults with insomnia were randomized to either MBT or placebo.[93] We synthesized outcomes from these studies when possible (Table 8).

Table 8. Efficacy of multicomponent behavioral therapy or brief behavioral therapy in older adults

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
MBT/BBT vs. passive control (3 RCTs; N=146)	Global Outcomes	PSQI score	1 (79)			Favors MBT/BBT WMD = -2.90 [-4.22 to -1.58]	Insufficient (study limitations, unknown consistency)
	Sleep Outcomes	Sleep onset latency, self-report, minutes	3 (146)			Favors MBT/BBT WMD = -10.43 [-16.31 to -4.55]	Low (moderate study limitations)
		Total sleep time, self-report, minutes	3 (146)			NS WMD = -18.61 [-46.82 to 9.60]	Insufficient (moderate study limitations, imprecise)
		Wake time after sleep onset, self-report, minutes	3 (146)			Favors MBT/BBT WMD = -14.90 [-22.66 to -7.14]	Low (moderate study limitations)
		Sleep efficiency	3 (146)			Favors MBT/BBT WMD = 6.33 [3.38 to 9.29]	Low (moderate study limitations)

BBT = brief behavioral therapy; CI = confidence intervals; MBT = multicomponent behavioral therapy; NS = no significant difference; WMD = weighted mean difference

Global Outcomes

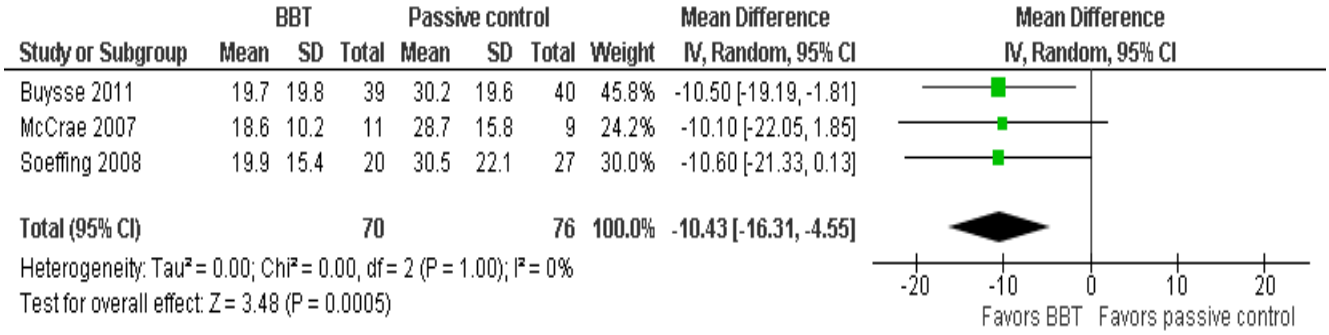
In the one trial reporting PSQI scores, participants receiving BBT saw a statistically significant difference from the passive control group at followup. Multicomponent behavioral interventions or BBT participants scored an average of 3 points lower on PSQI than passive controls.

Sleep Outcomes

Two of three sleep outcomes improved. Sleep outcomes were reported in all multicomponent behavioral intervention and BBT efficacy trials. Improvements in sleep onset latency favored BBT over passive control in all three trials. The pooled estimate shows that multicomponent behavioral therapies or BBT reduced sleep onset latency by more than 10 minutes over passive control (Figure 17). All three trials reported total sleep time, showing no statistically significant increase when compared with passive control patients. Significant decreases in wake time after sleep onset were demonstrated in two trials (Figure 18).[90,92] The pooled estimate shows that multicomponent behavioral therapies or BBT reduced wake time after sleep onset by nearly 15 minutes compared with passive control.

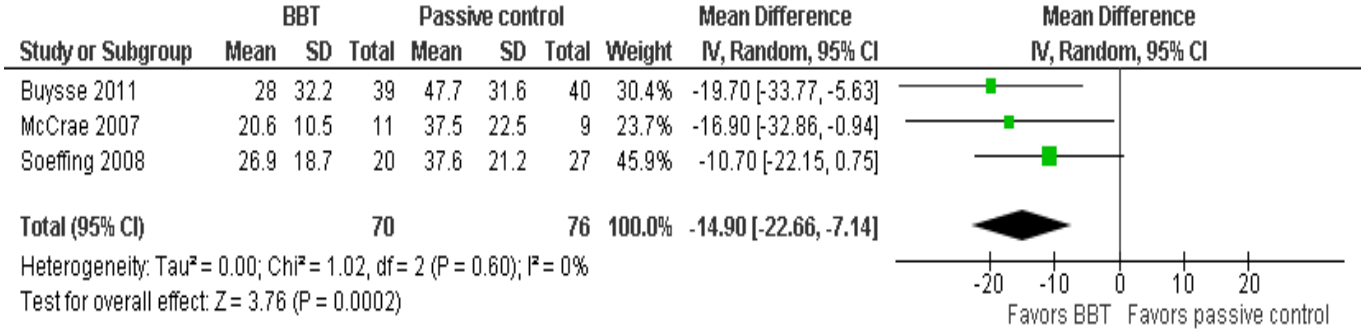
The pooled estimate shows that older BBT participants increased their sleep efficiency more than 6 percentage points over passive control participants.

Figure 17. Efficacy of multicomponent behavioral or brief behavioral therapy in older adults: sleep onset latency



CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 18. Efficacy of multicomponent behavioral therapy or brief behavioral therapy in older adults: wake time after sleep onset



CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

One trial reported functioning, mood, and quality of life outcomes. Buysse et al. reported the difference in SF-36 scores from baseline to post-treatment (4 weeks). Those in the BBT group reported less disability after 4 weeks (3.85 [SE=1.76]) and those in the passive control group reported more (-2.33 [SE=1.73]).

Adverse Effects

Specific adverse effects were not reported. One trial reported study withdrawals or loss to followup (5%) but neither reported withdrawals or loss to followup by group.[90,91]

Efficacy of Sleep Restriction in the General Adult Population

Overview of Studies

One trial assessed the efficacy of sleep restriction therapy in the general adult population.[94] This study provides insufficient evidence to draw conclusions regarding the efficacy of sleep restriction therapy in the general adult population.

Efficacy of Sleep Restriction in Older Adults

Overview of Studies

We included studies as efficacy of sleep restriction (SR) if they had an active SR arm and passive control arm (wait-list control, no treatment, or sleep hygiene/sleep education). We identified two trials that compared SR to a passive control in older adults (Table 9).[95,96] Both trials were conducted in the United States. Studies differed in how the sleep restriction was delivered. 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).[95] The mean duration of insomnia in the one study which reported it by group was 10.8 years.[95] Risk of bias was predominantly moderate.

Table 9. Efficacy of sleep restriction in older adults: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Individual SR vs. passive control (2 RCTs; N=141)	Global Outcomes	Remission (ISI ≤8)	1 (94)	23% (10/44)	4% (2/50)	Favors SRT RR = 5.68 [1.32 to 24.54 ARR = 18.7 NNT = 5	Insufficient (moderate study limitations)
		Responders (ISI score decreases over 6 points)	1 (73)	50% (17/34)	15% (6/39)	Favors SRT RR = 3.25 [1.45 to 7.30] ARR = 35 NNT = 2.8	Insufficient (moderate study limitations)
		ISI mean change	1 (94)				Insufficient (moderate study limitations)
	Sleep Outcomes	Sleep onset latency, self-report, minutes (at <6 months)	2 (141)			NS WMD = -11.38 [-27.74 to 4.99]	Insufficient (moderate study limitations, imprecise, inconsistent)
		Sleep onset latency, self-report, minutes (at >6 months)	1 (47)			NS WMD = -14.00 [-26.86 to -1.14]	Insufficient (moderate study limitations, imprecise, inconsistent)
		Total sleep time, self-report, minutes (at <6 months)	2 (141)			NS WMD = -17.57 [-102.36 to 67.21]	Insufficient (study limitations, imprecise, inconsistent)
		Total sleep time, self-report, minutes (at >6 months)	1 (47)			NS WMD = -8.50 [-43.71 to 26.71]	Insufficient (study limitations, imprecise, inconsistent)
		Wake time after sleep onset, self-report, minutes	1 (94)			Favors SRT MD = -24.47 [-40.98 to -7.96]	Insufficient (moderate study limitations, unknown consistency)

Table 9. Efficacy of sleep restriction in older adults: overview and strength of evidence (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Individual SR vs. passive control (2 RCTs; N=141) (continued)	Sleep Outcomes (continued)	Sleep efficiency	1 (94)			NS	Insufficient (moderate study limitations, unknown consistency)
		Sleep quality	1 (94)			Favors SRT SMD= 0.74 [0.32 to 1.16]	Insufficient (moderate study limitations, unknown consistency)

ARR = absolute risk reduction; CI = confidence intervals; ISI-Insomnia Severity Index; MD = mean difference; NS = No significant difference; NNT = number needed to treat; RR = risk ratio; SMD = standardized mean difference; SRT = sleep restriction therapy; WMD = weighted mean difference

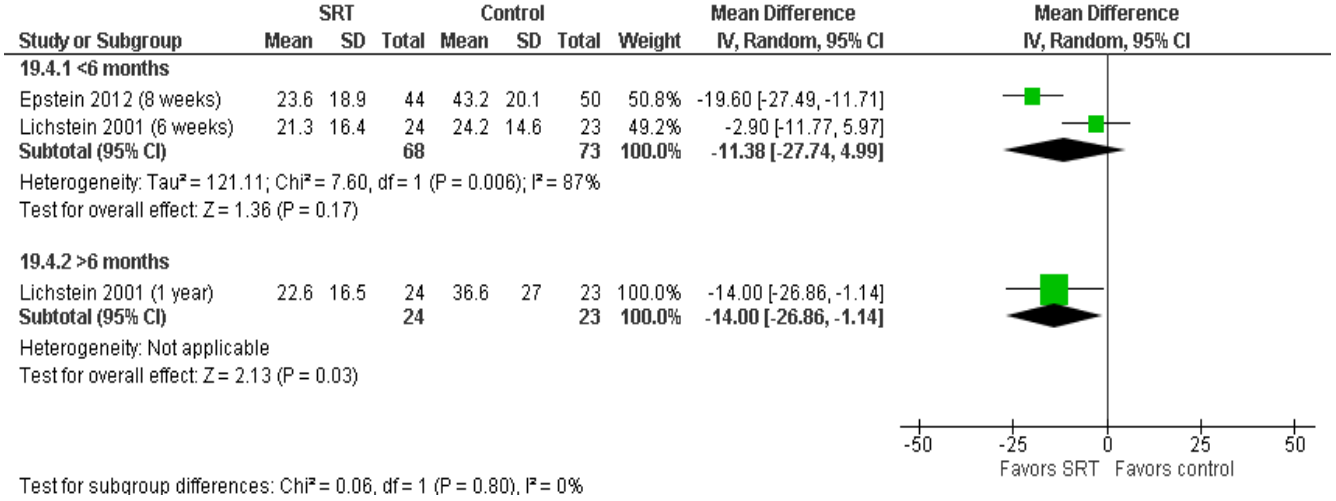
Global Outcomes

Evidence on global outcomes was insufficient to draw conclusions because only one study reported these outcomes. It found that sleep restriction led to greater proportion of sleep restriction therapy participants to achieve remission (achieving an ISI score ≤7 at followup) and response.[95] Sleep restriction participants also achieved better ISI scores compared with passive comparison with a five point improvement in ISI score. This change was lower than the 7 point change associated with "response."

Sleep Outcomes

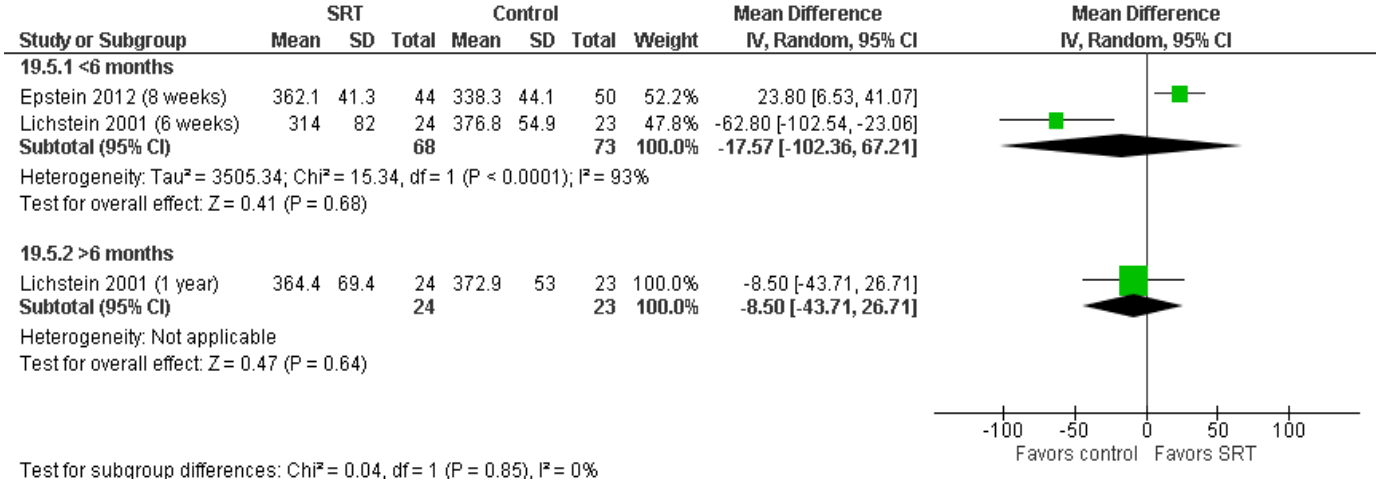
Evidence was insufficient to draw conclusions regarding most sleep outcomes. Sleep outcomes were reported in all older adult sleep restriction efficacy trials (Figures 19 and 20). The two trials showed different results resulting in serious inconsistency. Pooled data show a large range in post-intervention sleep onset latency and total sleep time. Due to the large range and heterogeneity, the pooled differences were not statistically significant. Since sleep restriction limits time in bed, it is to be expected that total sleep time would not differ significantly between sleep restriction and comparison groups. Mean sleep efficiency with sleep restriction was not significantly different than those in passive control at followup in one study. Sleep quality was reported in one trial.[95] Mean sleep quality of those in the sleep restriction treatment group was significantly higher than those in passive control at followup.

Figure 19. Efficacy of sleep restriction among older adults: sleep onset latency



CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 20. Efficacy of sleep restriction among older adults: total sleep time



CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

Epstein et al. reported STAI state anxiety, STAI trait anxiety, and Geriatric Depression Scale scores for both groups and found no statistically significant differences post-treatment on STAI trait anxiety, but found statistically significant improvements in STAI state anxiety and Geriatric Depression Scale scores for the sleep restriction group when compared to passive control.[95]

Adverse Effects

Specific adverse effects were not reported.

Efficacy of Stimulus Control in the General Adult Population

Overview of Studies

We identified two RCTs that assessed the efficacy of stimulus control to treat insomnia disorder in the general adult population (Table 10).[89,97] One was conducted in Australia[89] and one in Scotland.[97] Studies differed in how the stimulus control was delivered. We pooled data when sufficient data were provided.

Table 10. Efficacy of stimulus control in the general adult population: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Stimulus control vs. passive control (2 RCTs; N=68)	Global Outcomes	PSQI score	1 (40)			Favors Stimulus Control WMD = -2.40 [-4.07 to -0.73]	Insufficient (moderate study limitations, unknown consistency)
	Sleep Outcomes	Sleep onset latency, self-report, minutes	2 (68)	-	-	Favors Stimulus Control WMD = -31.24 [-45.26 to -17.22]	Low (moderate study limitations)
		Total sleep time, self-report, minutes	2 (68)	-	-	Favors Stimulus Control WMD = 43.54 [12.67 to 74.42]	Low (moderate study limitations, imprecise)
		Wake time after sleep onset, self-report, minutes	1 (40)	-	-	Favors Stimulus Control WMD = -37.60 [-67.65 to -7.55]	Insufficient (moderate study limitations, imprecise, inconsistent)
		Sleep efficiency	1 (40)			Favors Stimulus Control WMD = 13.40 [6.44 to 20.36]	Insufficient (moderate study limitations, unknown consistency)

CI = confidence intervals; NS = No significant difference; WMD = weighted mean difference

Global Outcomes

Harris et al. reported mean PSQI scores and showed that scores were higher in the stimulus control group than the placebo group.[89]

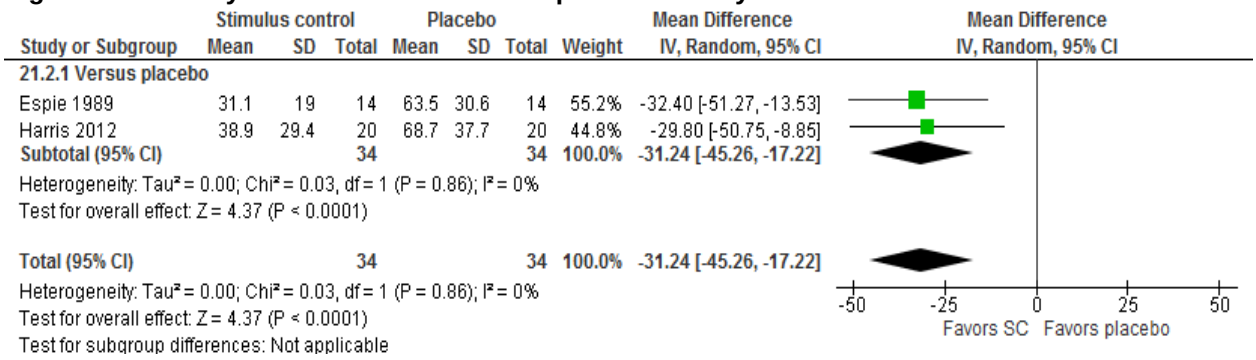
Sleep Outcomes

Poolable data on sleep outcomes were reported in two of the stimulus control efficacy trials (Figures 21 and 22).

Improvements in sleep onset latency and total sleep time were significantly different than passive control in both trials that reported poolable data. Pooled data show that stimulus control decreases sleep onset latency by over 30 minutes and increases total sleep time by nearly 45 minutes when compared with placebo.

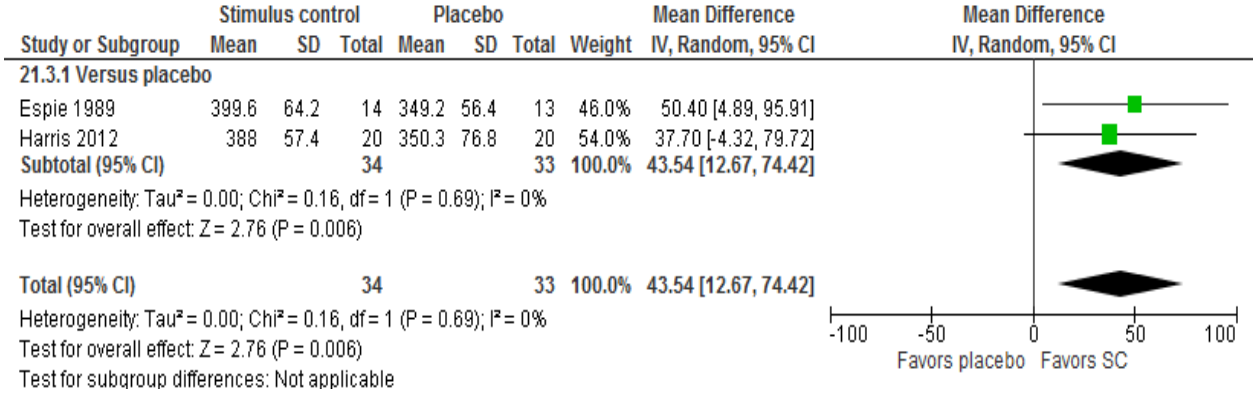
Other sleep outcomes were reported in one trial. Harris et al. showed that stimulus control decreases wake time after sleep onset and increases sleep efficiency. However, because these findings are from one small study, evidence is considered insufficient.

Figure 21. Efficacy of stimulus control: sleep onset latency



CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 22. Efficacy of stimulus control: total sleep time



CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

Neither trial reported functioning, mood, or quality of life outcomes

Adverse Effects

Specific adverse effects were not reported.

Efficacy of Stimulus Control in Older Adults

Overview of Studies

We identified two trials that compared stimulus control with passive control in older adults (Table 11).[95,98] One trial was conducted in the United States[95] and one was conducted in Canada.[98] The mean age across studies reporting age was around 70; most participants were female and 99 percent were white (in the trial that reported race).[95] The mean duration of insomnia in the three studies that reported it was 12.7 years. We pooled results when possible (Table 11).

Table 11. Efficacy of stimulus control in older adults: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Stimulus Control vs. passive control reporting sample size by group) ***(2 RCTs; N=113)***	Global Outcomes	Remission (ISI ≤7)	1 (94)	30 (13/44)	4 (2/50)	Favors SCT RR = 7.39 [1.76 to 30.94] ARR = 25.5 NNT = 4	Insufficient (moderate study limitations, imprecise, unknown consistency)
		Responders (change in ISI >6 points)	1 (94)	57% (21/37)	15% (6/39)	Favors SCT RR = 3.69 [1.68 to 8.11] ARR = NNT = 2.4	Insufficient (moderate study limitations, imprecise, unknown consistency)
		ISI mean change	1 (94)	-	-	Favors SCT MD = -5.10 [-7.02 to -3.18]	Insufficient (moderate study limitations)
	Sleep Outcomes	Sleep onset latency, self-report, minutes	2 (113)	-	-	NS WMD= -10.36 [-44.50 to 23.79]	Insufficient (moderate study limitations, imprecise, inconsistent)
		Total sleep time, self-report, minutes	2 (113)	-	-	Favors SCT WMD = 40.37 [23.47 to 57.27]	Low (study limitations)
		Wake time after sleep onset, self-report, minutes	1 (94)	-	-	Favors SCT MD = -26.60 [-38.11 to -15.09]	Insufficient (moderate study limitations, unknown consistency)
		Sleep efficiency	1 (94)	-	-	Favors SCT MD = 13.20 [9.92 to 16.48]	Insufficient (moderate study limitations, unknown consistency)
		Sleep quality	1 (94)	-	-	Favors SCT SMD = 0.99 [0.56 to 1.42]	Insufficient (moderate study limitations, imprecise, unknown consistency)

ARR = absolute risk reduction; CI = confidence intervals; MD = mean difference; NS = No significant difference; NNT = number needed to treat; RR = risk ratio; SCT = stimulus control therapy; SMD = standardized mean difference; WMD = weighted mean difference

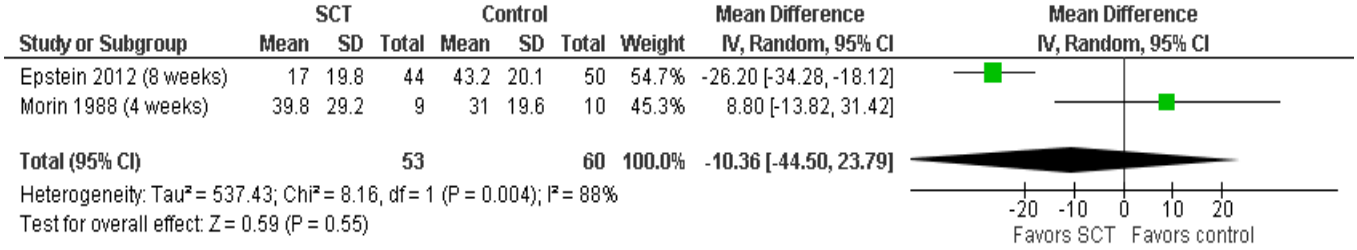
Global Outcomes

Global outcomes were reported by only one study and are therefore insufficient to draw conclusions regarding efficacy. The same study assessed insomnia remitters (achieving an ISI score ≤8 at followup).[95] Stimulus control achieved higher rates of remission compared with passive control. One study reported mean ISI scores.[95] Stimulus control resulted in a 5.10 point improvement in ISI score compared with passive control. This difference was less than the 7 points necessary for 'response' to treatment.

Sleep Outcomes

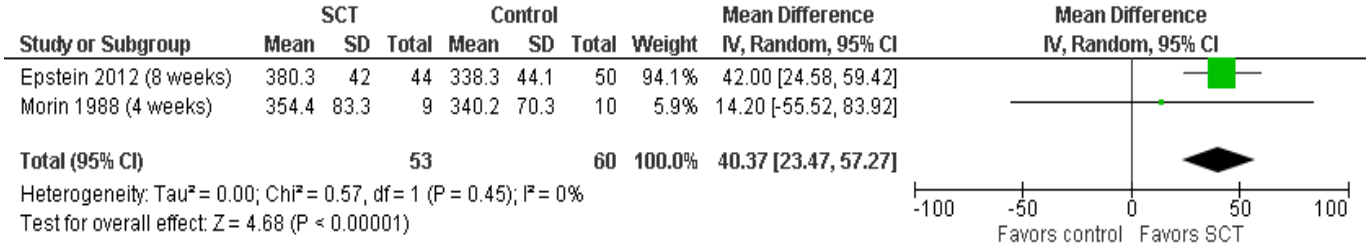
Sleep outcomes were reported in all older adult stimulus control efficacy trials. Changes in sleep onset latency were inconsistent across trials (Figure 23). Pooled data show a large range in post-intervention sleep onset latency. Due to the large range and heterogeneity, the pooled difference was not statistically significant. One trial showed a statistically significant difference in total sleep time among stimulus control participants when compared with passive treatment controls, while one did not. Pooled data showed total sleep time improved with stimulus control with a mean increase in total sleep time of over 40 minutes (Figure 24). One trial reporting wake time after sleep onset favored stimulus control. Mean sleep efficiency with stimulus control was significantly different than those in passive control at followup in one study. Sleep quality was reported in one trial. Mean sleep quality of those in the stimulus control treatment group was significantly higher than those in passive control at followup.

Figure 23. Efficacy of stimulus control among older adults: sleep onset latency



CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 24. Efficacy of stimulus control among older adults: total sleep time



CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

Epstein et al. reported STAI state anxiety, STAI trait anxiety, and Geriatric Depression Scale scores for both groups and found no statistically significant differences post-treatment.[95] Morin

and Azrin reported that they found no differences between stimulus control and passive control groups on STAI state anxiety, STAI trait anxiety, and Beck Depression Inventory from baseline to followup.[98]

Adverse Effects

Specific adverse effects were not reported. All trials reported withdrawals or loss to followup; however, not all of them reported by group.

Efficacy of Relaxation Therapy in the General Adult Population

Overview of Studies

We identified two randomized trials comparing relaxation therapy with passive control in the general adult population (Table 12).[55,97] Participants had a mean insomnia duration of several years. One trial was conducted in the United States[55] and one in the United Kingdom.[97] Both trials had a moderate risk of bias. Both trials randomized participants to relaxation therapy or passive control. Espie randomized participants to relaxation therapy, stimulus control, paradoxical intention placebo, or no treatment; only two arms (relaxation therapy and paradoxical intention placebo) are discussed in this section.[97] Edinger et al. randomized participants to progressive relaxation or a placebo treatment (quasi-desensitization).[55]

Table 12. Efficacy of relaxation therapy in the general adult population: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Placebo % (n/N)	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Relaxation vs. passive control (2 RCTs; N=77)	Sleep Outcomes	Sleep onset latency, self-report, minutes	1 (28)	-	-	NS MD = -6.10 [-19.64 to 40.11]	Insufficient (moderate study limitations, imprecise, unknown consistency)
		Total sleep time, self-report, minutes	2 (77)	-	-	NS MD = 10.23 [-19.64 to 40.11]	Insufficient (moderate study limitations, imprecise)

CI = confidence intervals; MD = mean difference; NS = no significant difference; WMD = weighted mean difference

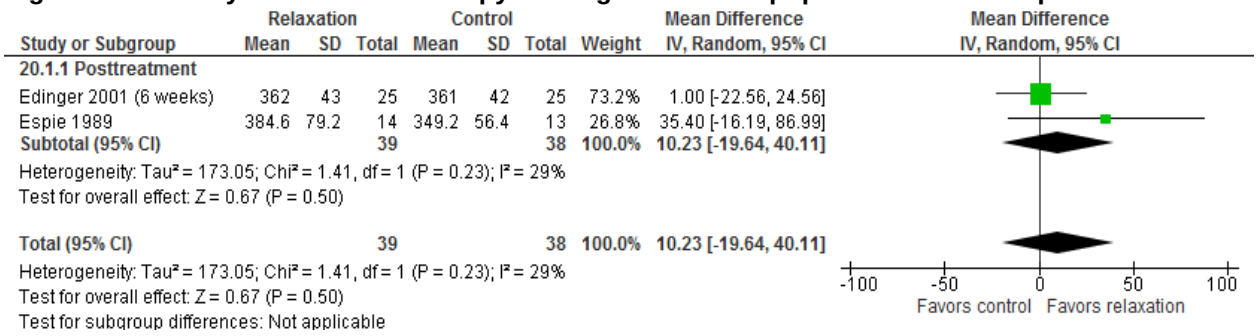
Global Outcomes

Neither trial reported global outcomes.

Sleep Outcomes

Both trials reported sleep outcomes. The pooled estimate shows that relaxation therapy was similar to placebo in reducing sleep onset latency (Figure 25) and total sleep time.

Figure 25. Efficacy of relaxation therapy in the general adult population: total sleep time



CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

No trials reported functioning, mood, and quality of life outcomes.

Adverse Effects

Specific adverse effects were not reported. All four trials reported withdrawals or loss to followup. None of the studies reported withdrawals or loss to followup by group.

Comparative Effectiveness of Psychological Treatments

Several trials included other comparisons of active interventions that we have not addressed specifically thus far. However, the lack of similar comparisons yields insufficient evidence to draw conclusions about the comparative effectiveness of different psychological interventions.

Three trials compared delivery modes of CBT-I. Bastien et al.[99] compared individual-, group-, and telephone-delivered CBT-I. Mimeault et al. included two arms that compared self-help CBT-I to self-help CBT-I with professional guidance.[64] Holmqvist et al. compared web-based versus phone-based CBT-I.[100] Lancee et al. compared self-help CBT-I with self-help CBT-I with support.[101,102] Rybarczyk et al. compared two types of CBT-I (self-help versus therapist led) in older participants, most of whom had comorbidities.[103] Pech et al. compared two multicomponent programs (both contained sleep hygiene education, stimulus control, and progressive relaxation; the two groups additionally got either cognitive therapy or problem solving therapy)[104] to stress management programs. Rybarczyk et al. randomized older participants to participants to CBT-I or stress management.[105] Two studies assessed the adjunctive efficacy of certain components. Jansson-Frojmark et al. assessed the adjunctive efficacy of a constructive worry program to a multicomponent behavioral treatment.[106] Riley et al. studied the adjunctive efficacy of behavioral prompts as adjunctive functions in a computer device provided to all participants.[107]

Efficacy of Pharmacologic Treatment

Key Points

- Most RCTs were small and of short duration. Minimally important differences were often not established or used. We found no eligible trials for many insomnia treatments and some insomnia pharmacological treatments are not specifically approved for insomnia disorders.
- Evidence from RCTs indicates 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 to placebo.
- Low strength evidence shows that eszopiclone improved one global outcome by a minimum important difference and improved several sleep outcomes, but not sleep onset latency in older adults. Evidence on adverse effects was insufficient. Low strength evidence shows that zolpidem improved sleep onset latency in older adults. Evidence on other outcomes was insufficient.
- The melatonin agonist, ramelteon did not improve global or sleep outcomes in a clinically meaningful way in the general population. 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.
- Long-term adverse effects were derived from observational studies and suggest that use of hypnotics may be associated with dementia but not mortality. Zolpidem but not benzodiazepines may be associated with fractures. Withdrawal due to any reason was common especially with ramelteon.
- The orexin receptor antagonist, suvorexant, improved global and sleep outcomes versus placebo (moderate strength evidence). Adverse effects did not differ between groups.
- Four small trials compared cognitive behavioral therapy for insomnia (CBT-I) versus nonbenzodiazepine hypnotics or benzodiazepines. Results were mixed and evidence was insufficient.

We identified 37 publications reporting 36 unique RCTs of acceptable risk of bias that evaluated pharmacologic treatments for insomnia disorder in the general adult population and in older adults. We found the most data on the newer FDA-approved drugs. Patients were typically diagnosed with insomnia disorder according to DSM IV criteria (Appendix E). While DSM-IV criteria require symptoms to be present for at least 1 month, the mean duration of symptoms was rarely reported. Additional enrollment criteria were based on thresholds for sleep onset latency (SOL), total sleep time (TST) and/or less frequently wake after sleep onset (WASO) and/or number of awakenings per night during a typical night over the month prior to enrollment. None used global measures for enrollment, though some also required that patients reported some

daytime dysfunction associated with insomnia. Only two trials reported severity based on scores of global measures such as the ISI in addition to a total sleep time of ≤6.5 hours and/or SOL of >30 minutes. When WASO was included, the threshold for enrollment ranged from 30 to 120 minutes. Trials rarely assessed treatments longer than 4 weeks. Most enrollees were female, of white race, and less than 50 years of age. Most studies were industry sponsored. Few antidepressant or benzodiazepine trials met eligibility criteria, primarily due to short treatment durations. Global outcomes were less often measured than sleep outcomes. Minimum important differences were identified for some instruments used to assess global outcomes, but these were not frequently used nor is it clear whether they are well established.

Efficacy of Nonbenzodiazepine Hypnotics in the General Adult Population

We identified 14 RCTs that assessed the efficacy of three nonbenzodiazepine hypnotics commonly used to treat insomnia disorder in the United States (eszopiclone [Lunesta], zaleplon [Sonata], and zolpidem [Ambien]) (Table 13).

Table 13. Efficacy of nonbenzodiazepine hypnotics: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean[a]	Placebo % (n/N) or Mean[a]	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Eszopiclone 2-3 mg vs. placebo (3 RCTs; N=1,929)	Global Outcomes	Remission from Insomnia disorder based on ISI	1 (825)	50 (272/547)	19 (52/278)	Favors eszopiclone RR = 2.66 [2.05 to 3.44] ARR = 0.31 [0.25 to 0.37] NNT = 4	Low (moderate study limitations and unknown consistency)
		ISI, mean change in scores	1 (828)	-9.2	-4.6	Favors eszopiclone MD = -4.60 [-5.26 to -3.94]	Low (moderate study limitations and unknown consistency)
	Sleep Outcomes	Sleep onset latency, self-report, minutes	3 (1,820)	43	61	Favors eszopiclone WMD = -19.1 [-24.1 to -14.1]	Moderate (moderate study limitations)
		Total sleep time, self-report, minutes	3 (1,820)	387	347	Favors eszopiclone WMD = 44.8 [35.4 to 54.2]	Moderate (moderate study limitations)
		WASO, self-report, minutes	3 (1,820)	36	46	Favors eszopiclone WMD = -10.8 [-19.8 to -1.70]	Low (moderate study limitations and inconsistent) [I^2=70%])
		Sleep quality	2 (992)	NA	NA	Favors eszopiclone SMD = 0.47 [0.32 to 0.61]	Moderate (moderate study limitations)
	Adverse Effects	Overall withdrawals	3 (1,927)	33 (450/1352)	41 (236/575)	Greater with placebo RR = 0.81 [0.66 to 1.00]; ARR = -0.06 [-0.17 to 0.04]	Low (moderate study limitations and imprecise)
		Withdrawals due to adverse events	3 (1,927)	9 (127/1352)	6 (36/575)	NS	Low (moderate study limitations and imprecise)
		Participants with ≥1 adverse event	2 (1,616)	79 (896/1141)	64 (303/475)	Greater with eszopiclone RR = 1.21 [1.08 to 1.36] ARR = 0.14 [0.07 to 0.20] NNH = 7	Moderate (moderate study limitations)

Table 13. Efficacy of nonbenzodiazepine hypnotics: overview and strength of evidence (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean[a]	Placebo % (n/N) or Mean[a]	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Zaleplon 5-20 mg vs. placebo (2 RCTs; N=973)	Global Outcomes	NR					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	1 (209)	10 mg 47 5 mg 59	10 mg 56 5 mg 56	Favors zaleplon with 10 mg dose MD = -9.9 [-19.5 to -0.4] NS with 5 mg dose MD = 2.5 [-9.3 to 14.3]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Total sleep time, self-report, minutes	2 (822)	-	-	NS (unable to pool data)	Low (moderate study limitations and imprecise)
		Sleep quality, *Improved sleep quality, self-report*	2 (879)	57 (376/656)	48 (108/223)	Favors zaleplon RR = 1.19 [1.02 to 1.38] ARR = 0.09 [0.01 to 0.17] NNT = 11	Moderate (moderate study limitations)
	Adverse Effects	Overall withdrawals	2 (971)	12 (85/726)	8 (20/245)	NS, 1.42 [0.89 to 2.26]	Low (moderate study limitations and imprecise)
		Withdrawals due to adverse events	2 (965)	4 (29/720)	2 (6/245)	NS, 1.63 [0.69 to 3.88]	Low (moderate study limitations and imprecise)
		Participants with ≥1 adverse event	2 (965)	71 (510/720)	73 (178/245)	NS, 0.96 [0.89 to 1.05]	Moderate (moderate study limitations)

Table 13. Efficacy of nonbenzodiazepine hypnotics: overview and strength of evidence (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean[a]	Placebo % (n/N) or Mean[a]	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Zolpidem 10-15 mg vs. placebo (6 RCTs; N=844)	Global Outcomes	NR					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	4 (373)	39	54	Favors zolpidem short-term WMD = -15.0 [-22.1 to -7.8]	Moderate (moderate study limitations)
		Total sleep time, self-report, minutes	3 (167)	391	366	Favors zolpidem short-term WMD = 23.0 [2.0 to 43.9]	Moderate (moderate study limitations)
		Sleep quality, *Improved sleep quality, self-report*	3 (557)	69 (200/289)	49 (130/268)	Favors zolpidem RR = 1.40 [1.20 to 1.65] ARR = 0.21 [0.09 to 0.33] NNT = 5	Moderate (moderate study limitations)
	Adverse Effects	Overall withdrawals	6 (859)	15 (69/456)	12 (50/403)	NS, 1.17 [0.84 to 1.65]	Low (moderate study limitations and imprecise)
		Withdrawals due to adverse effects	5 (828)	6 (25/440)	2 (6/388)	Greater with zolpidem RR = 2.80 [1.22 to 6.41] ARR= 0.04 [0.02 to 0.07] NNH= 25	Moderate (moderate study limitations)
		Participants with ≥1 adverse effect	4 (698)	68 (256/376)	67 (215/322)	NS, 1.05 [0.91 to 1.21]	Moderate (moderate study limitations)

Table 13. Efficacy of nonbenzodiazepine hypnotics: overview and strength of evidence (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean[a]	Placebo % (n/N) or Mean[a]	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Zolpidem 10 mg "as needed" vs. placebo (3 RCTs; N=607)	Global Outcomes	Clinical Global Impression – "Much or very much improved"	1 (243)	54 (67/124)	24 (29/119)	Favors zolpidem RR= 2.22 [1.55 to 3.16] ARR= 0.30 [0.18 to 0.41] NNT= 4	Low (moderate study limitations and unknown consistency)
	Sleep Outcomes	Sleep onset latency, self-report, minutes	2 (355)	37	52	Favors zolpidem WMD = -14.8 [-23.4 to -6.2]	Moderate (moderate study limitations)
		Sleep onset latency, self-report, mean change, minutes	1 (245)	-23	-19	NS, MD = -4.2 [-13.5 to 5.1]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Total sleep time, self-report, minutes	2 (355)	416	365	Favors zolpidem WMD = 48.1 [34.8 to 61.5]	Moderate (moderate study limitations)
		Total sleep time, self-report, mean change, minutes	1 (245)	75	63	NS, MD = 11.4 [-7.1 to 29.9]	Insufficient (moderate study limitations, imprecise, unknown consistency)
		Wake time after sleep onset, self-report, minutes	1 (192)	33	55	MD = -22.8 [-37 to -8.6]	Low (moderate study limitations, and Inconsistent)
		Wake time after sleep onset, self-report, mean change, minutes	1 (245)	-33	-31	NS,MD = -1.4 [-10.8 to 8.0]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
	Adverse Effects	Overall withdrawals	3 (607)	13 (39/304)	13 (38/303)	NS, RR = 1.0 [0.5 to 2.0]	Low (moderate study limitations, imprecise)
		Withdrawals due to adverse effects	3 (607)	4 (12/304)	1 (4/303)	NS ,RR = 2.8 [0.95 to 8.0]	Insufficient (study limitations, very imprecise)
		Participants with ≥1 adverse effects	1 (245)	19 (23/124)	15 (18/121)	NS, RR = 1.3 [0.7 to 2.2]	Insufficient (moderate study limitations, imprecise, and unknown consistency)

Table 13. Efficacy of nonbenzodiazepine hypnotics: overview and strength of evidence (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean[a]	Placebo % (n/N) or Mean[a]	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Zolpidem 3.5 mg SL vs. placebo (1 RCT; N=295)	Global Outcomes	NR					
	Sleep Outcomes	Sleep onset latency, self-report, minutes*, post middle of the night*	1 (295)	38	56	-18 [CI NR] (P<0.0001)	Low (moderate study limitations, unknown precision, and unknown consistency)
		Wake time after sleep onset, self-report, minutes, *post middle of the night*	1 (295)			NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Sleep quality, *Scale from 1 (extremely poor to 9 excellent)*	1 (295)	NA	NA	SMD = 0.38 [0.15 to 0.61]	Insufficient (moderate study limitations, imprecise and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (295)	8 (12/150)	6 (8/144)	NS, RR = 1.44 [0.61 to 3.42]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Withdrawals due to adverse effects	1 (295)	0 (0/150)	<1 (1/144)	NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)

Table 13. Efficacy of nonbenzodiazepine hypnotics: overview and strength of evidence (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean[a]	Placebo % (n/N) or Mean[a]	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Zolpidem 12.5 mg ER vs. placebo (1 RCT; N=1,018)	***Global Outcomes***	Clinical Global Impression – "Much or very much improved"	1 (1,016)	85 (567/667)	48 (168/349)	Favors zolpidem ER RR = 1.77 [1.58 to 1.98] ARR = 0.37 [0.31 to 0.43] NNT = 3	Low (unknown consistency)
	Sleep Outcomes	Sleep onset latency, self-report, mean change, minutes	1 (1,018)	~37	~28	Greater with zolpidem ER Approximately 9 minutes difference (graphically displayed) (P 0.001)	Low (unknown consistency)
		Total sleep time, self-report, mean change, minutes	1 (1,018)	~110	~85	Greater with zolpidem ER Approximately 25 minutes difference (graphically displayed) (P<0001)	Low (unknown consistency)
		Wake time after sleep onset, self-report, mean change, minutes	1 (1,018)	~-68	~-52	Greater with zolpidem ER Approximately 16 minutes difference (graphically displayed)	Low (unknown consistency)
	Adverse Effects	Overall withdrawals	1 (1,018)	36 (238/669)	48 (167/349)	Greater with placebo RR = 0.74 [0.64 to 0.86] ARR = -0.12 [-0.19 to -0.06]	Low (unknown consistency)
		Withdrawals due to adverse effects	1 (1,018)	8 (55/669)	5 (16/349)	Greater with zolpidem ER RR = 1.79 [1.04 to 3.08] ARR = 0.04 [0.01 to 0.07] NNH = 25	Low (unknown consistency)
		Participants with ≥1 adverse effect	1 (1,018)	63 (423/669)	51 (179/349)	Greater with zolpidem ER RR = 1.23 [1.10 to 1.39] ARR = 0.12 [0.06 to 0.018] NNH = 9	Low (unknown consistency)

ARR = absolute risk reduction; CI = confidence intervals; ER = extended release; ISI = Insomnia Sleep Index; MD = mean difference; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = No statistical difference; RR = risk ratio; SL = sublingual; SMD = standardized mean difference; WMD = weighted mean difference

a weighted by sample sizes

Efficacy of Eszopiclone (Brand Name Lunesta)

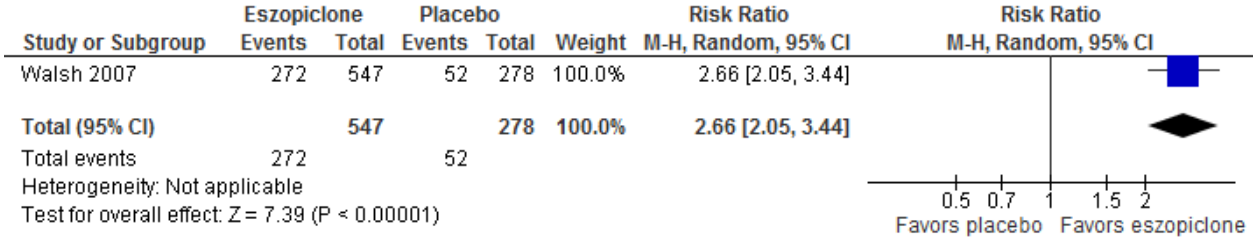
Overview of Studies

Three moderate risk of bias RCTs (n=1929) analyzed the efficacy of eszopiclone 2-3 mg daily[108-110] (Table 13). The mean age was 49 years; 63 percent were female. Most participants were white in the trials that reported race/ethnicity. All trials were conducted in the United States. Participants were randomized to 2 mg[110] or 3 mg eszopiclone.[108-110] One trial lasted 6 weeks[110] and two lasted 6 months.[108,109] All trials reported industry sponsorship and had moderate risk of bias.

Global Outcomes

Only Walsh et al. (n=825) reported clinically meaningful improvement in sleep based on ISI scores (Figure 26).[109] Eszopiclone more often resulted in remission or no clinically significant insomnia compared with placebo, indicated by an ISI score <7 at endpoint (50% vs. 19%) (low strength evidence). The difference in the mean change of ISI scores from baseline at 12 weeks of was -4.6 points (95% CI, -5.3 to -3.9) but this difference did not reach our minimum important difference of 7 points, indicating 'responder' to treatment.

Figure 26. Efficacy of eszopiclone: remitters

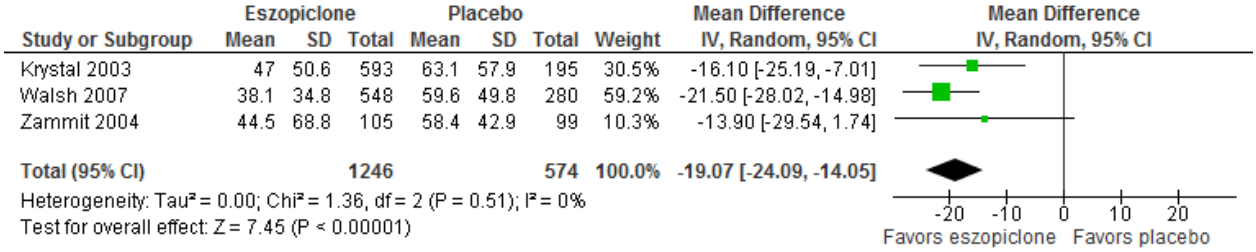


CI = confidence interval; M-H = Mantel-Haenszel; SD = standard deviation

Sleep Outcomes

Eszopiclone reduced sleep onset latency by 19 minutes and increased TST by 45 minutes compared with placebo (Figure 27). Mean sleep onset latency remained above 30 minutes in both groups in all three trials. Strength of evidence for both outcomes was moderate. Moderate strength of evidence also showed improved sleep quality with eszopiclone versus placebo. Low-strength evidence showed that eszopiclone decreased wake time after sleep onset more than placebo, but there was substantial heterogeneity between trials (I^2 = 70%). Within the two 6-month trials, Walsh et al.[109] reported greater improvement in wake time after sleep onset with eszopiclone compared with placebo (mean difference of 18 minutes) and Krystal et al.[108] reported eszopiclone was not more effective than placebo.

Figure 27. Efficacy of eszopiclone: sleep onset latency, minutes



CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

Secondary outcomes were rarely reported. Walsh et al. found that eszopiclone led to larger improvements in SF-36 domains of physical functioning, vitality, and social functioning than placebo.[109]

Adverse Effects

All three trials reported adverse effects. Withdrawal for any reason was higher with placebo than eszopiclone (41% vs. 33%). Withdrawals due to adverse effects did not significantly differ between groups (9% vs. 6%). Strength of evidence was low for both outcomes. A higher percentage of participants reported at least one adverse effect with eszopiclone than placebo (7% vs. 60%) (moderate strength of evidence). Krystal et al. reported a higher rate of serious adverse effects with eszopiclone than with placebo (3% vs. 1%) at 6 months.[108] Neither 6-month trial reported evidence of tolerance or withdrawal symptoms following discontinuation.[108,109] Specific adverse effects associated with eszopiclone use were somnolence (9% vs. 3% for placebo), unpleasant taste (23% vs. 3%), and myalgia (9% vs. 4%).

Efficacy of Zaleplon (Brand Name Sonata)

Overview of Studies

Two 4-week RCTs (n=973) compared zaleplon with placebo.[111,112] The mean age was 42 years; 61 percent were female. Participants were overwhelmingly white. One trial was conducted in the United States[112] and one was conducted in Canada and Europe.[111] Participants were randomized to 5, 10, or 20 mg doses. Both trials reported industry sponsorship and had moderate risk of bias.

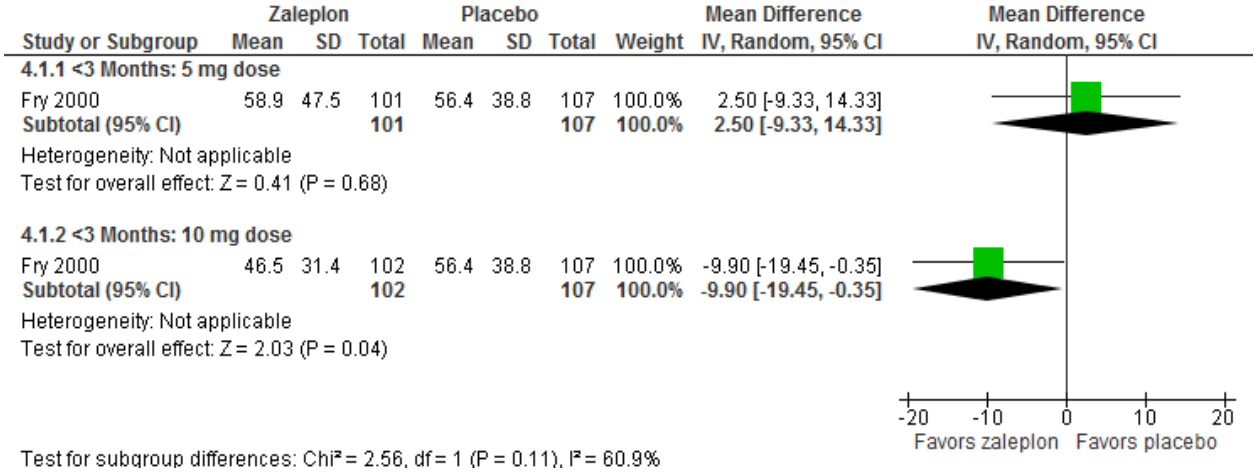
Global Outcomes

Neither zaleplon trial reported global outcomes.

Sleep Outcomes

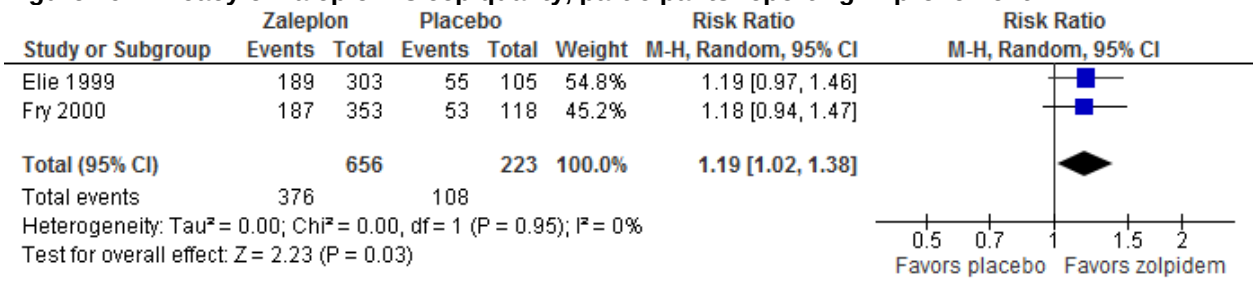
Fry et al. reported that zaleplon 10 mg but not 5 mg reduced mean sleep onset latency versus placebo (Figure 28).[112] Both trials reported that zaleplon did not consistently improve median total sleep time over placebo at 4 weeks. Participants randomized to any zaleplon dose were more likely than placebo participants to report improved sleep quality at week 4 (57% vs. 48%) (moderate strength of evidence) (Figure 29).[111,112] Individually, zaleplon doses of 5 and 20 mg, but not 10 mg, were superior to placebo in improving sleep quality at week 4 (57% vs. 48% and 60% vs. 48%, respectively).

Figure 28. Efficacy of zaleplon: subjective sleep latency, minutes



CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 29. Efficacy of zaleplon: sleep quality, participants reporting improvement



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CI = confidence interval; M-H = Mantel-Haenszel

Functioning, Mood, and Quality of Life

No functioning, mood, and quality of life outcomes were reported in zaleplon trials.

Adverse Effects

Adverse effects were reported in all trials. Low-strength evidence shows that zaleplon at any dose compared with placebo did not increase withdrawals for any reason (12% vs. 8%) or withdrawals due to adverse effects (4% vs. 2%). Moderate-strength evidence shows that the proportion of participants reporting at least one adverse event did not differ between the zaleplon and placebo groups (71% vs. 73%). No individual adverse effect was greater with zaleplon than placebo. Neither trial reported evidence of tolerance or withdrawal symptoms. No RCTs evaluated long-term efficacy or harms (1 year or longer) of zaleplon.

Zolpidem (Brand Name Ambien)

Overview of Studies

Six RCTs compared zolpidem with placebo.[60,111-115] Treatment duration was between 4 and 6 weeks for five of the trials. One trial was longer-term, with treatment duration up to 8 months.[115], The mean age was 44, and 58 percent were female among the 844 participants randomized. Participants were overwhelmingly white. Five trials were conducted in the United States[60,112-115] and one in Europe and Canada.[111] Four trials evaluated a 10 mg dose[60,111,112,115] and two trials

evaluated 10 and 15 mg doses.[113,114] One trial administered a 5 mg dose for participants 60 years of age or older.[115] Risk of bias was moderate in all trials. Three trials reported industry sponsorship, and two trials were supported by government funding. Sponsorship was unclear in one trial.[114]

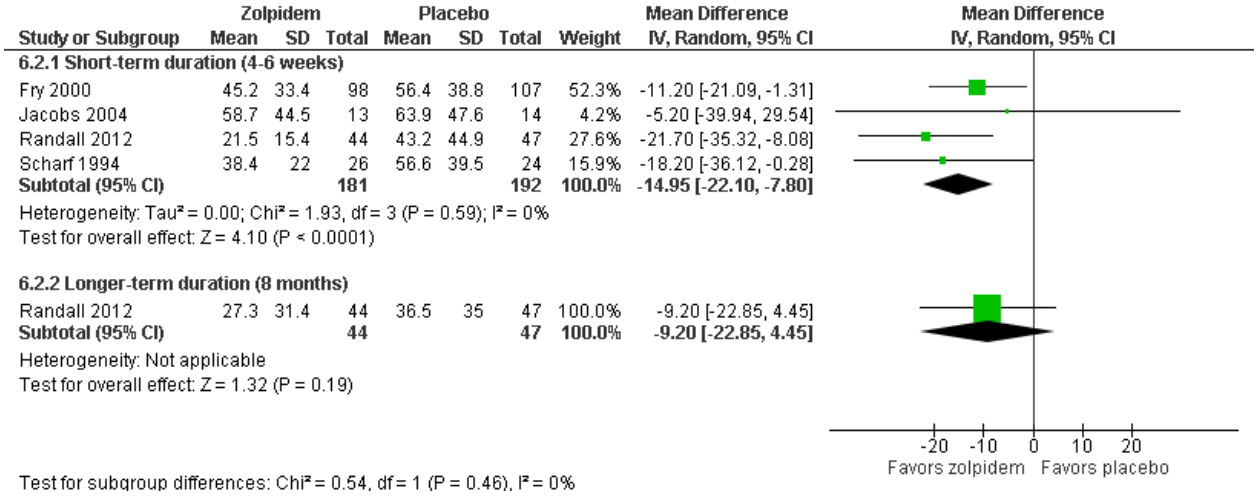
Global Outcomes

No zolpidem trial reported global outcomes.

Sleep Outcomes

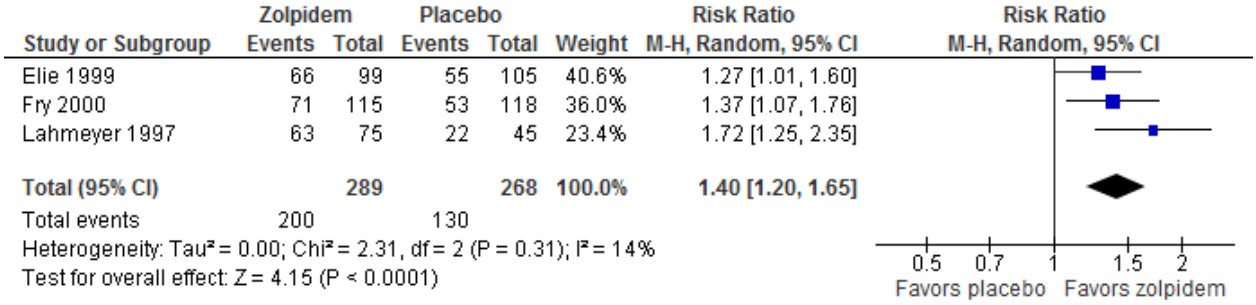
Moderate strength evidence showed that zolpidem 5-10 mg reduced sleep onset latency by 15 minutes compared with placebo in four trials lasting 4-6 weeks and reporting poolable data (Figure 30).[60,112,114,115] The one longer-term trial by Randall et al. reported that zolpidem was no more effective than placebo in improving sleep onset latency at over 8 months.[115] The 15 mg dose in Scharf et al. was better than placebo (28 minutes vs. 48 minutes reduction in sleep onset latency).[114] In the trials not pooled due to variations in how they reported outcomes, Lahmeyer et al. reported improvement in sleep onset latency at 4 weeks compared with placebo (reductions from baseline approximately 30 minutes vs. 10 minutes).[113] Elie reported that zolpidem was no more effective than placebo in improving sleep onset latency at week 4.[111] Moderate strength evidence shows that zolpidem improved sleep quality or the proportion of participants "getting a better night's sleep" more than placebo (69% vs. 49%) (Figure 31). Lahmeyer et al. reported that 10 and 15 mg zolpidem improved clinical global impression of sleep quality over placebo (both 84% vs. 49%).[113] Short-term, moderate strength evidence showed that zolpidem 5-10 mg increased total sleep time by 23 minutes compared with placebo in three trials reporting poolable data (Figure 32).[60,112,114,115] In the trials not pooled, zolpidem did not consistently improve total sleep time or sleep quality compared with placebo across trials. The one longer-term trial (n=91) reported that zolpidem was no more effective than placebo in increasing total sleep time or improving other subjective sleep outcomes (wake time after sleep onset, sleep quality) over 8 months.[115]

Figure 30. Efficacy of zolpidem: subjective sleep latency, minutes



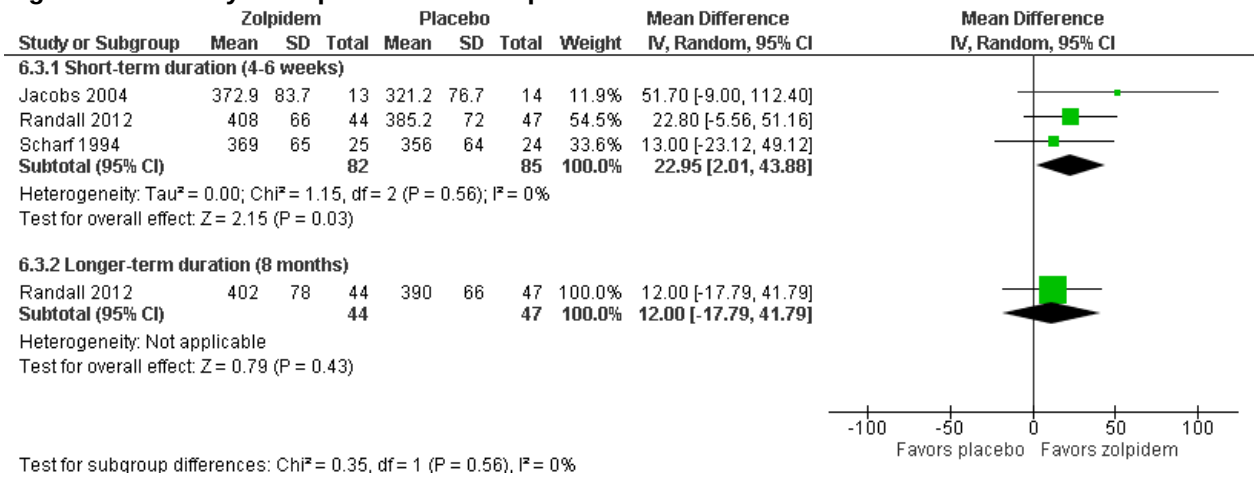
CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 31. Efficacy of zolpidem: sleep quality, participants reporting Improvement



CI = confidence interval; M-H = Mantel-Haenszel

Figure 32. Efficacy of zolpidem: total sleep time



CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

No functioning, mood, and quality of life outcomes were reported in zolpidem trials.

Adverse Effects

Study withdrawals for any reason (15% vs. 12%) or reporting of at least one adverse effect (68% vs. 67%) were not greater with zolpidem than with placebo. Strength of evidence was low and moderate, respectively. Moderate-strength evidences suggests that zolpidem resulted in more withdrawals due to adverse effects than placebo (6% vs. 2%). Among adverse effects reported, somnolence was greater with zolpidem than placebo (10% vs. 3%). Frequencies of other adverse effects were comparable to placebo. Two trials reported a higher incidence of withdrawal symptoms and rebound insomnia following discontinuation of zolpidem compared with placebo.[111,112] Incidence of withdrawal symptoms and rebound insomnia did not differ between treatment groups in the other two trials.[113,114]

Zolpidem 'As Needed'

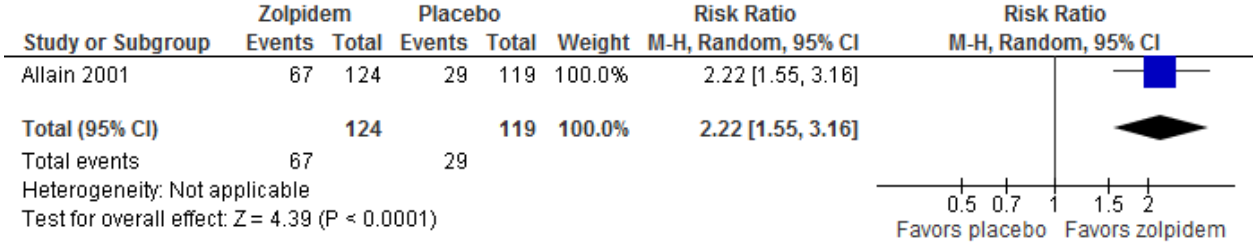
Overview of Studies

We identified three eligible RCTs that compared zolpidem 'as needed' with placebo.[116-118] One lasted 12 weeks[117] one 8 weeks,[118] and one 4 weeks.[116] Among the 607 randomized, the mean age was 44, and 73 percent were female. Perlis et al. reported more female in the placebo arm (81%) than the zolpidem arm (69%).[117] Most participants in the one trial that reported race/ethnicity were white.[117] Two trials were conducted in the United States[117,118] and one in France.[116] Participants were randomized to 10 mg zolpidem or placebo 'as needed' in all trials. Two trials reported industry sponsorship.[116,117] Sponsorship was unclear in one trial.[118] Risk of bias was moderate for all trials.

Global Outcomes

Only Allain et al. reported a global outcome (Figure 33).[116] Low-strength evidence showed that zolpidem "as needed" led to more than a two-fold increase in clinician rated global impression (CGI) "much or very much improvement" versus placebo (54% vs. 24%).

Figure 33. Global improvement of zolpidem 'as needed,' participants reporting improvement

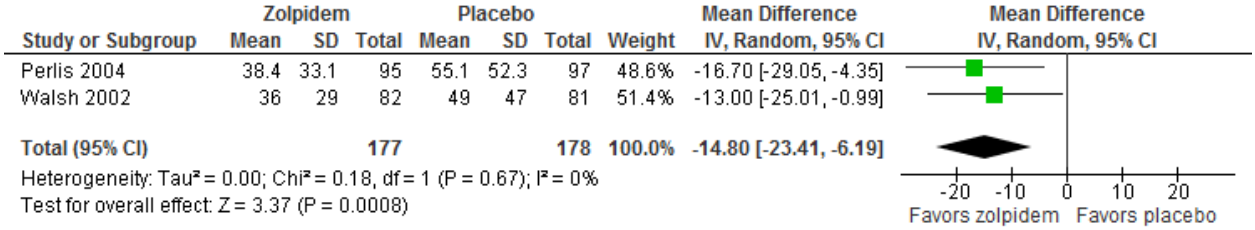


CI = confidence interval; M-H = Mantel-Haenszel

Sleep Outcomes

In two trials reporting poolable data, moderate-strength evidence showed that zolpidem 10 mg 'as needed' reduced sleep onset latency by 15 minutes (Figure 34) and increased total sleep time by 48 minutes compared with placebo (95% CI, 35 to 62) on nights when medication was taken.[117,118] There were no significant improvements in SOL between groups when all nights (nights zolpidem was taken and not taken combined) were considered. Allain et al. reported no significant improvements versus placebo in sleep onset latency, total sleep time, wake time after sleep onset, and number of awakenings after sleep onset with zolpidem 'as needed.'[116] Compared with placebo, Perlis et al. reported significant improvements with zolpidem 'as needed' in wake time after sleep onset (-22 minutes (95% CI, -37 to -9) and number awakenings after sleep onset on the nights zolpidem was taken.[117] There were no significant improvements between groups when data for all nights were pooled for these outcomes.

Figure 34. Subjective sleep latency, minutes: zolpidem 'as needed' versus placebo



CI = confidence interval; IV= inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

Zolpidem 10 mg 'as needed' led to greater improvement in the Medical Outcomes Sleep (MOS) questionnaire compared with placebo (SMD 0.48 [95% CI, 0.22 to 0.74]); treatment effects did not differ for any SF-36 domain.[116]

Adverse Effects

Zolpidem 'as needed' and placebo were similar in the number of study withdrawals for any reason (13% vs. 13%) or withdrawals due to adverse effect (4% vs. 1%). The strength of evidence was low and insufficient, respectively. Adverse effects associated with zolpidem 'as needed' included anxiety, somnolence, mood alterations, hallucinations, and depression. We identified no RCTs that evaluated the long-term effects (1 year or longer) of zolpidem 'as needed.'

Efficacy of Zolpidem, Special Formulations: Zolpidem Sublingual

Overview of Studies

One 4-week trial compared low-dose zolpidem sublingual 3.5 mg 'as needed' with placebo in participants with difficulty returning to sleep after middle-of-the-night awakenings.[119] Among the 295 randomized, the median age was 43; 68 percent were female and 64 percent were white. The trial was industry sponsored and conducted in the United States. Risk of bias was moderate.

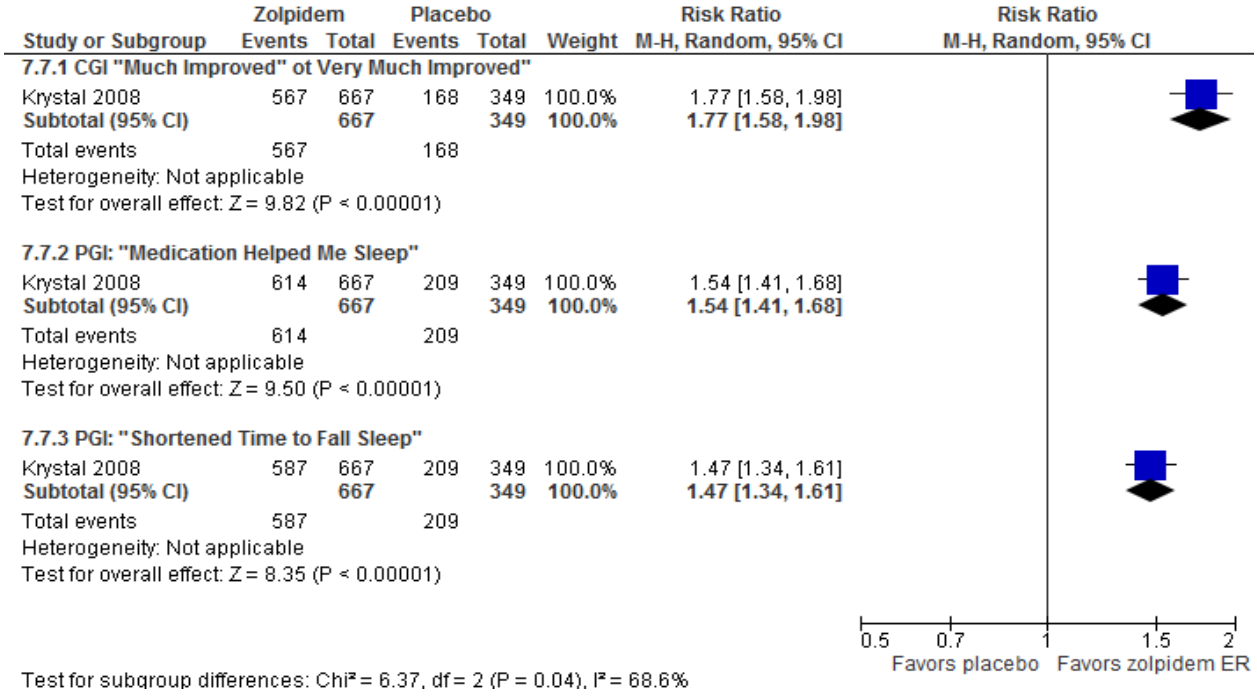
Global Outcomes

No global outcomes were reported for zolpidem SL.

Sleep Outcomes

Zolpidem sublingual reduced sleep onset latency after middle-of-the-night awakenings compared with placebo by 18 minutes (low strength evidence) (Figure 35).[119] Zolpidem sublingual did not improve total sleep time or wake time after sleep onset following middle of the night awakening over placebo at 4 weeks. The strength of evidence was insufficient for both outcomes. Improvement in sleep quality was reported with zolpidem sublingual during nights when medication was taken.

Figure 35. Efficacy of zolpidem extended release: clinical global impression and patient's global impression items at week 24, participants reporting improvement



CI = confidence interval; M-H = Mantel-Haenszel

Functioning, Mood, and Quality of Life

No functioning, mood, and quality of life outcomes were reported for zolpidem sublingual.

Adverse Effects

Withdrawals for any reason (8% vs. 6%) were not different with zolpidem sublingual and placebo. A similar number of participants withdrew due to adverse effects (0% vs. <1%) and reported at least one adverse effect (19% each).[119] The strength of evidence was insufficient for both outcomes. Specific adverse effects associated with zolpidem sublingual were headache (3%) and nausea and fatigue (1% each). Nasopharyngitis (3% was the most commonly reported adverse effect with placebo. No deaths occurred during the trial. We identified no trials that evaluated long-term efficacy and harms (1 year or longer) for zolpidem sublingual.

Efficacy of Zolpidem, Special Formulations: Zolpidem Extended Release

Overview of Studies

Krystal et al., compared zolpidem extended-release 12.5 mg taken at least 3 nights per week with placebo over 24 weeks.[120] Among the 1018 randomized, the mean age was 46; 61 percent were female and 65 percent were white. The trial was industry sponsored and conducted in the United States. Risk of bias was low.

Global Outcomes

Clinician-rated CGI outcome, "much or very much improvement," favored zolpidem extended release over placebo (85% vs. 48%) (low strength of evidence).

Sleep Outcomes

Improvements in sleep onset latency, total sleep time, and wake time after sleep onset were greater in the zolpidem extended release group compared with the placebo group. Strength of evidence was low for all outcomes. Zolpidem extended release led to greater improvements in Patient's Global Impression (PGI) items compared with placebo (insufficient evidence).[120] More than 90 percent of participants randomized to zolpidem extended release reported "medication helped me sleep" compared with 60 percent of the participants randomized to placebo (insufficient evidence).

Functioning, Mood, and Quality of Life

Krystal et al. reported that the Epworth Sleepiness Scale was significantly lower in the zolpidem extended release group compared with the placebo group during the double-blind treatment phase.[120] At month 5, mean change from baseline was -2.5 and -1.8 points in the zolpidem extended release and placebo groups, respectively (p=0.02).

Adverse Effects

Withdrawals for any reason were greater with placebo than zolpidem extended release (48% vs. 36%).[120] Conversely, withdrawals due to adverse effects were greater with zolpidem extended release than placebo (8% vs. 5%). Reports of at least one adverse effect were also greater with zolpidem extended release than placebo (63% vs. 51%). Strength of evidence was low for all outcomes. No rebound insomnia was reported over the first 3 nights following discontinuation of zolpidem extended release.

Efficacy of Nonbenzodiazepine Hypnotics in Older Adults

Eszopiclone

Overview

A single randomized, double-blind, placebo-controlled trial (n=388) evaluated eszolpiclone in older adults (Table 14).[121] The mean age of enrollees was 72 years; 63 percent were female. Most participants were white. Participants randomized to eszopiclone received a 2 mg dose. The duration of the study was 12 weeks. The trial was conducted in the United States. Risk of bias was moderate and the trial reported industry sponsorship.

Table 14. Efficacy of nonbenzodiazepine hypnotics in older adults: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean Minutes	Placebo % (n/N) or Mean Minutes	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Eszopiclone 2 mg vs. placebo (1 RCT; N=388)	Global Outcomes	Remission from Insomnia disorder based on ISI	1 (386)	37 (71/193)	24 (47/193)	Favors eszopiclone RR = 1.51 [1.11 to 2.06] ARR = 0.13 [0.3 to 0.22] NNT = 8	Low (moderate study limitations and unknown consistency)
		ISI, mean change in scores	1 (362)	-5.7	-3.4	Favors eszopiclone MD -2.30 [-3.30 to -1.30]	Low (moderate study limitations and unknown consistency)
	Sleep Outcomes	Sleep onset latency, self-report, minutes, *mean change from baseline*	1 (382)	-25	-20	MD = -4.7 [-14.1,to4.7]	Insufficient (moderate study limitations, imprecise and unknown consistency)
		Total sleep time, self-report, minutes, *mean change from baseline*	1 (382)	63	33	Favors eszopiclone MD = 30.0 [19.7 to 40.3]	Low (moderate study limitations and unknown consistency)
		Wake time after sleep onset, self-report, minutes, *mean change from baseline*	1 (380)	-36	-15	Favors eszopiclone MD = -21.6 [-29.6 to -13.6]	Low (moderate study limitations and unknown consistency)
		Sleep quality	1 (388)	NA	NA	Favors eszopiclone SMD = 0.24 [0.04 to 0.44]	Low (moderate study limitations and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (388)	24 (47/194)	24 (46/194)	NS, RR = 1.02 [0.72 to 1.46]	Insufficient (moderate study limitations, imprecise and unknown consistency)
		Withdrawals due to adverse effects	1 (388)	7 (14/194)	5 (9/194)	NS, RR = 1.56 [0.69 to 3.51]	Insufficient (moderate study limitations, imprecise and unknown consistency)
		Participants with ≥1 adverse effect	1 (388)	59 (115/194)	51 (98/194)	NS, RR = 1.17 [0.98 to 1.41]	Insufficient (moderate study limitations, imprecise and unknown consistency)

Table 14. Efficacy of nonbenzodiazepine hypnotics in older adults: overview and strength of evidence (continued)

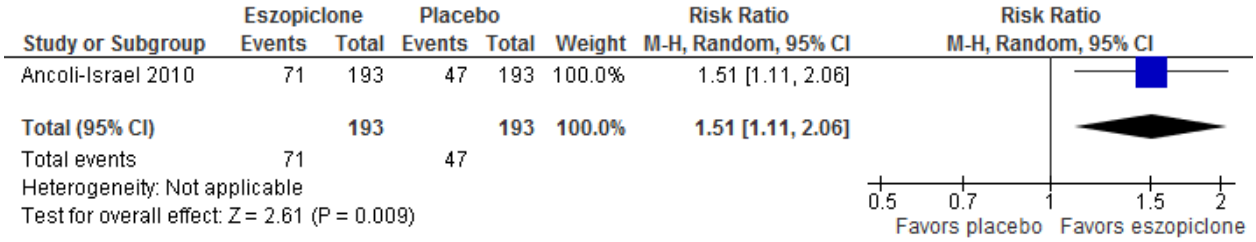
Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean Minutes	Placebo % (n/N) or Mean Minutes	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Zolpidem 5 mg vs. placebo (1 RCT; N=166)	Global Outcomes	Not reported					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes, *mean change from baseline*	1 (152)	-40	-21	Favors zolpidem MD = -18.3 [-31.2 to -5.4]	Low (moderate study limitations and unknown consistency)
		Total sleep time, self-report, minutes, *mean change from baseline*	1 (152)	70	52	NS, MD = 18.2 [-3.2 to 39.6]	Insufficient (moderate study limitations, imprecise and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (166)	7 (6/82)	12 (10/84)	NS, RR = 0.61 [0.23, 1.61]	Insufficient (moderate study limitations, imprecise and unknown consistency)
		Withdrawals due to adverse effects	1 (166)	2 (2/82)	7 (6/84)	NS, RR = 0.34 [0.07, 1.64]	Insufficient (moderate study limitations, imprecise and unknown consistency)
		Participants with ≥1 adverse effect	1 (166)	63 (52/82)	56 (47/84)	NS, RR = 1.13 [0.88, 1.46]	Insufficient (moderate study limitations, imprecise and unknown consistency)

ARR = absolute risk reduction; CI = confidence intervals; MD = mean difference; NA = not applicable; NS = No significant difference; NNT = number needed to treat; RR = risk ratio; SMD = standardized mean difference

Global Outcomes

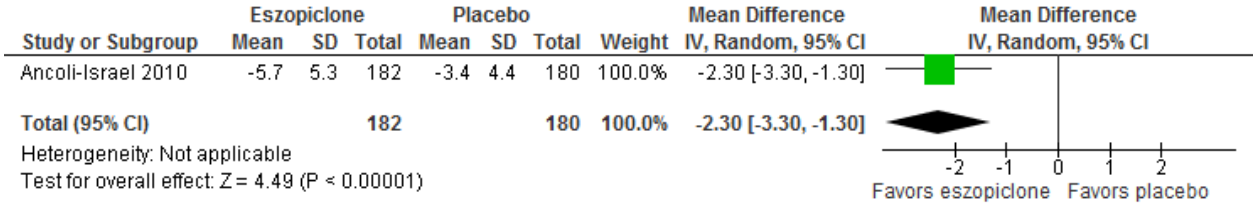
Low-strength evidence shows that compared with placebo, eszopiclone more often resulted in remission or no clinically significant insomnia, indicated by an ISI score <7 at endpoint (37% vs. 24%) (Figure 36). The mean difference in mean change from baseline in ISI scores over 12 weeks of was -2.3 points, but this difference did not reach our minimum important difference of 7 points, indicating 'responder' to treatment (Figure 37).

Figure 36. Efficacy of eszopiclone in older adults: remitters



CI = confidence interval; M-H = Mantel-Haenszel

Figure 37. Efficacy of eszopiclone in older adults: ISI scores, mean change from baseline over 12 weeks

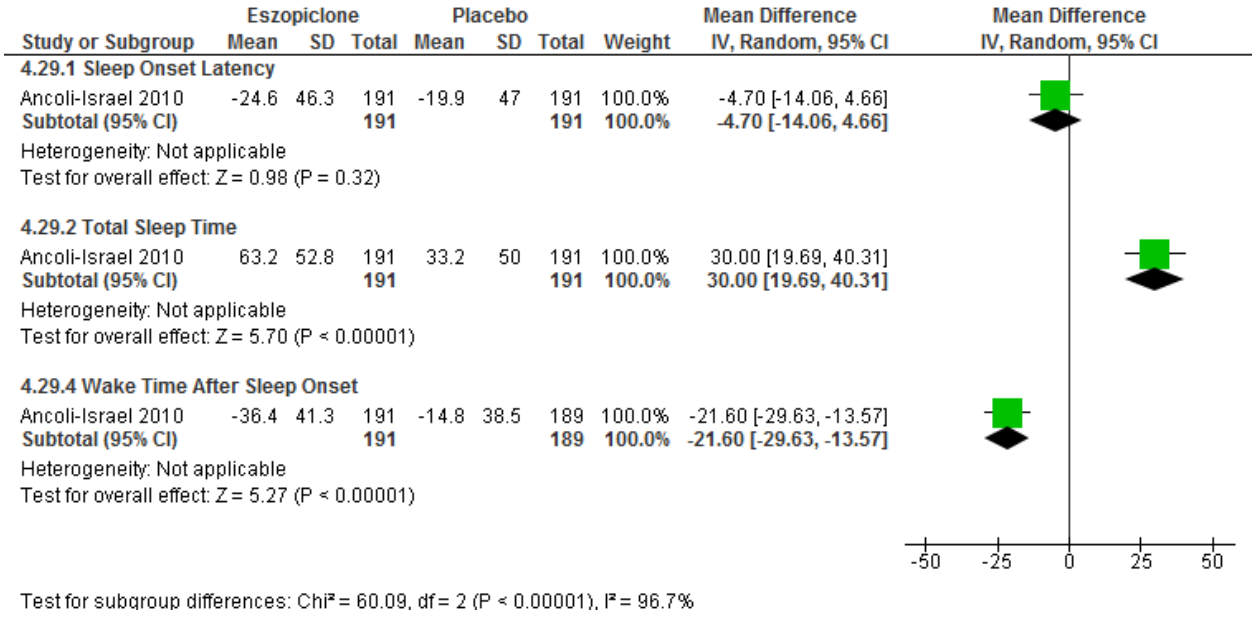


CI = confidence interval; IV = inverse variance; SD = standard deviation

Sleep Outcomes

Subjective sleep onset latency was not improved with eszopiclone versus placebo in older adults (insufficient strength of evidence). Compared with placebo, improvements were reported for total sleep time and wake time after sleep onset (Figure 38). Over 12 weeks, differences in the mean changes from baseline were 30 minutes for total sleep time and -22 minutes for wake time after sleep onset. Small significant improvement in sleep quality was also observed. Strength of evidence for was low for these sleep outcomes.

Figure 38. Efficacy of eszopiclone in older adults: patient-reported sleep outcomes, mean changes from baseline



CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

Quality of life was evaluated with the 36-Item Short-Form Health Survey (SF-36). Compared with placebo, statistically significant improvements were observed in the vitality and general health scales at week 12.

Adverse Effects

There were no statistically significant differences in study withdrawals, participants reporting at least one adverse effect (insufficient strength of evidence), and study withdrawals due to adverse effects (insufficient strength of evidence), between the eszopiclone and placebo groups. The specific adverse effect associated with eszopiclone use was unpleasant taste (12% vs. 2% in the placebo arm). There were two deaths in the eszopiclone group: one participant committed suicide, and one died of arteriosclerotic heart disease. Based on continued improvements in sleep outcomes in the eszopiclone group during the discontinuation phase, no evidence of rebound effect was reported. However, the percentage of participants with ISI total scores categorized as "no insomnia" and "sub-threshold insomnia" declined in the eszopiclone group from 78 percent at week 12 when treatment was discontinued to 53 percent at week 16. A regression of sleep latency in the eszopiclone group to the level of the placebo group was also observed at day 28 after the drug was withdrawn.

Zolpidem

Overview

We identified one randomized, double-blind, placebo-controlled trial evaluating zolpidem that enrolled older adults.[122] The study was a four-arm trial that also included triazolam and temazepam. The trial randomized 166 participants between the ages of 59 and 85 years. Sex and race were not reported. Participants randomized to zolpidem received a 5 mg dose. The duration of

the study was 4 weeks. The trial was conducted in the United States. Risk of bias was moderate and the trial reported industry sponsorship.

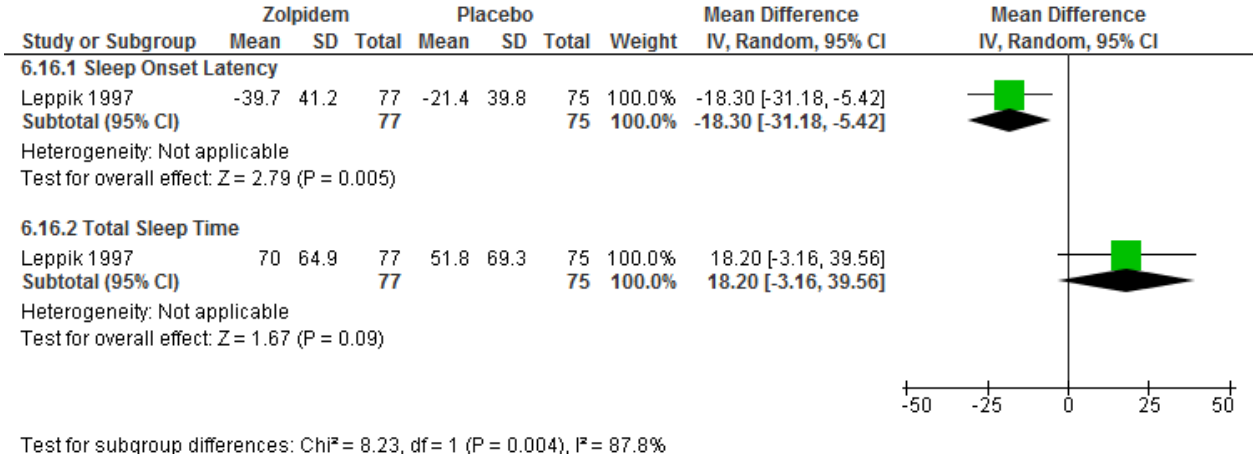
Global Outcomes

Leppik et al. did not report a global outcome.[122]

Sleep Outcomes

Subjective sleep onset latency was improved with zolpidem versus placebo in older adults (low-strength evidence) (Figure 39). Mean decreases from baseline were 40 and 21 minutes for the zolpiem and placebo groups, respectively. Total sleep time was not improved with zolpidem (insufficient evidence).

Figure 39. Efficacy of zolpidem in older adults: patient-reported sleep outcomes, mean changes from baseline



CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

Leppik 1997 et al. did not report functioning, mood, and quality of life outcomes.[122]

Adverse Effects

There were no statistically significant differences in study withdrawals, study withdrawals due to adverse effects, and participants reporting at least one adverse effect between the zolpidem and placebo groups (insufficient evidence). No specific adverse effect was greater with zolpidem compared with placebo. One participant in the placebo group died during the trial.

Efficacy of Nonbenzodiazepine Hypnotics in Patients With Chronic Low Back Pain

Overview of Studies

We identified one randomized, double-blind, placebo-controlled trial evaluating eszopiclone in participants with both chronic insomnia and chronic low back pain (Table 15).[123] All participants also received naproxen 500 mg twice a day. The trial randomized 58 participants with a mean age of 43; 63 percent were female. Slightly more participants were African-American (46%) than

white (44%). Participants randomized to eszopiclone received a 3 mg dose. The duration of the study was 1 month. The trial was conducted in the United States. Risk of bias was moderate and the trial reported industry sponsorship.

Table 15. Efficacy of nonbenzodiazepine hypnotics in participants with chronic low back pain: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean Minutes	Placebo % (n/N) or Mean Minutes	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Eszopiclone 3 mg vs. placebo (1 RCT; N=58)	Global Outcomes	Remission from insomnia disorder based on ISI Mean change from baseline	0	-9.6	-3	Favors eszopiclone MD = -6.6 [-9.3 to -3.6]points	Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes, Mean change from baseline	1 (52)	23	14	NS, MD = 8.8 [-2.1 to 19.7]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Total sleep time, self-report, minutes, Mean change from baseline	1 (52)	412	389	Favors eszopiclone MD 86.5 [58.6 to 114.4]	Insufficient (moderate study limitations, and unknown consistency)
		Wake time after sleep onset, self-report, minutes, Mean change from baseline	1 (52)	37	76	Favors eszopiclone MD = -49.5 [19.1 to 80.0]	Insufficient (moderate study limitations and unknown consistency)
		Sleep quality	1 (52)	NA	NA	Favors eszopiclone SMD= 0.60 [0.03 to 1.17]	Insufficient (moderate study limitations, imprecise and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (58)	12 (4/33)	40 (10/25)	Favors eszopiclone RR 0.30 [0.11 to 0.85]	Insufficient (moderate study limitations, imprecise and unknown consistency)
		Withdrawals due to adverse effects	1 (58)	0 (0/33)	0 (0/25)	NS, NA	Insufficient (moderate study limitations, imprecise and unknown consistency)
		Participants with ≥1 adverse effect	1 (58)	6 (2/33)	4 (1/25)	NS, RR = 1.52 [0.15 to 15.78]	Insufficient (moderate study limitations, imprecise and unknown consistency)

CI = confidence intervals; NS = No significant difference; MD = mean difference; NA = not applicable; RR = risk ratio; SMD = standardized mean difference

Global Outcomes

Remission or no clinically significant insomnia, indicated by an ISI score, was not reported. The difference in mean change of ISI scores from baseline at week 4 of was -6.6 points [95% CI, -9.3 to -3.6]), favoring eszopiclone versus placebo, but this difference did not reach our minimum important difference of 7 points, indicating 'responder' to treatment.

Sleep Outcomes

Insufficient strength of evidence shows improvement with eszopiclone versus placebo in sleep outcomes at week 4 in adults with low back pain.

Functioning, Mood, and Quality of Life

Functioning, mood, and quality of life outcomes were not reported.

Adverse Effects

Compared with placebo, overall study withdrawals were lower in the eszopiclone group. The evidence was insufficient for all outcomes.

Efficacy of Melatonin and Ramelteon in the General Adult Population

Melatonin

Overview of Studies

We identified one RCT that compared melatonin 2 mg prolonged release (PR) with placebo reported in two publications (Table 16).[124,125] Initially, the 791 randomized participants were randomized to melatonin PR or placebo for a 3-week, double-blind, period. After the 3 weeks, the melatonin group remained on melatonin while those in the placebo group were re-randomized to melatonin PR or placebo for a 26-week extension period (a total of 711 participants [534 melatonin and 177 placebo]). Our review focuses on the outcomes evaluated during the 26-week extension period. Demographic data for the 711 participants entering the extension period were not provided. However, among the 722 participants completing the initial 3-week period, mean age was 62 years, 69 percent were female, and nearly all were white (99%). The trial was conducted in Scotland, reported industry sponsorship, and had a moderate risk of bias.

Table 16. Efficacy and comparative effectiveness of melatonin and melatonin agonists: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean Minutes[a]	Placebo % (n/N) or Mean Minutes[a]	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Melatonin prolonged release vs. placebo 1 RCT; N=711)	Global Outcomes	PSQI global score	1 (700)	NR	NR	MD = -0.39 [-0.71 to -0.08]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
	Sleep Outcomes	Sleep onset latency, self-report, minutes	1 (700)	NR	NR	MD = -6 [-10 to -2.1]	Insufficient (moderate study limitations, and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (711)	21 (113/534)	24 (43/177)	NS, 0.87 [0.64 to 1.18]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Withdrawals due to adverse effects	1 (711)	5 (26/534)	6 (10/177)	NS, 0.86 [0.42 to 1.75]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Participants with ≥1 adverse effect	1 (711)	74 (394/534)	77 (136/177)	NS, 0.96 [0.87 to 1.06]	Insufficient (moderate study limitations and unknown consistency)

Table 16. Efficacy and comparative effectiveness of melatonin and melatonin agonists: overview and strength of evidence (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean Minutes[a]	Placebo % (n/N) or Mean Minutes[a]	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Ramelteon vs. placebo (5 RCTs; N=3124)	Global Outcomes	Not reported					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	5 (2972)	57	59	NS, WMD = -3.1 [-7.4 to 1.2]	Low (moderate study limitations, imprecise, inconsistent)
		Total sleep time, self-report, minutes	5 (2781)	350	350	NS, WMD = 0.1 [-10 to 10.1]	Low (moderate study limitations, imprecise, inconsistent)
		Wake time after sleep onset, self-report, minutes	2 (721)	83	76	NS, WMD = 5.9 [-6.1 to 17.9]	Low (moderate study limitations, imprecise)
		Sleep quality	5 (2973)	NA	NA	Favors Ramelteon SMD = -0.08 [-0.16 to -0.01]	Low (moderate study limitations and inconsistent)
	Adverse Effects	Overall withdrawals	2 (1594)	12 (116/987)	10 (62/607)	Greater with Ramelteon RR = 1.47 [1.11 to 1.94] AR = 0.05 [-0.02 to 0.12]	Low (moderate study limitations and imprecise)
		Withdrawals due to adverse effects	3 (1999)	2 (29/1261)	2 (15/738)	NS, RR = 1.23 [0.47 to 3.25]	Low (moderate study limitations and imprecise)
		Participants with ≥1 adverse effect	3 (1999)	46 (579/1262)	46 (336/737)	NS, RR = 1.03 [0.93 to 1.13]	Moderate (moderate study limitations)

ARR = Absolute risk reduction; CI = confidence intervals; MD = mean difference; NS = No significant difference; RR = risk ratio; SMD = standardized mean difference
[a]Weighted by sample sizes.

Global Outcomes

Evidence was insufficient regarding melatonin PR improving global outcomes. The mean difference in PSQI scores between groups was statistically significant but very small (-0.39 points [95% CI, -0.71 to -0.08]).

Sleep Outcomes

Insufficient-strength evidence found melatonin PR improved subjective sleep onset latency. The mean difference between groups was statistically significant but small (6 minutes [95% CI 2 to 10]). Other sleep outcomes were not reported.

Functioning, Mood, and Quality of Life

Overall, melatonin PR improved WHO-5 quality of life scores compared with placebo. The mean difference between groups was 0.46 points (95% CI, 0.11 to 0.81).

Adverse Effects

Study withdrawals for any reason (21% vs. 24% placebo), withdrawals due to adverse effects (5% vs. 6%), and the proportion of participants reporting at least one adverse effect (74% vs. 77%) were similar with melatonin PR and placebo. Strength of evidence was insufficient for all outcomes. There were 15 serious adverse effects in the melatonin prolonged release group and nine (including one death) in the placebo group. There were no differences in type or frequency of adverse effects.

Ramelteon (Brand Name Rozerem)

Overview of Studies

We identified five RCTs that met our inclusion criteria.[126-129] Two of the trials, NCT00237497 and NCT00671567, only had results published in a systematic review. The trials randomized 3124 participants; mean age was 45; 63 percent were female. In the two trials that reported race/ethnicity, most participants were white. Two trials were conducted in the United States,[126,129] one in Japan,[128] and two were multinational.[126,127] Dosing ranged from 4 to 16 mg. All trials were short term (4 to 5 weeks) with the exception of Mayer et al., which lasted 6 months.[127] All trials reported industry sponsorship and had moderate risk of bias.

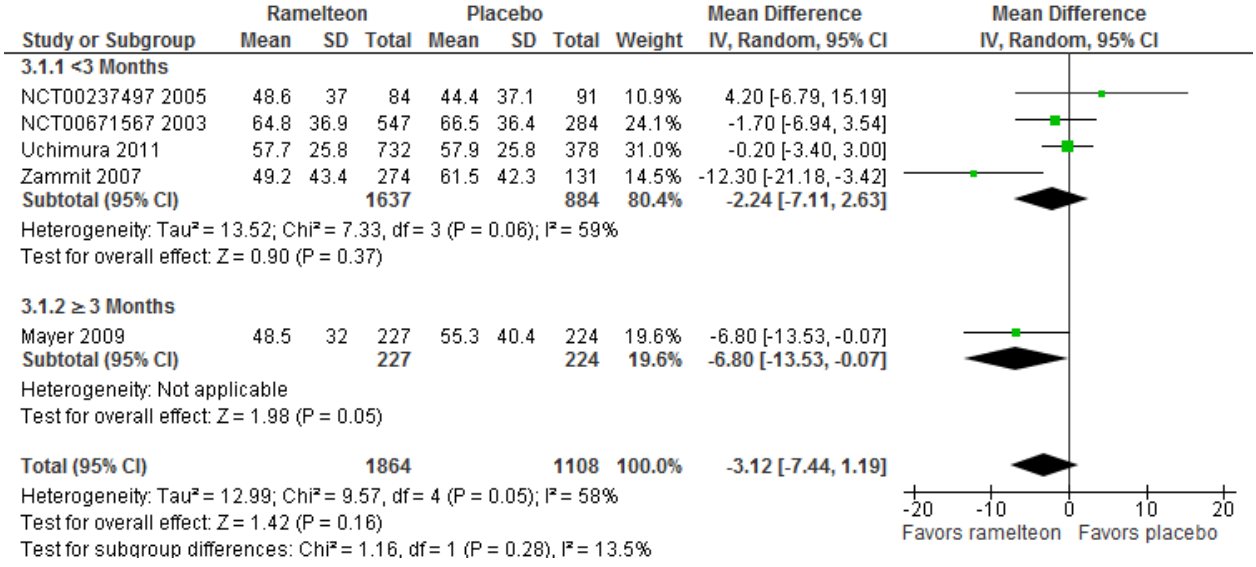
Global Outcomes

None of the ramelteon trials reported global outcomes.

Sleep Outcomes

Patient-reported sleep outcomes from the five trials meeting eligibility criteria are presented in Figure 40. Ramelteon did not reduce sleep onset latency compared with placebo (low-strength evidence). The only study longer than 3 months[127] reported an improvement in sleep onset latency of -6.8 minutes (95% CI, -13.5 to -0.1).[127]

Figure 40. Efficacy of ramelteon: subjective sleep latency, minutes



CI = confidence interval; IV = inverse variance; SD = standard deviation

Low-strength evidence found that ramelteon did not significantly improve total sleep time or wake time after sleep onset compared to placebo. Ramelteon statistically improved sleep quality compared with placebo, but the effect size was less than small (ES 0.08), indicating little difference between groups (low-strength evidence). The 6-month trial by Mayer et al., the only trial lasting more than 3 months, reported no difference between treatment groups on any sleep outcome.[127]

Functioning, Mood, and Quality of Life

Functioning, mood, and quality of life outcomes were not reported.

Adverse Effects

Not all trials reported adverse effects. Ramelteon resulted in more withdrawals than placebo (12% vs. 10%; p=0.007; k=2; low strength evidence). Ramelteon and placebo were similar in withdrawals due to adverse effects (2% vs. 2%) and participants having at least one adverse event (46% vs. 46%) (strength of evidence was low and moderate, respectively). No specific adverse effect was greater with ramelteon than with placebo. Neither trial reported evidence of tolerance or withdrawal symptoms. No randomized studies evaluated long-term effects (1 year or longer) of ramelteon.

Efficacy of Melatonin and Ramelteon in Older Adults

Overview

We identified one randomized, double-blind, placebo-controlled trial evaluating ramelteon that enrolled older adults (Table 17).[130] Additional outcomes data for this trial were obtained from the systematic review by Kuriyama et al.[126] The three-arm trial randomized 829 participants with a mean age of 72; 59 percent were female. Race was not reported. Participants were randomized to 4 or 8 mg dose. Study duration was 5 weeks. The trial was conducted in the United States. Risk of bias was moderate and the trial reported industry sponsorship.

Table 17. Efficacy of melatonin agonists in older adults: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean Minutes	Placebo % (n/N) or Mean Minutes	Results and Magnitude of Effect [95% CI]; I^2	Strength of Evidence (Rationale)
Ramelteon vs. placebo, older adults (1 RCT; N=829)	Global Outcomes	Not reported					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	1 (826)	61	71	Favors Ramelteon MD = -10.1 [-15.6 to -4.6]	Low (moderate study limitations, and unknown consistency)
		Total sleep time, self-report, minutes	1 (825)	336	330	NS, MD = 5.9 [-2 to 13.8]	Insufficient (moderate study limitations imprecise, and unknown consistency)
		Sleep quality	1 (826)	NA	NA	NS	Insufficient (moderate study limitations, imprecise and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (829)	15 (82/555)	17 (46/274)	NS, RR = 0.88 [0.63 to 1.23]	Insufficient (moderate study limitations, imprecise and unknown consistency)
		Withdrawals due to adverse effects	1 (829)	3 (15/555)	3 (8/274)	NS, RR = 0.93 [0.40 to 2.16]	Insufficient (moderate study limitations, imprecise and unknown consistency)
		Participants with ≥1 adverse effect	1 (829)	56 (313/555)	51 (141/274)	NS, RR = 1.10 [0.96 to 1.26]	Insufficient (moderate study limitations, imprecise and unknown consistency)

CI = confidence intervals; MD = mean difference; NS = No significant difference

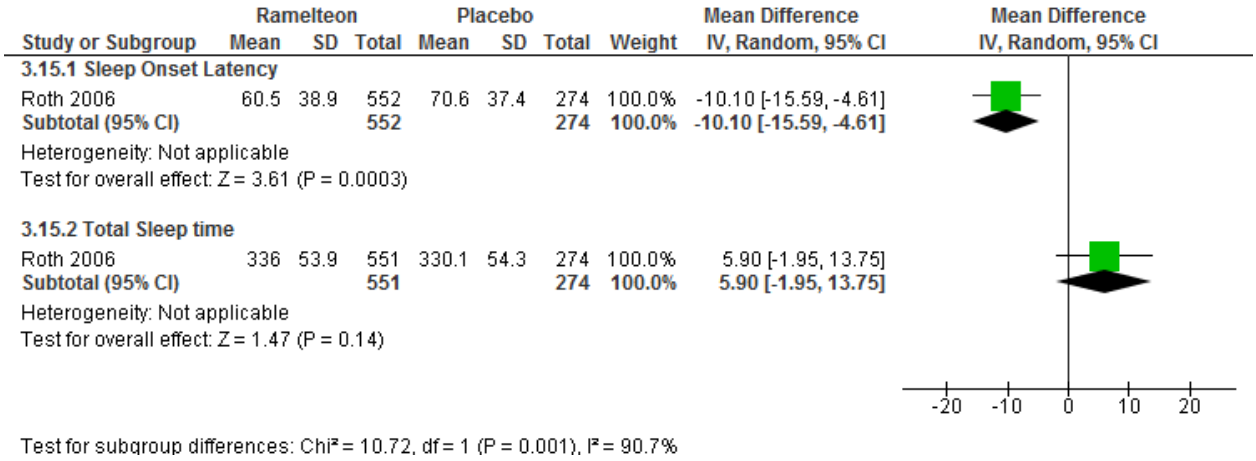
Global Outcomes

A global impression inventory was completed by both participants and clinicians. No statistically significant differences between treatment groups were reported (data were not reported).

Sleep Outcomes

Patient-reported sleep outcomes from all included trials are presented in Figure 41. Ramelteon dosage arms were combined for analyses (Figure 41).[126] Ramelteon reduced sleep onset latency by 10 minutes compared with placebo. Ramelteon did not improve total sleep time or sleep quality over the 5 week study duration. Strength of evidence for sleep onset latency was low and insufficient for the other outcomes.

Figure 41. Efficacy of ramelteon in older adults: subjective sleep latency and total sleep time, minutes



CI = confidence interval; IV = inverse variance; SD = standard deviation.

Functioning, Mood, and Quality of Life

Roth et al. did not report functioning, mood, and quality of life outcomes.

Adverse Effects

We found no statistically significant differences in study withdrawals, study withdrawals due to adverse effects, or participants reporting at least one adverse effect between the ramelteon and placebo groups. Strength of evidence was insufficient for all outcomes. No specific adverse effect was greater with ramelteon compared with placebo.

Efficacy of Benzodiazepine Hypnotics in the General Adult Population

Overview of Studies

We identified one eligible RCT[72] that assessed the efficacy of benzodiazepine, temazepam, versus placebo in the general adult population (Table 18).

Table 18. Efficacy and comparative effectiveness of the benzodiazepine hypnotics in general adult populations: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean Minutes	Placebo % (n/N) or Mean Minutes	Results and Magnitude of Effect [95% CI]	Strength of Evidence
Temazepam vs. placebo 1 RCT; n=39	Global Outcomes	Not reported	0				Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	1 (34)	20	51	Favors temazepam MD = -30.9 [-50.4 to -11.4]	Insufficient (moderate study limitations, and unknown consistency)
		Total sleep time, self-report, minutes	1 (34)	406	313	Favors temazepam MD = 93.5 [47.6 to 139.4]	Insufficient (moderate study limitations, and unknown consistency)
		Sleep efficiency, percent	1 (34)	86	72	Favors temazepam MD = 14.1 [5.8 to 22.4]	Insufficient (moderate study limitations, and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (39)	15 (3/20)	10.5 (2/19)	NS, RR = 1.4 [0.3 to 7.6]	Insufficient (moderate study limitations, very imprecise and unknown consistency
		Withdrawals due to adverse effects	1 (39)	15 (3/20)	0 (0/19)	NS, RR = 6.7 [0.4 to 121.1]	Insufficient (moderate study limitations, very imprecise and unknown consistency

CI = confidence interval; MD = mean difference; NS = no significant difference

Efficacy of Temazepam in the General Adult Population

Overview of Studies

One RCT[72] met our inclusion criteria and compared temazepam to placebo in the general adult population. Wu et al. randomized participants to cognitive behavioral therapy alone, temazepam alone, cognitive behavioral therapy with temazepam, or placebo drug alone. For this aspect of the review we examined only the temazepam and placebo arms. Demographic information was not reported for the temazepam and placebo arms separately, but among the four treatment arms, the mean age was 38 years and 53 percent were female. Temazepam recipients initially received 7.5 mg nightly with gradual increases up to 30 mg, and then a decrease to 15 mg in the last treatment week for a total of 8 weeks. The trial was conducted in China and had government funding and was assessed as having a moderate risk of bias.

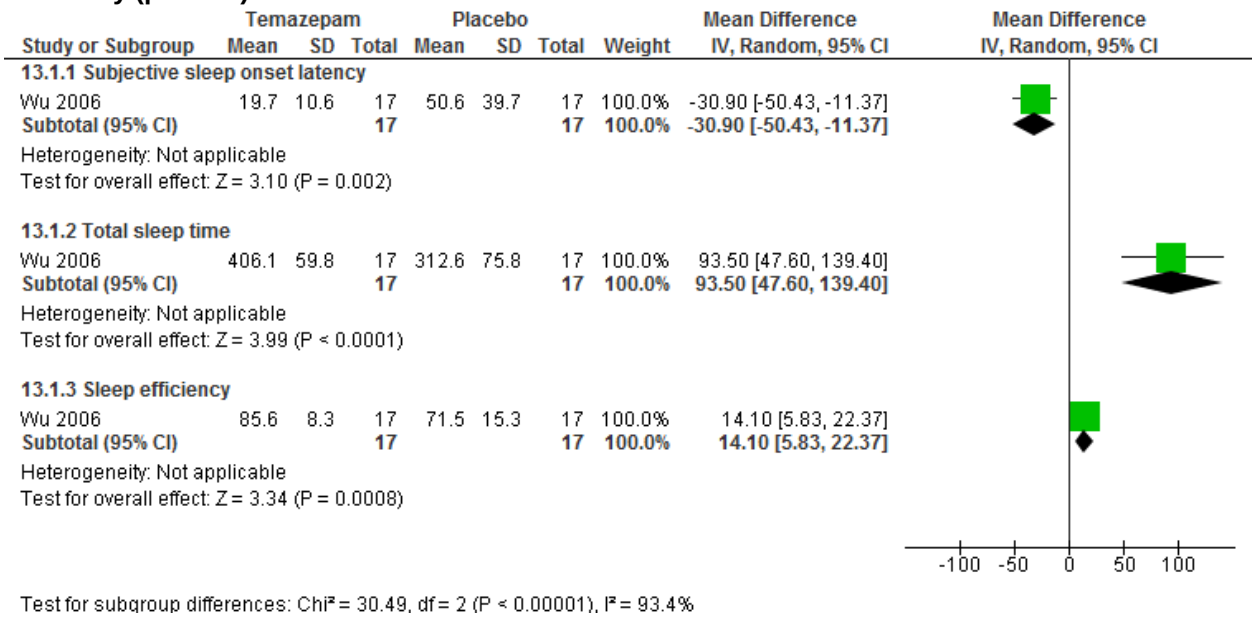
Global Outcomes

Wu et al.[72] did not report global outcomes.

Sleep Outcomes

Sleep outcomes are presented in Figure 42. Temazepam reduced SOL by 31 minutes, increased TST by 94 minutes, and improved sleep efficiency by 14 percentage points compared with placebo. Evidence was insufficient for all outcomes.

Figure 42. Efficacy of temazepam: sleep latency minutes, total sleep time minutes, and sleep efficiency (percent)



CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

Temazepam significantly reduced the daytime dysfunction component of the PSQI compared with placebo.

Adverse Effects

There were no significant differences in overall withdrawals or withdrawals due to adverse effects between temazepam and placebo. Specific adverse effects were not reported. Strength of evidence was insufficient.

Efficacy of Benzodiazepine Hypnotics in Older Adults

We identified one RCT that met our inclusion criteria and assessed the efficacy and adverse effects of the benzodiazepine temazepam in older adults (Table 19).[74]

Table 19. Efficacy of the benzodiazepine hypnotics in older adults: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean Minutes	Placebo % (n/N) or Mean Minutes	Results and Magnitude of Effect [95% CI]	Strength of Evidence
Temazepam vs. placebo 1 RCT; n=40	Sleep Outcomes	Total sleep time, self-report, minutes	1 (35)			NS, MD = 33.2 [-7.1 to 73.5]	Insufficient (moderate study limitations, very imprecise and unknown consistency
		Wake time after sleep onset, self-report, minutes	1 (35)			Favors temazepam MD = -22.3 [-36.3 to -8.3]	Insufficient (moderate study limitations, and unknown consistency)
		Sleep efficiency, percent	1 (35)			Favors temazepam MD = 9.2 [2.8 to 15.6]	Insufficient (moderate study limitations, and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (40)	15 (3/20)	10 (2/20)	NS, RR = 1.5 [0.3 to 8.0]	Insufficient (moderate study limitations, very imprecise and unknown consistency)
		Withdrawals due to adverse effects	1 (40)	15 (3/20)	0 (0/20)	NS, RR = 7.0 [0.4 to 127.3]	Insufficient (moderate study limitations, very imprecise and unknown consistency)

CI = confidence interval; MD = mean difference; NS = no significant difference

Efficacy of Temazepam in Older Adults

We identified one RCT[74] that met our inclusion criteria and compared temazepam with placebo among older adults. Morin et al.[74] et al. randomized participants to cognitive behavioral therapy alone, temazepam alone, cognitive behavioral therapy with temazepam, or placebo drug alone. For this aspect of the review, we examined only the temazepam and placebo arms. Morin et al.[74] included only adults at least 55 year old; the 40 participants randomized had a mean age of 65 years and 60 percent were female; Morin et al.[74] did not report other baseline characteristics. Morin et al. randomized participants to temazepam 7.5 mg nightly, with increases up to 30 mg nightly possible, depending on response and adverse effects; or to placebo drug. The trial lasted 8 weeks, was conducted in the United States, had government sponsorship, and was assessed as having a moderate risk of bias.

Global Outcomes

Morin et al.[74] did not report any global outcomes.

Sleep Outcomes

Morin et al.[74] found that wake time after sleep onset and sleep efficiency were significantly better with temazepam than placebo (insufficient evidence), but there was no significant difference in total sleep time (insufficient evidence).

Functioning, Mood, and Quality of Life

Morin et al.[74] found no significant difference in the Sleep Impairment Index with temazepam compared with placebo (insufficient evidence).

Adverse Effects

There was no significant difference between temazepam and placebo groups in the proportion of participants withdrawing for any reason or withdrawing due to adverse effects.

Efficacy of Antidepressants in the General Adult Population

Overview of Studies

We identified two RCTs that compared doxepin with placebo in the general adult population[131,132] (Table 20). Hajak et al.[131] randomized 47 participants to doxepin 25 mg (increasing to 50 mg of doxepin as needed) or placebo. Krystal et al. [132] randomized 229 participants to either doxepin 3 mg, doxepin 6 mg, or placebo. Because different doses of doxepin were used, efficacy outcomes could not be pooled.

Both trials had active treatment lasting 4 weeks. Overall, the mean age was 45, and 74 percent were female. Only Krystal et al. 2011[132] reported ethnicity: in that trial, 48 percent of participants were white. Hajak et al.[131] was conducted in Germany and Krystal et al.[132] was conducted in the United States. Both RCTs reported industry sponsorship. Both trials had moderate risk of bias.

Table 20. Efficacy of doxepin in the general adult population

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean Minutes	Placebo % (n/N) or Mean Minutes	Results and Magnitude of Effect (95% CI)	Strength of Evidence
Doxepin vs. placebo, 2 RCTs; n analyzed=261	Global Outcomes	Global improvement, based on Clinical Global Impression Scale	1 (40)			Favors doxepin MD = -0.58 [-1.05 to -0.12]	Insufficient (moderate study limitations, unknown consistency)
	Sleep Outcomes	Total sleep time, self-report, minutes	1 (221)			Favors doxepin 3 mg MD= 11.9 [CI NR] (P = 0.05) Favors doxepin 6 mg MD = 17.3 [CI NR] (P = 0.004)	Low (moderate study limitations, unknown consistency)
		Wake time after sleep onset, self-report, minutes	1 (221)			Favors doxepin 3 mg MD = −10.2 [CI NR] (P = 0.02) Favors doxepin 6 mg MD = −14.2 (CI NR) (P = 0.001)	Low (moderate risk of bias, unknown consistency)
		Sleep quality	1 (40)			Favors doxepin	Insufficient (moderate study limitations, unknown consistency)
	Adverse Effects	Overall withdrawals	2 (276)	12 (21/177)	12 (12/99)	NS, RR = 1.01 [0.52 to 1.96]	Insufficient (moderate study limitations, imprecise)
		Withdrawals due to adverse effects	2 (276)	4 (7/177)	4 (4/99)	NS, RR 1.19 [0.36 to 3.93]	Insufficient (moderate study limitations, imprecise)
		Participants with ≥1 adverse effect	2 (268)	42 (73/172)	43 (41/96)	NS, 1.11 [0.96 to 1.27]	Low (moderate study limitations, imprecise,)

CI = confidence interval; MD = mean difference; NS = no significant difference

Global Outcomes

Hajak et al.[131] found doxepin significantly enhanced global improvement on the Clinical Global Impression Scale compared with placebo (2.42 vs. 3.00, where lower scores indicate more improvement) (insufficient strength of evidence). Hajak et al. found no significant differences between treatment groups in severity of illness from the Clinical Global Impression Scale.

Sleep Outcomes

Krystal et al.[132] found that both doxepin doses significantly improved total sleep onset and wake time after sleep onset compared with placebo (Table 20). Strength of evidence was low for both outcomes. Hajak et al.[131] found that doxepin 25 mg significantly improved sleep quality compared with placebo (52 vs. 41 on a 100-point visual-analog scale).

Functioning, Mood, and Quality of Life

Krystal et al.[132] found no significant differences between the doxepin dose groups and placebo in the Digit Symbol Substitution Test, the Symbol Copying Test, or daytime sleepiness at 4 weeks. Hajak et al.[131] found doxepin 25 mg significantly improved energy and working ability compared with placebo.

Adverse Effects

There were no significant differences in overall study withdrawals, study withdrawals due to adverse effects, participants reporting at least one adverse effect, daytime somnolence, or headache between participants receiving doxepin versus placebo.

Efficacy of Antidepressants in Older Adults

Overview of Studies

We identified two RCTs[133,134] that compared doxepin with placebo in older adults (Table 21). Krystal et al.[133] randomized 240 participants to either doxepin 1 mg, doxepin 3 mg, or placebo. Lankford et al.[134] randomized 255 participants to doxepin 6 mg or placebo. Because different doses of doxepin were used, efficacy outcomes could not be pooled. Krystal et al.[133] had an active treatment duration of 12 weeks and Lankford et al.[134] was 4 weeks. The mean age was 72, 65 percent were female, and 84 percent were white. Both RCTs were conducted in the United States and reported industry sponsorship. Lankford et al.[134] had low risk of bias and Krystal et al.[133] had moderate risk of bias.

Table 21. Efficacy of doxepin in older adults

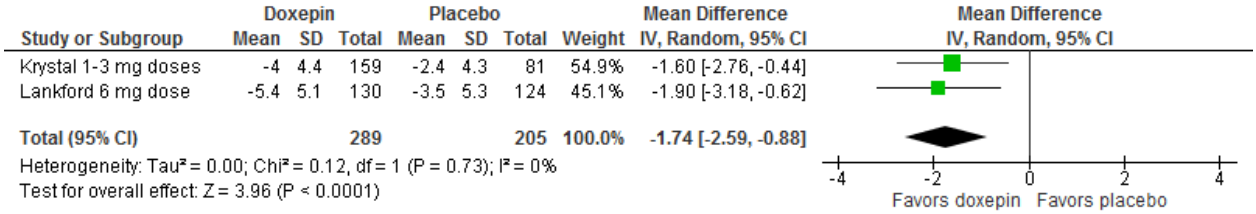
Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean Minutes	Placebo % (n/N) or Mean Minutes	Results and Magnitude of Effect (95% CI)	Strength of Evidence
Doxepin 1-6 mg vs. placebo ***2 RCTs; n=495***	Global Outcomes	ISI mean. Mean change from baseline	2 (494)	-4.6	-3.1	Favors doxepin WMD = -1.7 [-2.6 to -0.9]	Moderate (moderate study limitations)
	Sleep Outcomes	Sleep onset latency, self-report, minutes. Mean change from baseline	1 (240)	-16	-1	Favors doxepin 1-3 mg MD = -14.7 [-24.0 to -5.4]	Low (moderate study limitations, unknown consistency)
		Total sleep time, self-report, minutes. Mean change from baseline	2 (494)	71	44	Favors doxepin WMD = 23.9 [12.0 to 35.7]	Moderate (moderate study limitations)
		Wake time after sleep onset, self-report, minutes. Mean change from baseline	1 (254)	-50	-33	Favors doxepin(6 mg dose), MD = -17.0 [-29.3 to -4.7]	Low (unknown consistency)
		Sleep efficiency	0				Insufficient
		Sleep quality scale from -3 to 3 (-3 = extremely poor and 3 = excellent) at endpoint	2 (494)	1- 3 mg 0.8-0.9 6 mg 0.4	 0.2 0.2	Favors doxepin, all trials report significant improvement versus placebo at endpoint	Low (moderate study limitations)
	Adverse Effects	Overall withdrawals	2 (495)	7 (21/289)	11 (22/206)	NS, RR = 0.63 [0.35 to 1.12]	Low (moderate study limitations imprecise)
		Withdrawals due to adverse events	2 (495)	2 (5/289)	2 (4/206)	NS, RR = 0.73 [0.20 to 2.69]	Insufficient (moderate study limitations, very imprecise)
		Participants with ≥1 adverse event	2 (494)	32 (93/289)	34 69/205)	NS, RR = 0.87 [0.60 to 1.26]	Low (moderate study limitations, imprecise)

CI = confidence interval; ISI = Insomnia Severity Index; MD = mean difference; NS = no significant difference; SMD = standardized mean difference

Global Outcomes

Both trials reported ISI scores. Our analyses found ISI scores were significantly improved with pooled doxepin 1-6 mg doses compared with placebo from 4 to 12 weeks, with a weighted mean difference of -1.9 points [95%CI -2.9 to -1.0] (Figure 43). Mean change in ISI scores at endpoint ranged from -3.4 (1 mg) to -5.4 points (6mg) in the doxepin groups and -2.4 to -3.5 in the placebo groups, respectively. Strength of evidence was moderate.

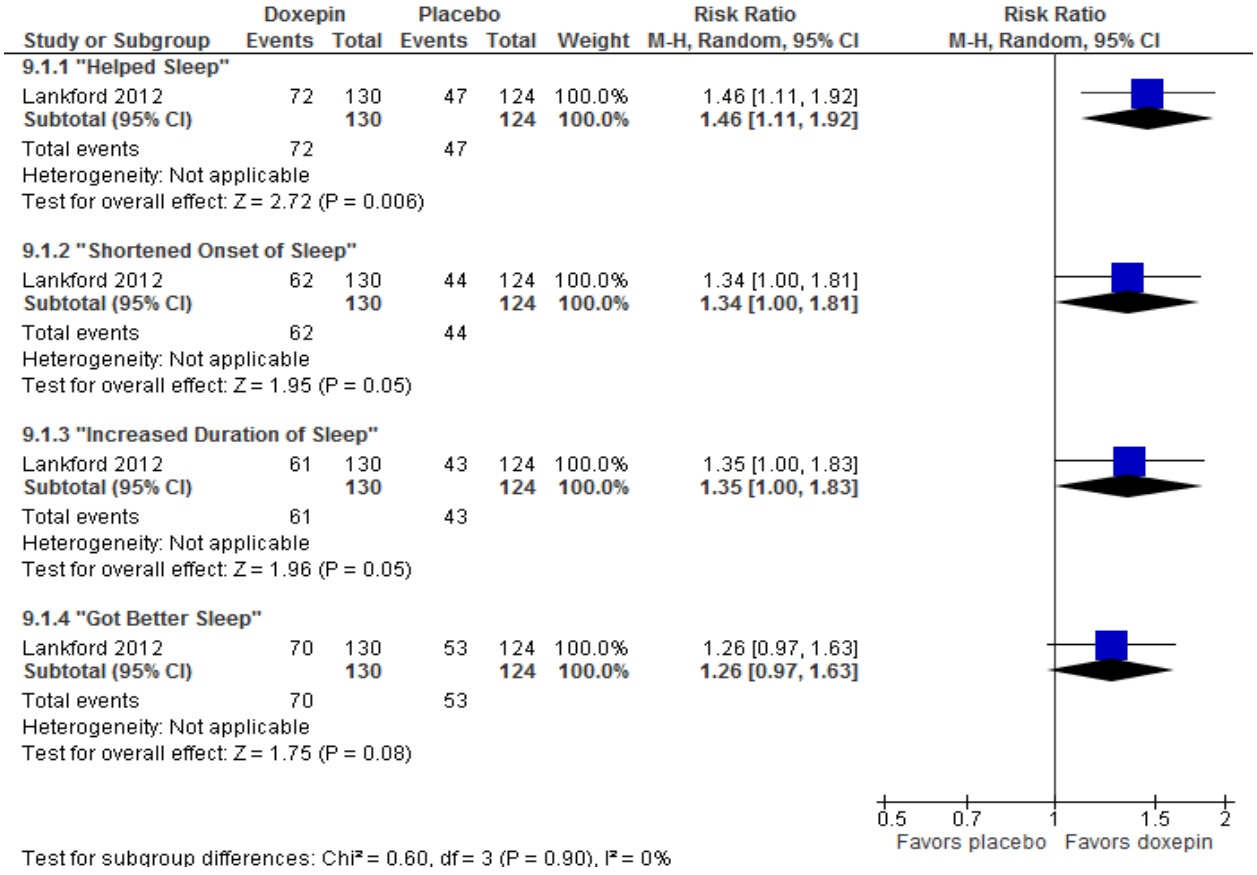
Figure 43. Efficacy of doxepin in older adult population: ISI scores, mean change from baseline



CI = confidence interval; IV = inverse variance; SD = standard deviation

Lankford et al.[134] found that doxepin 6 mg significantly improved three of four sleep components of the PGI scale compared with placebo at 4 weeks (Figure 44). Lankford et al.[134] found CGI scores were not significantly different with doxepin 6 mg compared with placebo at 4 weeks. Krystal et al. 2010[133] found that CGI scores were significantly better with doxepin 1 mg or doxepin 3 mg versus placebo at 12 weeks

Figure 44. Efficacy of doxepin in older adults: patient global impression of sleep quality at final visit, participants reporting improvement

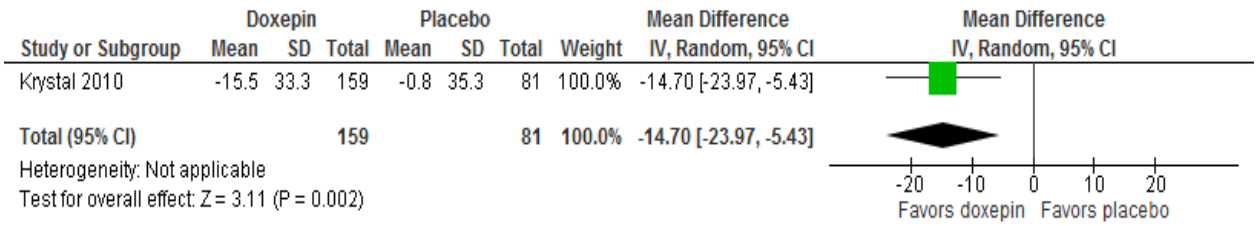


CI = confidence interval; SD = standard deviation; M-H Mantel-Haenszel

Sleep Outcomes

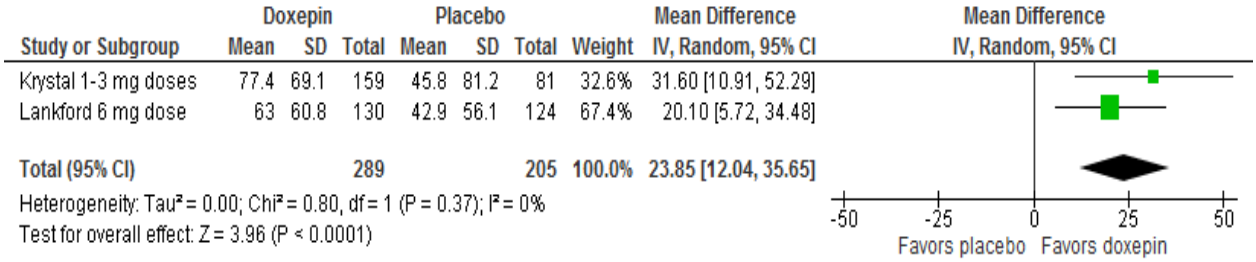
Krystal et al.[133] reported significant improvement in sleep onset latency with doxepin compared with placebo (low strength of evidence) (Figure 45). Moderate strength evidence found improvements in total sleep time by 24 minutes (Figure 46) compared with placebo. Lankford et al.[134] also reported that doxepin 6 mg improved WASO (Figure 47) an all studies reported improvement in sleep quality compared with placebo. At 12 weeks, Krystal et al. found all five sleep quality components of the PGI scale were significantly better with doxepin 1 mg and doxepin 3 mg compared with placebo.

Figure 45. Efficacy of doxepin in older adult population: sleep onset latency, mean change from baseline



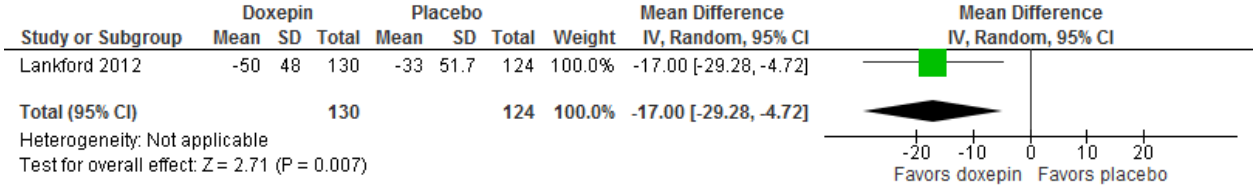
CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 46. Efficacy of doxepin in older adult population: total sleep time, mean change from baseline



CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 47. Efficacy of doxepin in older adult population: wake time after sleep onset, mean change from baseline



CI = confidence interval; IV = inverse variance; SD = standard deviation

Krystal et al. 2010[133] found no significant differences in next-day residual function and effects between both doxepin doses and placebo in the Digit Symbol Substitution Test, the Symbol Copying Test, or daytime sleepiness at 12 weeks.

Adverse Effects

There were no significant differences in overall study withdrawals, study withdrawals due to adverse effects, participants reporting at least one adverse event, or daytime somnolence, between participants receiving doxepin versus placebo. However, there were significantly fewer headaches (RR 0.29 [95% CI 0.29 to 0.70]) among participants receiving doxepin versus placebo.

Efficacy of Suvorexant in the General Population and Older Adults

Overview of Studies

We identified three RCTs that compared the orexin receptor antagonist, suvorexant, to placebo in mixed general and older populations (Table 22).[135,136] Two of the trials were reported in one publication.[137] The three trials randomized 2811 participants; mean age was 58; 62 percent were female. Most participants were white. The majority of the participants in the trial by Michelson et al. were aged 65 years of age or older (59%).[135] Based on ISI scores at baseline, the participants typically had clinical insomnia of moderate severity. The two trials reported by Herring et al. evaluated two dose groups, a 20 mg (for participants <65 years of age)/15 mg (for participants ≥65 years) dose group and a 40 mg (<65 years)/30 mg (≥65 years) dose group.[136] Michelson et al. evaluated the combined doses of 40 mg (<65 years) and 30 mg (≥65 years).[136] The dose recommended is 10 mg but should not exceed 20 mg daily. Strength of evidence was determined for the lower 20/15 mg dose group (n=1260 participants). The trials included in Herring et al were short term, lasting 3 months. Michelson et al. was longer-term, with a double-blinded, treatment phase of one year. All trials reported industry sponsorship and had an overall moderate risk of bias.

Table 22. Efficacy of orexin receptor antagonists in the general population and older adults: overview and strength of evidence

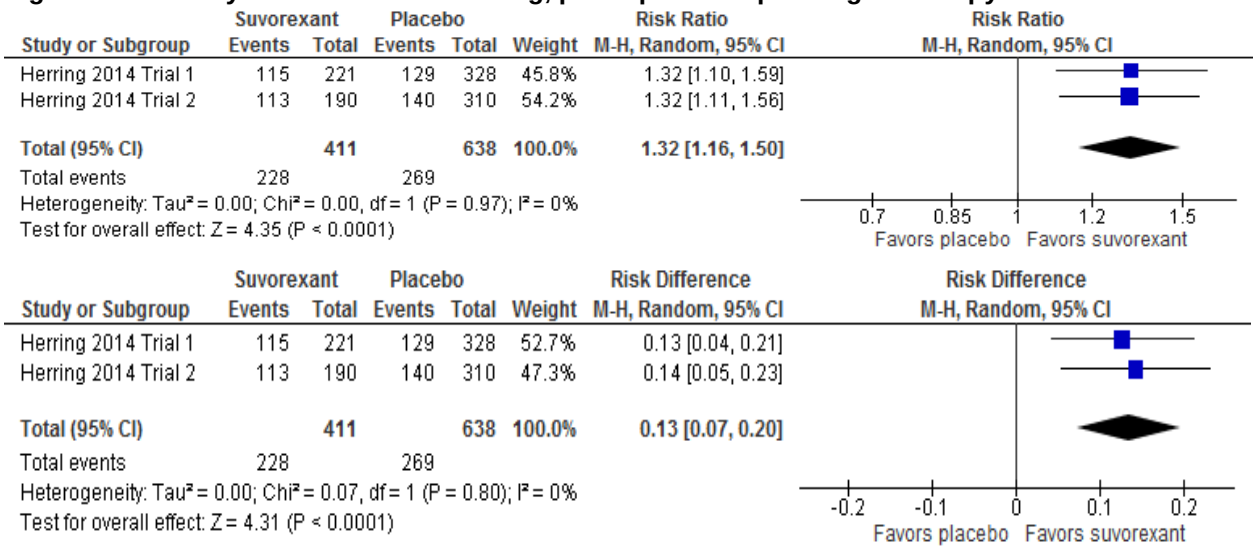
Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N) or Mean Minutes[a]	Placebo % (n/N) or Mean Minutes[a]	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Suvorexant 15 or 20 mg vs. placebo (2 RCT; N=1260)	Global Outcomes	Response to therapy based on ISI (≥6 point improvement from baseline)	2 (1049)	55 (228/411)	42 (269/638)	Favors suvorexant RR = 1.32 [1.16 to 1.50]; ARD = 0.13 [0.07 to 0.20] NNT = 8	Moderate (moderate study limitations)
		ISI, mean change in scores	2 (1084)	-6	-5	Favors suvorexant WMD = -1.2 [-1.8 to -0.6]	Moderate (moderate study limitations)
	Sleep Outcomes	Sleep onset latency, self-report, minutes, Mean change from baseline	2 (1089)	-25	-19	Favors suvorexant WMD = -6.0 [-10.0 to -1.9]	Moderate (moderate study limitations)
		Total sleep time, self-report, minutes, Mean change from baseline	2 (1089)	55	39	Favors suvorexant WMD = 16.0 [4.7 to 27.2]	Moderate (moderate study limitations)
		Wake time after sleep onset, self-report, minutes, *mean change from baseline*	2 (1089)	-35-	-30	Favors suvorexant WMD = -4.7 [-8.9 to -0.5]	Moderate (moderate study limitations)
		Sleep quality (based on 1-4 scale), *mean change from baseline*	2 (1089)	NA	NA	Favors suvorexant SMD = 0.20 [0.08, 0.32]	Moderate (moderate study limitations)
	Adverse Effects	Overall withdrawals	2 (1266)	12 (58/494)	12 (96/772)	NS, RR = 0.95 [0.70 to 1.29]	Low (moderate study limitations and imprecise)
		Withdrawals due to adverse effects	2 (1260)	3 (15/493)	5 (40/767)	NS, RR = 0.59 [0.28 to 1.26]	Low (moderate study limitations and imprecise)
		Participants with ≥1 adverse effect	2 (1260)	46 (229/493)	47 (358/767)	NS, RR = 0.99 [0.88 to 1.12]	Moderate (moderate study limitations)

ARD = absolute risk difference; CI = confidence intervals; NS = No significant difference; NNT = number needed to treat; RR = risk ratio; WMD = weighted mean difference
[a]Weighted by sample sizes.

Global Outcomes

Short-term, both trials evaluating 20/15 mg doses of suvorexant reported clinically meaningful improvement in sleep based on ISI scores (Figure 48).[136] Moderate-strength evidence shows that compared with placebo, suvorexant more often resulted in response to therapy, indicated by a in the ISI score (55% vs. 42%). The mean difference in ISI scores at 3 months of was -1.2 points (95% CI, -1.8 to -0.6) but this difference was below the minimum important difference of 7 points, indicating 'responder' to treatment.

Figure 48. Efficacy of suvorexant 20/15 mg, participants responding to therapy



CI = confidence interval; SD = standard deviation; M-H = Mantel-Haenszel

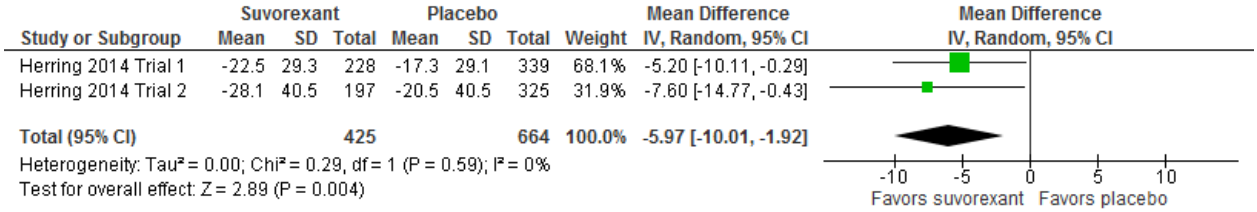
Higher Dose (40/30 mg) Findings

Comparable to the 20/15 mg group, suvorexant 40/30 mg more often resulted in response to therapy compared with placebo short-term (55% vs. 42%). Pooled results from all three trials found the mean difference in ISI scores at 3 months of was -1.7 points (95% CI, -2.3 to -1.0) but this difference was also below the minimum important difference of 7 points. At one year, Michelson et al. reported marginally significant improvement versus placebo. The mean difference between groups was -0.9 (95% CI, -1.8 to -0.0).[135]

Sleep Outcomes

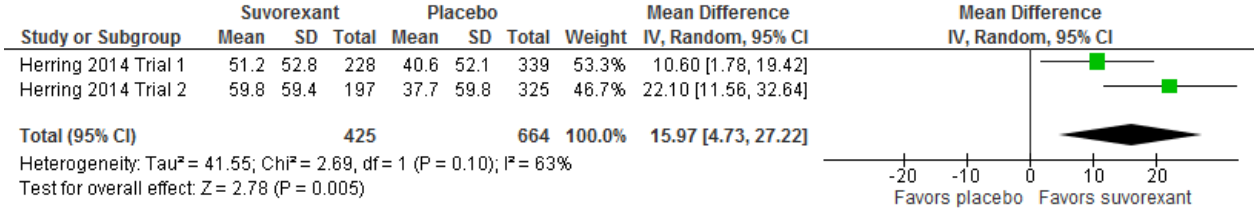
Moderate strength evidence shows suvorexant 15 or 20 mg treatment reduced sleep onset latency by 6 minutes compared with placebo (Figure 49).[136] However, mean sleep onset latency remained above the 30 minute threshold indicating 'no insomnia' in both groups in all three trials. Compared with placebo, short-term suvorexant 20/15 mg therapy also improved TST by 16 minutes (Figure 50) (moderate strength evidence). WASO and sleep quality were improved with suvorexant versus placebo but the magnitude of the improvements were small (moderate strength of evidence).

Figure 49. Efficacy of suvorexant 20/15 mg: subjective sleep latency, mean change from baseline in minutes



CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 50. Efficacy of suvorexant 20/15 mg: subjective total sleep time, mean change from baseline in minutes



CI = confidence interval; IV = inverse variance; SD = standard deviation

Higher Dose (40/30 mg) Findings

Short-term suvorexant 40/30 mg treatment reduced sleep onset latency by 10 minutes and increased TST by 23 minutes compared with placebo.[136] Similar to findings in the lower dose groups, mean sleep onset latency remained above the 30 minute threshold indicating 'no insomnia' in both groups in all three trials. At one year, improvements were comparable to short-term.[135]

Functioning, Mood, and Quality of Life

Functioning, mood, and quality of life outcomes of interest were rarely reported. Over one year, suvorexant 40/30 mg had no effect on mood compared with placebo, based on assessment with the Quick Inventory of Depressive Symptomatology-Self Report.[135]

Adverse Effects

Low strength evidence found withdrawal for any reason and withdrawals due to adverse effects did not significantly differ between the suvorexant 20/15 mg and placebo groups short-term.[136] Moderate strength evidence found no difference between groups in the proportions of participants reporting at least one adverse effect. The specific adverse effect most associated with short-term suvorexant 20/15 mg use was somnolence (7% vs. 3% for placebo; RR 2.5 [1.4 to 4.4]). One death was reported in the placebo group due to cerebrovascular accident. Suicidal ideation was reported in one suvorexant and placebo participant each (<1%). Incidence of excessive daytime sleepiness was reported in three participants in the suvorexant group and one in the placebo group. One incidence each of hypnagogic hallucination, hypnopompic hallucination, and sleep paralysis were reported in the suvorexant group, none in the placebo group. There were no differences in incidence of falls (4 vs. 7 for placebo) and motor vehicle accidents or violations (10 vs. 12) between the suvorexant and placebo groups.

Higher Dose (40/30 mg) Findings: Short Term (3 Months)

Similar to the findings of the suvorexant 20/15 mg group, withdrawal for any reason, withdrawals due to adverse effects and participants reporting at least one adverse effect did not significantly differ between the placebo groups.[136] Somnolence was the most common adverse effect associated with suvorexant use, 11 percent versus 3 percent for placebo (RR 3.97 [2.58 to 6.09]).[135,136] Two participants died during the trials, one in suvorexant group due to hypoxic-ischemic encephalopathy and one in the placebo group due to cerebrovascular accident. Suicidal ideation was reported in two suvorexant participants and one placebo participant.

Higher Dose (40/30 mg) Findings: Long Term (1 Year)

Withdrawal for any reason (suvorexant 38% vs. 37% for placebo), withdrawals due to adverse effects (12% vs. 9%), and participants reporting at least one adverse effect (70% vs. 64%) did not significantly differ between the suvorexant 40/30 mg and placebo groups.[135] Specific adverse effects associated with suvorexant 40/30 mg use were somnolence (13% vs. 3% for placebo), fatigue (7% vs. 2%), and dry mouth (5% vs. 2%). Suicidal ideation was reported for four suvorexant participants (<1%), leading to study withdrawal for two of the participants. Excessive daytime sleepiness was more common in the suvorexant group (2.5% vs. 0.8% for placebo). Three incidences of hypnagogic hallucination and one each of somnambulism and hypnopompic hallucination were reported in the suvorexant group and none in the placebo group. There were no differences in incidence of falls between the suvorexant and placebo groups (2% vs. 3%).

Comparative Effectiveness of Pharmacologic Interventions for Insomnia Disorder

Zolpidem Versus Temazepam

Overview of Study

We identified one RCT that compared the nonbenzodiazepine zolpidem 10 mg to the benzodiazepine temazepam 20 mg over a 4 week treatment period (Table 23).[138] Among the 223 randomized, baseline characteristics were available for 159 participants; mean age was 46 years; 67 percent were female. The trial was conducted in the Netherlands, reported industry sponsorship, and had a moderate risk of bias.

Table 23. Comparative effectiveness of nonbenzodiazepines versus benzodiazepines: overview and strength of evidence

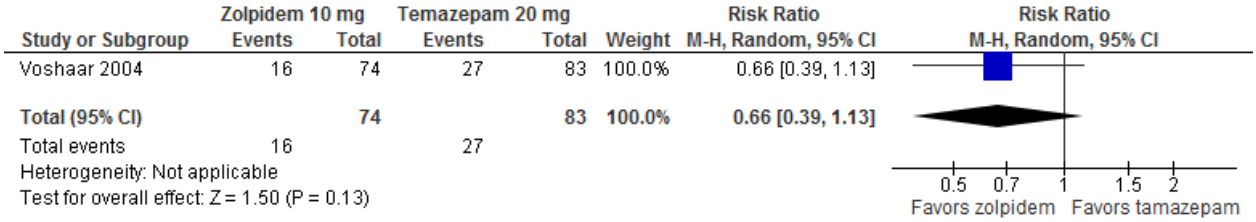
Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment A % (n/N) or Mean Minutes	Treatment B % (n/N) or Mean Minutes	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Zolpidem 10 mg vs. Temazapam 20 mg (1 RCT; N=223)	Global Outcomes	CGI, much-very much improved	1 (157)	21.6 (16/74)	32.5 (27/83)	NS, RR= 0.66 [0.39 to 1.33]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
	Sleep Outcomes	Sleep onset latency, self-report, minutes	1 (159)	46	46	NS, MD = 0.0 [-10.4 to 10.4]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Total sleep time, self-report, minutes	1 (159)	413	386	Favors zolpidem MD = 27.0 [2.1 to 51.9]	Low (moderate study limitations and unknown consistency)
		Wake time after sleep onset, self-report, minutes	1 (159)	40	39	NS, MD = 1.0 [-10.5 to 12.5]	Insufficient (moderate risk of bias, imprecise, and unknown consistency)
	Adverse Effects	Overall withdrawals	0				Insufficient
		Withdrawals due to adverse effects	0				Insufficient
		Participants with ≥1 adverse effect	0				Insufficient

CI = confidence intervals; MD = mean difference; NS = No statistically significant difference mean difference

Global Outcomes

Evidence was insufficient to assess differences between groups in global outcomes. Following 4 weeks of treatment (Figure 51), Voshaar et al. found that 22 percent in the zolpidem group and 33 percent in the temazepam group reported that symptoms were "much-very much" improved on the CGI.

Figure 51. Comparative effectiveness of zolpidem versus temazepam: global improvement, participants reporting improvement

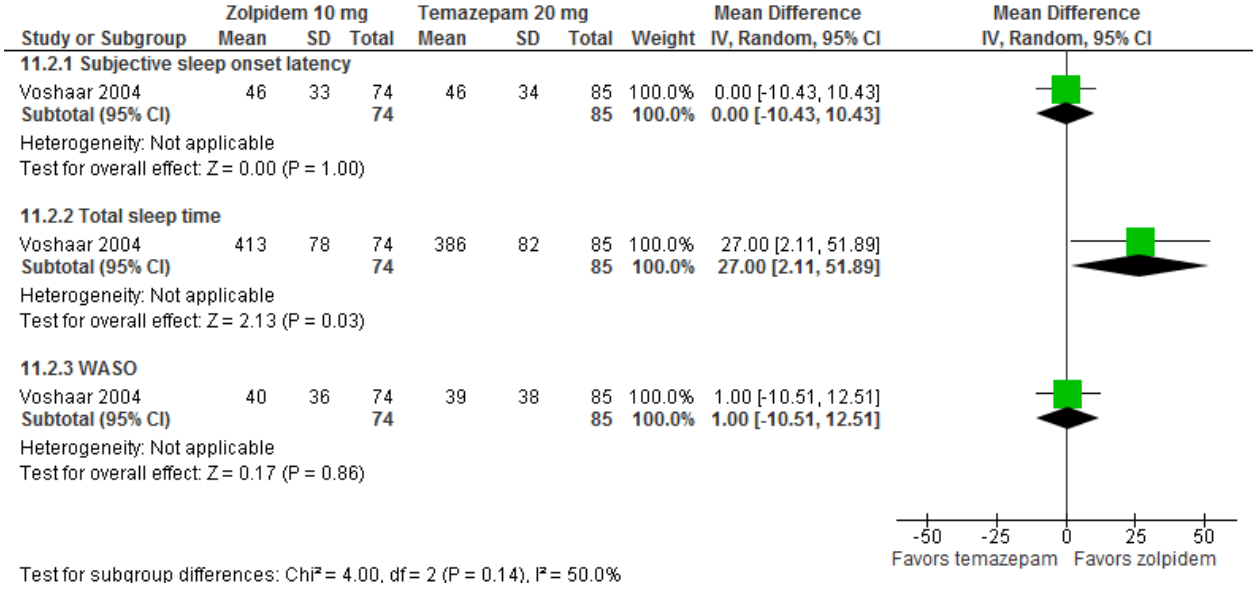


CI = confidence interval; IV = inverse variance; SD = standard deviation

Sleep Outcomes

Sleep outcomes are presented in Figure 52. Evidence was insufficient to assess sleep outcomes. Voshaar et al. found that total sleep time improved with zolpidem compared with temazepam. There were no differences between groups for sleep onset latency and wake time after sleep onset.

Figure 52. Comparative effectiveness of zolpidem versus temazepam: subjective sleep outcomes



CI = confidence interval; IV = inverse variance; SD = standard deviation

Functioning, Mood, and Quality of Life

No functioning, mood, and quality of life outcomes were reported.

Adverse Effects

Overall withdrawals, withdrawals due to adverse effects, and participants with at least one adverse effect were not reported according to treatment arm. Nine participants withdrew due to an adverse effect. No participant experienced a major adverse effect.

Zolpidem Versus Zaleplon

Overview of Studies

We identified two 4-week RCTs evaluating zaleplon versus placebo that also included a zolpidem arm (Table 24).[111,112] Head-to-head comparisons between zaleplon and zolpidem were not provided, which limited our assessment of comparative effectiveness. Among the 965 participants randomized to zaleplon or zolpidem, mean age was 42 years, 62 percent were female, and most were white (91%). One trial was conducted in the United States[112] and one was conducted in Canada and Europe.[111] Participants were randomized to zaleplon 5, 10, or 20 mg doses and zolpidem 10 mg. Both trials reported industry sponsorship and had moderate risk of bias.

Table 24. Efficacy and comparative effectiveness of nonbenzodiazepines: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment A % (n/N) or Mean Minutes	Treatment B % (n/N) or Mean Minutes	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Zaleplon 5-20 mg vs. Zolpidem 10 mg 2 RCTs; N=965)	Sleep Outcomes	Sleep onset latency, self-report, minutes	1 (301)	59	45	Favors zolpidem 10 mg dose versus zaleplon 5 mg dose MD= -13.7 [-25.1 to -2.3] NS zolpidem 10 mg versus zaleplon 10 mg	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Total sleep time, self-report, minutes	2 (965)	-	-	No direct comparison and reported data do not allow analysis	Insufficient
		Sleep efficiency	0				Insufficient
		Sleep Quality, *Improved sleep quality, self-report*	2 (870)	57 (376/656)	64 (137/214)	NS, RR = RR 0.90 [0.80 to 1.01]	Moderate (moderate study limitations)
	Adverse Effects	Overall withdrawals	2 (965)	12 (85/726)	12 (28/239)	NS, RR = 0.98 [0.66 to 1.46]	Low (moderate study limitations and imprecise)
		Withdrawals due to adverse effects	2 (958)	4 (29/720)	6 (14/238)	NS, RR = 0.68 [0.36 to 1.27]	Low (moderate study limitations and imprecise)
		Participants with ≥1 adverse effect	2 (958)	7 (510/720)	7 (175/238)	NS, RR = 0.95 [0.87, 1.03]	Moderate (moderate study limitations)

CI = confidence intervals; MD = mean difference; NS = no statistically significant difference

Global Outcomes

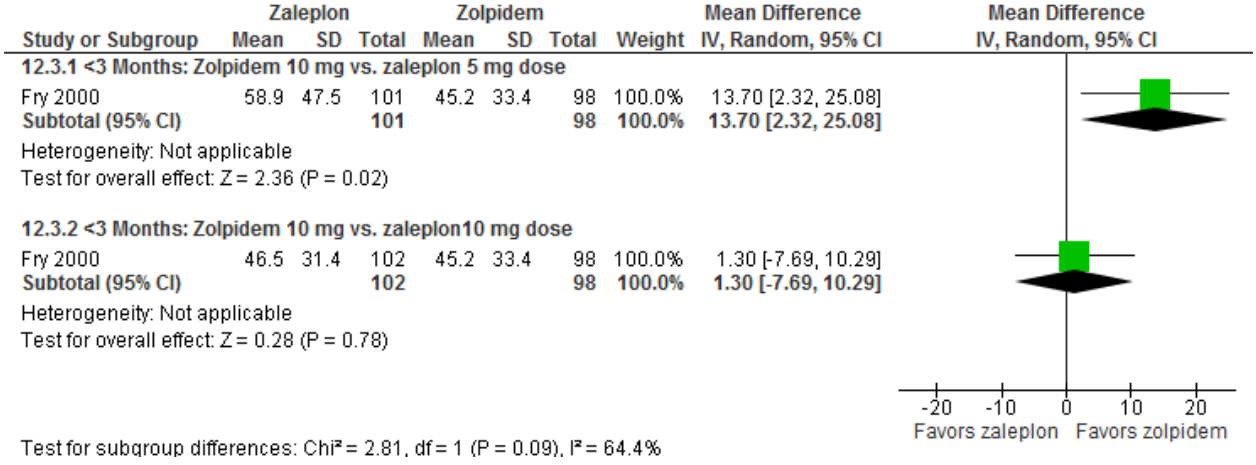
The included trials did not report global outcomes.

Sleep Outcomes

Sleep outcomes from included trials are presented in Table 24, and Figures 53 and 54. Zolpidem 10 mg improved sleep onset latency compared with zaleplon 5 mg by approximately 14 minutes.[112] Improvements in sleep onset latency were similar between the zolpidem and zaleplon 10 mg dose groups (insufficient evidence). We could not evaluate the comparative effectiveness of the two nonbenzodiazepine agents for total sleep time from the data reported (insufficient evidence). Both trials reported that zaleplon and zolpidem did not consistently improve median total sleep time compared with placebo over the 4 week study durations.

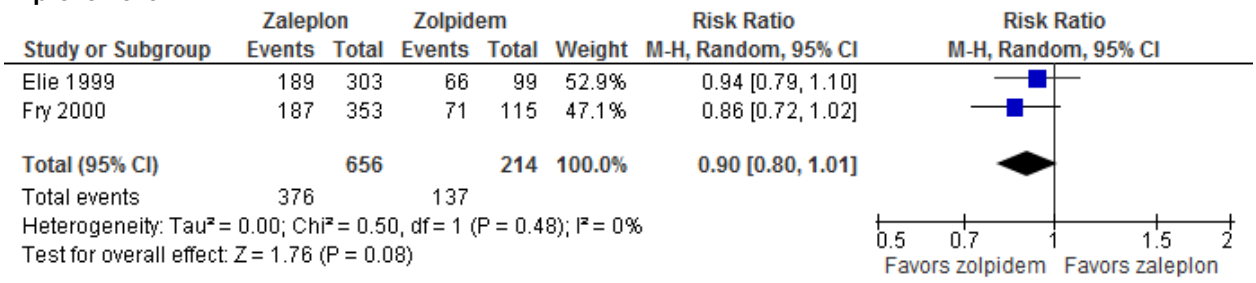
Sleep quality with zaleplon was similar to zolpidem at week 4 (57% vs. 64%) (moderate strength of evidence). There were also no significant differences between the individual zaleplon doses versus zolpidem at week 4.

Figure 53. Comparative effectiveness of zaleplon versus zolpidem: sleep onset latency



CI = confidence interval; IV = inverse variance; SD = standard deviation

Figure 54. Comparative effectiveness of zaleplon versus zolpidem: sleep quality, participants reporting improvement



CI = confidence interval; SD = standard deviation; M-H = Mantel-Haenszel

Functioning, Mood, and Quality of Life

No functioning, mood, and quality of life outcomes were reported in the included trials.

Adverse Effects

Adverse effects were reported in both trials. There were no differences in withdrawals for any reason (12% each) and the proportion of participants reporting at least one adverse event (7% each) between the zaleplon and zolpidem groups. Withdrawals due to adverse effects were comparable between groups. Incidences of withdrawal symptoms and rebound insomnia following discontinuation were reported for zolpidem. Neither trial reported evidence of tolerance or withdrawal symptoms associated with zaleplon use.

Long-Term Adverse Effects: Analysis of Observational Studies

We used data from 12 observational studies including open-label extensions of RCTs to assess long-term harms of pharmacological treatments of insomnia.[139-150] We included studies that reported harms if: (1) study population included adults with chronic insomnia without other major diagnoses such as cancer, Parkinson's, etc. or the hypnotics evaluated were only those that were FDA-indicated for insomnia and were likely administered for sleep disorders; (2) study duration was at least 6 months; and (3) study reported on at least 100 persons. Outcomes included percentage of individuals withdrawing from pharmacological treatments, reasons for withdrawal (lack of efficacy, adverse effects, other), any serious adverse effects (i.e., mortality), and specific adverse effects associated with the drug of interest. Followup duration ranged from 6 months to 12 years.

Any Hypnotic Drug

Four studies provided information on long-term harms with hypnotic drugs. Results suggest a correlation between hypnotic use and dementia and fractures; results regarding a correlation with mortality were mixed.

Using data from longitudinal electronic medical records, a matched cohort survival analysis identified 10,529 patients who received hypnotic prescriptions and compared them with 23,676 matched controls who did not receive hypnotic prescriptions.[144] The study was conducted in the United States. Participants were matched by age, sex and smoking status and were followed for a mean of 2.5 years. Overall mean age was 54 years, 63 percent were female, and most were white. During the study interval from 2002 to 2006, zolpidem was the most commonly prescribed hypnotic (41%, n=4338), followed by temazepam (20%, n=2076). The participants were stratified into tertiles based on the number of doses prescribed per year. For the participants prescribed 0.4-18 pills per year (n=3491) of any hypnotic, the hazard ratio (HR) of death was 3.60 [95% CI, 2.92 to 4.44] compared with participants who were not prescribed hypnotics. For the participants prescribed 18-132 (n=3548) and >132 pills (n=3490) per year the HRs were 4.43 [95% CI, 3.67 to 5.36] and 5.32 [95% CI, 4.50 to 6.30], respectively, indicating a dose-response association. Kripke et al. also reported increased hazards of incidental major cancers for the middle and upper dose tertile groups. A major limitation to this study was that residual confounding could not be fully excluded, due to possible biases that affected which patients were prescribed hypnotics in addition to possible imbalances in surveillance.

A prospective cohort study examined the association between hypnotic usage and mortality over a 12-year period.[142] The study, conducted in France, included older participants aged at least 65 years without dementia at baseline. Median age was 73 years, and 59 percent were female. Among the 6696 participants, 1454 were confirmed regular users of hypnotics, mainly benzodiazepines, and 5242 did not use hypnotics. Overall, 72 percent of participants reported at least one insomnia complaint (82% for hypnotic users vs. 70% for nonhypnotic users). Mortality

was not significantly associated with hypnotic use. Over a median followup time of 8.9 years, all-cause mortality was not significantly different between groups, 22 percent (326/1454) in hypnotic user group compared with 19 percent (981/5242) in the nonhypnotic user group. Following adjustment for confounders, the HR was 1.03 [95% CI, 0.84 to 1.28]. Results were similar when limited to benzodiazepine use only. Study limitations included the unavailability of hypnotic dose data, low participation rate at baseline, and the nonrandom exclusion of participants with missing data at baseline.

A retrospective, case-control study from Korea evaluated the risk of fractures related with zolpidem in elderly insomnia patients.[143] The 1508 study participants were mostly female (80%) and 31 percent had a history of osteoporosis. Cases were defined as subjects who had a diagnosis of a fracture, mainly in the femur. Hazard period exposures (1 day length prior to the fracture date) and control exposures (periods of the same length at 5, 10, 15, and 20 weeks prior to the fracture date) were established at a one-to-four ratio, resulting in 1508 hazard period exposures and 6032 control period exposures. During the hazard and control periods, 431 had used zolpidem more than once. Analysis of the data found use of zolpidem was associated with significant increase in the risk of with a fracture. The crude odds ratio was 1.84 [95% CI, 1.47 to 2.30]. Following adjustment of the effect of other drugs that can increase the risk of fall or fracture, the odds ratio was 1.72 [95% CI, 1.37 to 2.16]. Among the 703 patients that had used benzodiazepines more than once during the same exposure periods, there was no difference in risk of fracture (adjusted odds ratio 1.00 [95% CI, 0.83 to 1.21]).

A retrospective cohort study from Taiwan aimed to examine whether hypnotic use increased the risk of dementia in older adults.[140] Using a large population database, the study cohort was comprised of 5693 subjects, median age 65 years and 56 percent female, with long-term insomnia who had been prescribed hypnotics, mainly nonbenzodiazepines (49%) followed by benzodiazepines (34%). The control group, in a five-to-one-ratio and matched by age and sex, comprised 28,465 subjects without insomnia. All subjects were examined over a 3-year period. Over the 3 year interval, 4 percent (220/5693) of 5693 subjects with insomnia and prescribed hypnotics were diagnosed with dementia compared with 1.5 percent (424/28,465) of the controls. Following adjustment for confounders, the HR was 2.34 [95% CI, 1.92 to 2.85]. Risk of dementia with hypnotic use was also greater in both male and female subgroups. Subjects aged between 50 and 65 years had the highest risk of dementia with an HR of 5.22 [95% CI, 2.62 to 10.41]. There was no difference in risk between nonbenzodiazepine versus benzodiazepine use (HR 1.01 [95% CI 0.76 to 1.33]. Limitations to the study included the inability to control for all confounders (educational level, personal history of smoking and alcohol consumption, body mass index, socioeconomic status) and a relatively short followup period that may not have been long enough for patients to develop dementia.

Specific Nonbenzodiazepines

Six studies provided longer term harms information on specific nonbenzodiazepines. Results suggest a correlation between nonbenzodiazapine use and mortality, major injury, fracture,

The previously discussed study by Kripke et al. also compared zolpidem alone (n=4338) with no hypnotic use (n=23,671).[144] Comparable to any hypnotic prescribed, doses were stratified into tertiles of 5-130 (n=1453), 130-800 (n=1456), and >800 (n=1427) mg per year. Zolpidem use was associated with increased hazard of death for all tertiles, with HRs of 3.93 [95% CI, 2.98 to 5.17], 4.54 [95% CI, 3.46 to 5.95], and 5.69 [95% CI, 4.58 to 7.07], respectively. As with the findings of any hypnotic prescribed, a dose-response association was demonstrated. Increased hazard of

incidental major cancers was only found in the upper dose tertile group (HR 1.28 [95%CI 1.03 to 1.59]).

A retrospective matched cohort study conducted in Taiwan examined the risk of major injury (head injury or fracture) requiring hospitalization in patients prescribed zolpidem.[145] Participants and data were obtained from the Taiwan National Health Insurance population-based cohort database. Investigators identified 8188 participants who were at least 18 years of age and received a first prescription for zolpidem between January 2000 and December 2009 and compared them with 32,752 age- and sex-matched patients who were not prescribed hypnotic therapies. Overall mean age was 39 years and 49 percent were female. Use of zolpidem was found to be associated with risk of a major head injury or fracture requiring hospitalization compared with nonusers of hypnotics (adjusted HR 1.67 [95% CI, 1.19 to 2.34]). The incidence rate of major injury was 60.1 cases per 10,000 person-years in the zolpidem user group versus 36.7 cases per 10,000 person-years in the nonuser control group. A dose-response association was demonstrated when zolpidem dosage was increased. The adjusted HRs for the 71-800, 801-1600, and >1600 mg per year dosage groups were 2.04 [95% CI, 1.32 to 3.13], 4.37 [95% CI, 2.12 to 9.01], and 4.74 [95% CI, 2.38 to 9.42], respectively. The HR for major injury in zolpidem users in the younger cohort (aged 18-54 years) was 1.70 [95% CI, 1.15 to 2.51] after adjusting for diabetes, sleep disorder, alcohol-related disorders and other variables. The adjusted HR for major injury in the older zolpidem user cohort (aged >55 years) was not statistically significant. Limitations of the study included possible unmeasured or unknown confounders and the data in NHI claims are primarily intended for administrative billing purposes and have not been verified scientifically.

A case-control study conducted in the United States explored the association of zolpidem use and risk of hip fracture in older adults (≥ 65 years of age).[150] The participants were enrolled in the New Jersey Medicaid program and information was extracted from January 1993 to June 1995. The cases included 1222 patients who underwent surgical repair of a hip fracture. They were matched by age and sex to controls in a 4 to 1 ratio (n=4888). Overall mean was 83 years, 84 percent were female, and most were white race. Zolpidem use was reported in 1.6 percent of the cases compared with 0.7 percent of the controls. Zolpidem use was found to be associated with a significant increased risk of hip fracture compared with no zolpidem use. The adjusted odd ratio (OR) was 1.95 [95% CI, 1.09 to 3.51]. An increased risk of hip fracture was also observed with benzodiazepines (adjusted OR 1.46 [95% CI 1.21 to 1.76]). A possible limitation of the study was confounding by indication (i.e., selection bias). The study authors attempted to control for a patient's underlying risk of hip fracture by adjusting their analyses for age, sex, and several markers of frailty, but it is possible that residual confounding by indication may have remained.

One open-label extension of two RCTs conducted in the United States and Europe evaluated the long-term use of zaleplon 5-10 mg doses in 576 older adults with insomnia disorder.[139] Participants were followed 6 to 12 months following initial double-blind treatment phases. Mean ages of the participants were 73 and 72 years for the U.S. and European populations, respectively. No other demographic details were provided. No deaths occurred during the study. The most commonly reported specific adverse effects were headache (27%) and infection (13%).

One open-label extension of an RCT conducted in the United States evaluated the long-term use of eszopiclone 3 mg in 471 adults with chronic insomnia.[147] Participants were followed an additional 6 months following an initial 6-month double-blind treatment phase. Mean age of the participants was 46 years, and 63 percent were female. Among the participants, 111 were previously randomized to placebo during the double-blind phase of the RCT and then switched to eszopiclone for the open-label period (the placebo-eszopiclone (PBO-ESZ) group). The remaining

360 participants remained on eszopiclone for the open-label period (ESZ-ESZ group). Overall, 19 percent withdrew (89/471) from the study for any reason. Approximately 4 percent withdrew due to adverse effects. Incidence of withdrawal due to adverse effects and of treatment-related adverse effects was higher in the PBO-ESZ group compared with the ESZ-ESZ group (6% and 44% vs. 3% and 28%, respectively). The most common reasons for withdrawal due to adverse effects were unpleasant taste and anxiety, reported in two participants each. Among the 471 participants, the most common adverse effects considered treatment-related were unpleasant taste (7%), headache (5%), somnolence (4%), abnormal dreams and dizziness (3% each). Incidence of was much greater in the unpleasant taste in the PBO-ESZ group compared with the ESZ-ESZ group (20% vs. 3%). A serious adverse effect was reported for 11 participants (2%) leading to study withdrawal in two participants. These events included chest pain, accidental injury, atrial fibrillation, and diabetes.

An older open-label study conducted in France evaluated zolpidem use in 107 adults with insomnia over 6 months.[148] The initial dose of zolpidem was 20 mg, but the dose could be adjusted downward or upward according to efficacy and tolerability. Mean age of the participants was 63 years, and 69 percent were female. The trial was not completed by 19 percent (20/107) of the participants, with adverse effects accounting for 37 percent (7/20) of the withdrawals. Among the seven participants withdrawing due to adverse effects, two withdrew during the 7-day placebo run-in period before active treatment was initiated. Reasons for withdrawal were not indicated. There were 42 adverse effects experienced by 24 patients (22%) which were possibly or probably associated with treatment. These events included malaise, vertigo, and anterograde amnesia (five events each). All participants reporting vertigo (five) or confusion (two) were at least 70 years of age. An additional 22 participants (27 events) reported adverse effects considered unrelated to the study drug. The five withdrawals during active treatment were due to these events. Specific adverse events were not described.

Specific Benzodiazepines

The previously discussed study by Kripke et al. also compared temazepam alone (n=2076) with no hypnotic use (n=23,671).[144] Comparable to any hypnotic prescribed, doses were stratified into tertiles of 1-240 (n=798), 240-1640 (n=613), and >1640 (n=665) mg per year. Temazepam use was associated with increased hazard of death for all tertiles, with HRs of 3.71 [95% CI, 2.55 to 5.38], 4.15 [95% CI, 2.88 to 5.99], and 6.56 [95% CI, 5.03 to 8.55], respectively. As with the findings of any hypnotic prescribed, a dose-response association was demonstrated. Increased hazard of incidental major cancers was found in the middle and upper dose tertile groups (HR 1.28 [95% CI 1.03 to 1.59] and 1.99 [95% CI 1.57 to 2.52]).

Melatonin Agonists

Two studies reported longer-term harms related to ramelteon. Adverse effects were common but rarely severe or requiring study withdrawal. However, study withdrawal for any reason was common. One open-label study evaluated the ramelteon in 190 Japanese participants with chronic insomnia.[149] The participants had a mean age of 48 years and 69 percent were female. Participants received ramelteon 4 or 8 mg (titrated to 16 mg according to efficacy or lowered due to tolerability issues) for 24 weeks. Seven participants (4%) were withdrawn from the study due to adverse effects. Types of adverse effects that led to withdrawal were not described. An additional 21 participants withheld or discontinued treatment due to adverse effects. A total of 358 adverse effects were reported by 147 participants (77%), most deemed mild in severity. The most common specific adverse events were nasopharyngitis (24%), upper respiratory tract infections (6%),

eczema (6%), and headache (4%).There were two serious adverse effects that required hospitalization: pyelonephritis and synovitis.

One open-label study conducted in the United States evaluated the long-term use of ramelteon in 1213 participants with chronic insomnia.[146] The participants were divided into two groups. The adult group of 965 participants was aged 18 to 64 years and received ramelteon 16 mg over a 48-week treatment phase. The older adult group, aged at least 65 years, received ramelteon 8 mg. Most participants were female (59%). In the adult group, 62 percent had withdrawn for any reason by the end of the 48-week interval. Primary reasons for withdrawal were adverse effects (12%) and lack of efficacy (18%). Adverse effects associated with study withdrawal were not reported. For adult participants taking ramelteon for 6 months or 1 year, 81 percent reported at least one adverse effect at both time intervals. The most common adverse effects included nasopharyngitis (14% at 6 months, 15% at 1 year) and headache (13% and 14%). Somnolence was reported for 8 percent of the participants at both intervals. Two participants in the 18 to 64 year adult group died in motor vehicle accidents (neither was reported driving). Other serious adverse effects included prolactinoma and brain neoplasm in one participant each, and uterine fibroids in three participants. The prolactinoma was considered possibly treatment related.

In the older adult group, 58 percent had withdrawn for any reason by the end of the 48-week interval. Primary reasons for withdrawal were adverse effects (12%) and lack of efficacy (25%). For the older adult participants taking ramelteon for 6 months or 1 year, the incidence of at least one adverse effect was 83 and 85 percent, respectively. The most common adverse effects included nasopharyngitis (10% at 6 months, 11% at 1 year) and somnolence (9% and 10%). One participant was diagnosed with bladder cancer and one with colon cancer.

Efficacy and Comparative Effectiveness of Complementary and Alternative Medicine Treatments

Key Points

- A previous high quality systematic review found insufficient evidence on the efficacy of acupuncture as a treatment alone or as an adjunctive treatment. Updating results from this review, we conclude that the evidence remains insufficient to draw conclusions about the efficacy of acupuncture used alone or as an adjunctive treatment for insomnia disorder.
- A variety of other complementary and alternative interventions have been studied with RCTs and systematic reviews to determine efficacy in treating insomnia. These include homeopathy, valerian, bright light therapy, isoflavones, magnesium supplementation, chamomile extract, Simillimum, and Wuling capsule. Evidence is insufficient to draw conclusions regarding their efficacy in treating insomnia disorder because similar comparisons across studies did not exist and trials were often small with methodologic limitations.

Efficacy of Acupuncture

Overview of Included Studies

We identified one relevant systematic review addressing efficacy of acupuncture for insomnia disorder that was of sufficient quality to include in lieu of de novo extraction (Table 25). Cheuk et al.[27] searched bibliographic databases through October 2012, had no language restrictions,

distinguished different types of acupuncture, and included 33 primary studies. Twenty one of 33 trials included trials involved treatments lasting 4 or more weeks.

We identified two RCTs assessing the efficacy of acupuncture for insomnia that were not included in the previous systematic review (Table 26).[151,152] Hatchel et al. randomized participants to acupuncture or sham acupuncture and had moderate risk of bias; the study was underpowered but could be pooled with one comparison in the previous systematic review.[151] (Acupuncture versus sham acupuncture was included in the Cheuk et al. review.) We also identified one trial that assessed acupuncture as an adjunct therapy.[152] Adjunctive acupuncture versus other treatment alone was compared in Cheuk et al. Huo et al.[152] randomized participants to acupuncture using meridian and Anmian acupoints or to acupuncture using only meridian acupoints, had moderate risk of bias, and can be used to update the Cheuk et al. analysis for one outcome.

Hachul et al.[151] was conducted in Brazil, enrolled only females, randomized 18 participants, and had a study duration of 5 weeks.[151] Huo et al., a 4-week study, was conducted in China.[152]

Table 25. Efficacy of acupuncture: description and conclusions from previous systematic review

Study Information	Literature Through; SR Quality	Population; Relevant Comparison	Author Conclusion Strength of Evidence
Cheuk, 2012[27] Cochrane Depression, Anxiety and Neurosis Group) 33 trials (all high risk of bias) Only 17 trials provided relevant outcomes data	Literature search through October 2012 Good	Individuals clinically diagnosed with insomnia using standardized criteria Any type of acupuncture versus a passive control (no treatment, placebo; sham acupuncture)	"Due to poor methodological quality, high levels of heterogeneity and publication bias, the current evidence is not sufficiently rigorous to support or refute acupuncture for treating insomnia. Larger high-quality clinical trials are required." Insufficient

Table 26. Efficacy of acupuncture in the general adult population: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Intervention % (n/N) or Mean (SD)	Control % (n/N) or Mean (SD)	Results and Magnitude of Effect (95% CI)	Strength of Evidence
Acupuncture vs. sham acupuncture ***1 SR; 8 RCT; n=364***	Global Outcomes	PSQI	8 (364)			WMD = -2.1 [-3.2 to -1.0]	Insufficient (high study limitations)
	Sleep Outcomes	NR					Insufficient
	Adverse Effects	Total adverse events	1 (32)	6 (1/16)	0 (0/16)	OR = 3.19 [0.12 to 84.43]	Insufficient (high study limitations)
Adjunctive acupuncture vs. single treatment ***1 SR; 4 RCT; N=206***	Global Outcomes	PSQI	4 (206)			WMD = -2.5 [-3.2 to -1.8]	Insufficient (high study limitations)
	Sleep Outcomes						
	Adverse Effects	Total adverse effects	1 (45)	0% 0/23	27% (6/22)	OR = 0.05 [0.00 to 1.03]	Insufficient (high study limitations)

CI = confidence interval; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation; WMD = weighted mean difference

Global Outcomes

Cheuk et al.,[27] Hachul et al.,[151] and Huo et al.[152] reported PSQI scores. In the trial of acupuncture versus sham acupuncture, Hachul et al.[151] found no significant differences in PSQI scores and no significant change from baseline in either group. In contrast, in the trial of acupuncture at meridian and Anmian acupoints versus at meridian acupoints alone, Huo et al.[152] found significantly better (lower) PSQI scores with acupuncture at meridian and Anmian acupoints (5.49 vs. 7.77), but no significant improvements from baseline within either group. Updating the Cheuk et al. review strengthens the evidence for these two comparisons (Figures 55 and 56). However, because all the trials in that review were rated high risk of bias, we maintain that this evidence is insufficient.

Figure 55. Efficacy of acupuncture in the general adult population: PSQI score

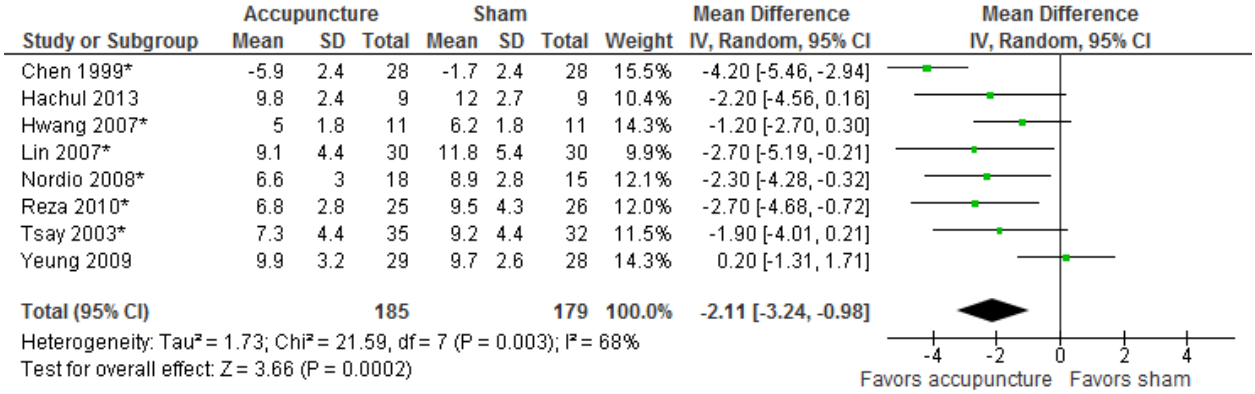
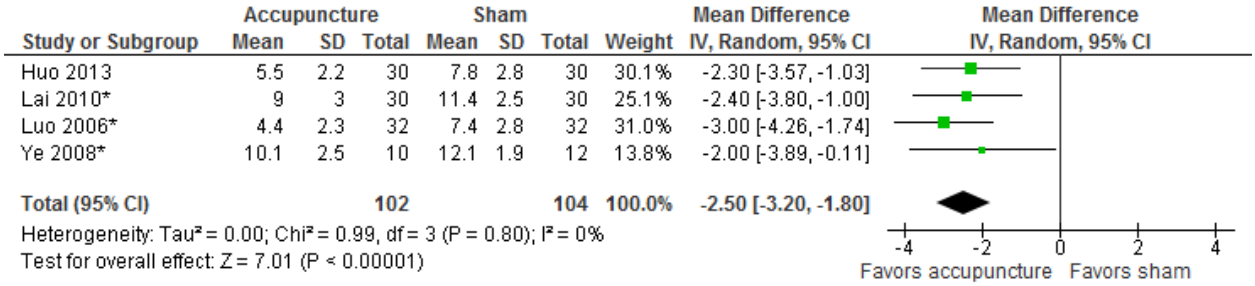


Figure 56. Efficacy of adjunctive acupuncture in the general adult population: PSQI score



Sleep Outcomes

Neither of the studies published since Cheuk et al. reported sleep outcomes; therefore, we could not update those outcomes.

Functioning, Mood, and Quality of Life

In their trial of acupuncture versus sham acupuncture, Hachul et al.[151] reported the Beck Depression Inventory but found no significant difference between groups in scores (33.28 vs. 32.5) and no significant improvement from baseline within either group. Hachul et al.[151] also reported the World Health Organization Quality of Life score. They found no significant difference between treatment groups in any component and significant improvement from baseline for only

the psychological component within the acupuncture group. In their trial of acupuncture at meridian and Anmian acupoints versus meridian acupoints alone, Huo et al.[152] found significantly better therapeutic efficacy and lower self-rating depression scores (25.53 vs. 30.80) but not self-rating anxiety scores (31.23 vs. 32.00) for meridian and Anmian acupoints. Self-rating depression scores and self-rating anxiety scores improved significantly from baseline within both groups. Huo et al.[152] also found significantly better treatment efficacy in the meridian plus Anmian acupuncture group.

Adverse Effects

Fewer than half of the studies included in Cheuk et al. reported adverse effects, and the adverse effects that were reported were minor. Compared with an intervention used by an RCT in this review, the Cheuk et al. systematic review[27] found no significantly greater risk for adverse effects for needle acupuncture versus placebo or sham acupuncture (OR 3.19 [95% CI, 0.12 to 84.43]) or for needle acupuncture with other treatment versus other treatment alone (OR 0.05 [95% CI, 0.00 to 1.03]).

Huo et al.[152] reported withdrawals by treatment group. No withdrawals occurred in either treatment group. Updating the data from the systematic review provides insufficient evidence to draw conclusions about the rates of adverse effects between groups.

Efficacy of Homeopathy

Overview and Summary of Previous Systematic Review

We identified one relevant systematic review that examined homeopathy for insomnia.[153] The review was assessed as having fair quality and was therefore used in lieu of de novo extraction. Cooper et al. identified five RCTs of homeopathy for insomnia, all had high risk of bias; they identified another RCT in an update.[153,154] Only one RCT showed a significant difference in the sleep impairment index with homeopathy compared with placebo. Evidence is insufficient to draw conclusions about the efficacy of homeopathy for treating insomnia disorder.

One additional trial of homeopathy that was not included in the previous systematic review was identified.[155] This trial studied a population different than other studies, so is not used to update results from the previous systematic review. Harrison et al. randomized South African men between the ages of 18 and 40 to homeopathic complex or placebo before supper and at bedtime for 4 weeks.[155] The authors report that an intergroup analysis showed a significant difference in sleep onset latency (median 7 minutes lower in the experimental group). Overall withdrawals did not differ significantly between homeopathic complex and placebo.

Efficacy of Valerian

Overview and Summary of Previous Systematic Review

We identified one relevant systematic review that examined valerian for insomnia.[156] The review was assessed as having fair quality and was therefore used in lieu of de novo extraction (Table 27). Taibi et al.[156] identified 29 clinical trials and eight open-label studies of valerian for insomnia. Most studies found no significant difference in sleep outcomes between valerian and the control treatment.

Table 27. Efficacy of complementary and alternative medicine treatments: description and conclusions from previous systematic reviews

Study Information	Literature Through; SR Quality	Population; Relevant Comparison	Author Conclusion Strength of Evidence
Cooper, 2010[153,154] Homeopathy k=5 RCTs; n=199 k=8 observational studies: n unclear	Literature search through July 2009 Fair	Individuals with insomnia Homeopathic medicines versus placebo	The evidence available does not demonstrate a statistically significant effect of homeopathic medicines for insomnia treatment. Existing RCTs were of poor quality and were likely to have been underpowered. Insufficient

Taibi, 2007[156]
Valerian
k=29 RCTs;
n=1941
k=8 open label studies;
n=20 to 830 participants
	Search date not reported
	Fair
		Individuals with insomnia or sleep disturbance
		Valerian or valerian in combination versus mostly a passive control (placebo; other CAM)
			The evidence does not support the clinical efficacy of valerian as a sleep aid for insomnia. Valerian was found to be safe with only rare adverse effects.
			Insufficient

Efficacy and Comparative Effectiveness of Bright Light Therapy

Overview and Summary of Studies

We identified two trials that compared different exposures to bright light for insomnia disorder.[157,158] Evidence for all populations and outcomes was insufficient to draw conclusions because no two studies analyzed similar comparisons.

Friedman et al. randomized 61 older adults to bright (~4,000 lux) or dim light in the morning or evening and reports on 51 completers.[157] Mean age was 64.0 and 69 percent were female; mean insomnia duration was 15 years. Friedman et al. found that mean sleep onset latency and total sleep time were significantly different at both 3 and 6 months post-treatment. Subjective measures were similar in bright light and dim light groups postintervention.

Kirisoglu et al. randomized older adults to 20 or 45 minutes of daily exposure to 10,000 lux for 60 days.[158] Longer exposure (45 minutes compared with 20 minutes daily) resulted in shorter sleep latencies and longer total sleep times. Outcomes measured at 3 months and 6 months showed that exposure to 45 minutes of bright light was associated with shorter sleep onset latency and longer total sleep time.

Efficacy of Other CAM Treatments

Overview and Summary of Other Eligible CAM Trials

We identified four trials of other complementary and alternative medicine interventions that met our inclusion criteria and were not included in one of the eligible previous systematic reviews.[159-162] Interventions included Wuling capsule, isoflavones, magnesium supplementation, and chamomile extract. Evidence for these interventions is insufficient to draw conclusions about their efficacy in treating insomnia disorder.

Lin et al. randomized volunteers from the general adult population to three Wuling capsules or placebo three times a day for 4 weeks.[161] Lin et al. found no significant difference between Wuling capsule and placebo in PSQI.[161] Lin et al.[161] found no significant difference between Wuling capsule and placebo groups in physical, psychological, social, or environmental domains of the

World Health Organization Quality of Life Brief Scale. No significant differences were seen in overall withdrawals, withdrawals due to adverse effects, or the proportion of participants with at least one adverse effect between Wuling capsule and placebo groups. One participant withdrew from the Wuling capsule group because of an adverse effect. The most common adverse effects were dry mouth, dizziness, constipation, stomach bloating, stomach pain, and diarrhea.

Hachul et al. randomized post-menopausal females aged 50 to 65 to isoflavone 80 mg or placebo (frequency not reported); Hachul et al.[160] found a smaller proportion of females reported moderate or intense insomnia with isoflavone than with placebo. Overall withdrawals by treatment group, withdrawals due to adverse effects, or the proportion of participants with at least one adverse effect were not reported.

Abbasi et al. randomized 46 older adults to 500 mg magnesium or placebo daily for 8 weeks.[159] Compared with placebo, magnesium supplementation improved ISI scores, decreased sleep onset latency, and increased sleep efficiency. Total sleep time remained similar across groups.

Zick et al. randomized 34 patients ages 18 to 65 to 270 mg chamomile twice daily or placebo for 28 days. Sleep and daytime functioning outcomes were similar with chamomile and placebo postintervention.[162]

Comparative Effectiveness of Interventions of Different Types

We identified several trials that assessed the comparative effectiveness of interventions across intervention classes (psychological versus pharmacologic) or combination treatments across intervention classes.

Comparative Effectiveness of Pharmacologic Versus Psychological Interventions and Combination Treatments

Key Points

- Evidence was insufficient to draw conclusions regarding the comparative effectiveness of CBT-I versus hypnotic medication.

Overview of Included Studies

We identified three trials with moderate risk of bias that compared CBT-I to a commonly used sleep medication or the combination treatment to either CBT-I or drug therapy alone and/or CBT-I alone (Table 28).[60,72,74,163]

Table 28. Comparative effectiveness of drug versus CBT or combined drug/CBT: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Control % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Zolpidem 10 mg-5mg vs. CBT-I (1 RCT; N=30)	Global Outcomes	Not reported					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	1 (27)	59	34	NS, MD = 24.6 [-3.1 to 52.3]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Total sleep time, self-report, minutes	1 (27)	373	355	NS, MD = 17.7 [-33.4 to 68.8]	Insufficient (moderate study limitations, imprecise, and unknown consistency))
		Sleep efficiency, %	1 (27)	67	84	Favors CBT MD = -16.3 [-28.9 to -3.7]	Insufficient (moderate study limitations, and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (30)	13 (2/15)	7 (1/15)	NS, RR = 2.00 [0.20, 19.78]	Insufficient (moderate study limitations, very imprecise, and unknown consistency)
		Withdrawals due to adverse events	1 (30)	0 (0/15)	0 (0/15)	NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Participants with ≥1 adverse event	NR				Insufficient
Zolpidem 10 mg-5mg vs. Zolpidem and CBT-I (1 RCT; N=33)	Global Outcomes	Not reported					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	1 (24)	59	39	NS, MD = 20.2 [-17.0 to 57.4]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Total sleep time, self-report, minutes	1 (26)	373	367	NS, MD = 6.0 [-57.1 to 69.1]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Sleep efficiency, %	1 (24)	67	80	NS, MD =-13.2 [-27.9 to 1.5]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (33)	13 (2/15)	28 (5/18)	NS, RR = 0.48 [0.11 to 2.13]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Withdrawals due to adverse events	1 (33)	0 (0/15)	0 (0/15)	NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Participants with ≥1 adverse event	NR				Insufficient

Table 28. Comparative effectiveness of drug versus CBT or combined drug/CBT: overview and strength of evidence (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Control % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Temazepam 7.5-30 mg vs. CBT-I (1 RCT; N=39)	Global Outcomes	Not reported					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	1 (36)	20	32	Favors Temazepam MD = -12.0 [-20.9 to -3.1]	Insufficient (moderate study limitations, and unknown consistency)
		Total sleep time, self-report, minutes	1 (36)	406	364	Favors Temazepam MD = 42.6 [6.3 to 79.0]	Insufficient (moderate study limitations, and unknown consistency)
		Sleep efficiency, %	1 (36)	86	81	NS, MD = 5.1 [-2.3 to 12.5]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (39)	15 (3/20)	0 (0/19)	NS, RR = 6.67 [0.37 to 121.07]	Insufficient (moderate study limitations, very imprecise, and unknown consistency)
		Withdrawals due to adverse events	1 (39)	15 (3/20)	0 (0/19)	NS, RR = 6.67 [0.37 to 121.07]	Insufficient (moderate study limitations, very imprecise, and unknown consistency)
		Participants with ≥1 adverse event	NR				Insufficient
Temazepam 7.5-30 mg vs. Temazepam /CBT-I (1 RCT; N=39)	Global Outcomes	Not reported					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	1 (35)	20	17	NS, MD = 2.3 [-5.1 to 9.7]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Total sleep time, self-report, minutes	1 (35)	406	397	NS, MD = 9.4 [-30.0 to 49.3]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Sleep efficiency, %	1 (35)	86	87	NS, MD = -1.6 [-7.7 to 4.5]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (39)	15 (3/20)	5 (1/19)	NS, RR = 2.85 [0.32 to 25.07]	Insufficient (moderate study limitations, very imprecise, and unknown consistency)
		Withdrawals due to adverse events	1 (39)	15 (3/20)	0 (0/19)	NS, RR = 6.67 [0.37 to 121.07]	Insufficient (moderate study limitations, very imprecise, and unknown consistency)
		Participants with ≥1 adverse event	NR				Insufficient

Table 28. Comparative effectiveness of drug versus CBT or combined drug/CBT: overview and strength of evidence (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Control % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Older adults Temazepam 7.5-30 mg as needed vs. CBT-I (1 RCTs; N=38)	Global Outcomes	Not reported					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	0				Insufficient
		Total sleep time, self-report, minutes	1 (35)	384	352	NS, MD = 31.9 [-4.4 to 68.2]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Wake time after sleep onset, self-report, minutes	1 (35)	29	22	NS, MD = 7.2 [-5.0 to 19.3]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Sleep efficiency, %	1 (35)	83	85	NS, MD = -2.1 [-6.6 to 2.4]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (38)	15 (3/20)	0 (0/18)	NS, RR = 6.33 [0.35 to 114.81]	Insufficient (moderate study limitations, very imprecise, and unknown consistency)
		Withdrawals due to adverse events	1 (38)	15 (3/20)	0 (0/18)	NS, RR = 6.33 [0.35 to 114.81]	Insufficient (moderate study limitations, very imprecise, and unknown consistency))
		Participants with ≥1 adverse event	NR				Insufficient

Table 28. Comparative effectiveness of drug versus CBT or combined drug/CBT: overview and strength of evidence (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Treatment % (n/N)	Control % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Older adults Temazepam 7.5-30 mg as needed vs. Temazepam /CBT-I (1 RCTs; N=40)	Global Outcomes	Not reported					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	0				Insufficient
		Total sleep time, self-report, minutes	1 (36)	384	332	Favors temazepam MD = 52.0 [12.1 to 91.9]	Insufficient (moderate study limitations and unknown consistency)
		Wake time after sleep onset, self-report, minutes	1 (36)	29	21	NS, MD = 8.7 [-4.3 to 21.7]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Sleep efficiency, %	1 (36)	83	85	NS, MD = -2.2 [-8.2 to 3.9]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (38)	15 (3/20)	5 (1/20)	NS, RR = 3.00 [0.34 to 26.45]	Insufficient (moderate study limitations, very imprecise, and unknown consistency)
		Withdrawals due to adverse events	1 (38)	15 (3/20)	0 (0/20)	NS, RR = 7.00 [0.38 to 127.32]	Insufficient (moderate study limitations, very imprecise, and unknown consistency)
		Participants with ≥1 adverse event	NR				Insufficient

AR = absolute risk reduction; CI = confidence intervals; ER = extended release; MD = mean difference; ND = No statistically significant difference; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; RR = risk ratio; SL = sublingual; WMD = weighted mean difference

Zolpidem Versus CBT-I or Combined Zolpidem/CBT-I Therapy

One RCT compared nonbenzodiazepine zolpidem with CBT-I and combined zolpidem and CBT-I therapy.[60] A total of 63 participants were randomized, 15 each in the zolpidem, CBT-I, and placebo arms, and 18 in the combined therapy arm. Among the 48 participants randomized to zolpidem, CBT-I, and the combined therapy arms, mean age was 47 years, and 69 percent were female. Mean duration of insomnia was 10 years. Zolpidem 10 mg was administered nightly for 28 days, then 5 mg nightly for 7 days, and then 5 mg was taken every other night for the next 7 days. The trial was conducted in the United States and received support from industry. Jacobs et al. had moderate risk of bias.

Jacobs et al. did not report global outcomes. Post-treatment following 8 weeks of therapy, there were no differences in sleep onset latency and TST between the zolpidem, CBT-I, or combined therapy groups. Evidence was insufficient for both outcomes. There were significantly more participants in the CBT-I group who met the considered normal sleep criterion of a sleep latency of 30 minutes or less compared with the zolpidem group, 57 percent (8/14) versus 15 percent (2/13), respectively. The proportions of participants who met the considered normal sleep criterion of a sleep efficiency of 85 percent or more were not significantly different among the three treatment groups. There were eight withdrawals among the three arms of interest, two in the zolpidem group (13%), five in the combined therapy group (28%), and one CBT-I participant (7%). None of the withdrawals were attributed to adverse effects. Specific adverse effects were not reported. Strength of evidence was insufficient for withdrawals and adverse effects. At the 12-month followup assessment, improvements in sleep outcomes were maintained in the CBT group. Outcomes in the temazepam group were not reported.

Temazepam Versus CBT-I or Combined Temazepam/CBT-I Therapy

Two RCTs compared benzodiazepine temazepam with CBT-I and combined temazepam and CBT-I therapy.[72,74]

Wu et al. randomized 77 participants, 20 in the temazepam and 19 each in the CBT-I, combined therapy, and placebo arms. Demographic information was not reported for the temazepam, CBT-I, or combined therapy arms separately, but among the four treatment arms, the mean age was 38 years, and 53 percent were female. Temazepam recipients initially received 7.5 mg nightly with gradual increases up to 30 mg and then a decrease to 15 mg in the last treatment week for a total of 8 weeks. The trial was conducted in China and had government funding. Wu et al. had moderate risk of bias. Global outcomes were not reported. Post-treatment, temazepam was better than CBT-I in reducing sleep onset latency and increasing TST. There was no difference in sleep efficiency between the two groups. Evidence was insufficient for all outcomes. Insufficient evidence found no differences in sleep outcomes between the temazepam and combined therapy groups. Post-treatment, the proportions of participants who met normal sleep criteria, based on a sleep-onset latency $\leq$30 minutes and sleep efficiency $\geq$85 percent, were not significantly different among the three treatment groups. There were no differences among the three groups in the daytime dysfunction component of the PSQI. There were no significant differences in overall withdrawals or withdrawals due to adverse effects among the three groups. Three participants in the temzepam group withdrew due to adverse effects (15%). Specific adverse effects were not reported. Strength of evidence was insufficient for withdrawals and adverse effects. At the 8-month followup assessment, improvements in sleep outcomes were maintained in the CBT group while outcomes in the temazepam and combined therapy groups regressed to pretreatment conditions.

Morin et al. randomized 78 participants, 20 each in the temazepam, combined therapy, and placebo arms and 18 in the CBT-I arm.[74] Compared with Wu et al., the participants were older; the mean age was 65 years. Most participants were female (64%) and white (90%). The mean duration of insomnia was 17 years. Temazepam recipients initially received 7.5 mg nightly with gradual increases up to 30 mg as needed (participants were to use sleep medication at least 2 to 3 nights per week, but medication was made available all 7 nights) for a total of 8 weeks. The trial was conducted in the United States and had government sponsorship. Morin et al. had moderate risk of bias. Self-rated global improvements were greater in the combined therapy and CBT-I groups compared with the temzepam group at post-treatment. There were no differences in sleep outcomes assessed between the temazepam and CBT-I groups. TST was greater in the temazepam group compared with the combined therapy group. However, there was an imbalance in baseline TSTs, 340 minutes for the temazpam group versus 290 minutes in the combined therapy group and the mean changes from baseline to post-treatment were comparable between groups, approximately 40 minutes. Strength of evidence was insufficient for all outcomes. Four participants in the three active treatment arms withdrew from the trial, three in the temazepam group (due to adverse effects), one in the combined therapy group, and none in the CBT-I group. Specific adverse effects were not reported within this publication. Strength of evidence was insufficient for withdrawals and adverse effects. Long-term (24-month followup), improvements in sleep out outcomes were maintained in the CBT group but not in the temazepam group.

Comparative Effectiveness of Combined Pharmacologic and Psychological Interventions Versus Psychological Interventions

Key Points

- Evidence was mostly insufficient to draw conclusions regarding the comparative effectiveness of combined hypnotic medication and CBT-I versus CBT-I alone.

Overview of Included Studies

We identified four trials with moderate risk of bias that compared combined drug and CBT-I therapy to CBT-I alone (Table 29).[60,72,74,163]

Table 29. Comparative effectiveness of combined drug and CBT-I versus CBT-I: overview and strength of evidence

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Combined % (n/N)	CBT % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Combined Zolpidem/CBT-I therapy vs. CBT-I (2 RCTs; N=193)	Global Outcomes	Remitters to therapy based on ISI (score <8 points)	1 (149)	45 (33/74)	39 (29/75)	NS, RR = 1.15 [0.79 to 1.69]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Response to therapy based on ISI (≥8 points improvement from baseline)	1 (149)	61 (45/74)	60 (45/75)	NS, RR = 1.01 [0.78 to 1.31]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		ISI, mean change in scores	1 (160)	-8.8	-8.3	NS, MD = -0.5 [-1.6 to 0.6]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
	Sleep Outcomes	Sleep onset latency, self-report, minutes. *Mean change from baseline*	2 (187)	-15	-22	NS, WMD = 7.1 [-1.4 to 15.6]	Low (moderate study limitations, imprecise)
		Total sleep time, self-report, minutes. *Mean change from baseline*	2 (187)	12	7.5	NS, WMD = 4.5 [-30.5 to 39.4]	Insufficient (moderate study limitations, imprecise, inconsistent)
		Wake time after sleep onset, self-report, minutes. *Mean change from baseline*	1 (160)	-83	-69	Favors combined therapy MD = -14.2 [-25.1 to -3.4]	Low (moderate study limitations and unknown consistency)
		Sleep efficiency, %. *Mean change from baseline*	2 (187)	15	15	NS, WMD = -1.2 [-8.5 to 6.2]	Insufficient (moderate study limitations, imprecise, inconsistent)
	Adverse Effects	Overall withdrawals	2 (193)	11 (11/98)	6 (6/95)	NS, RR = 1.73 [0.66 to 4.55]	Insufficient (moderate study limitations, imprecise)
		Withdrawals due to adverse events	2 (193)	0 (0/98)	0 (0/95)	NS	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Participants with ≥1 adverse event	NR				Insufficient

Table 29. Comparative effectiveness of combined drug and CBT-I versus CBT-I: overview and strength of evidence (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Combined % (n/N)	CBT % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Combined Temazepam/CBT-I therapy vs. CBT-I (1 RCT; N=38)	Global Outcomes	Not reported					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	1 (37)	17	32	Favors combined, MD = -14.3 [-23.5 to -5.1]	Insufficient (moderate study limitations and unknown consistency)
		Total sleep time, self-report, minutes	1 (37)	397	364	NS, MD = 33.2 [-3.1 to 69.5]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Sleep efficiency, %	1 (37)	87	81	NS, MD = 6.7 [-1.1 to 14.5]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (38)	5 (1/19)	0 (0/19)	NS, RR = 3.00 [0.13, 69.31]	Insufficient (moderate study limitations, very imprecise, and unknown consistency)
		Withdrawals due to adverse events	1 (38)	0 (0/19)	0 (0/19)	NA	Insufficient (moderate study limitations, very imprecise, and unknown consistency)
		Participants with ≥1 adverse event	NR				Insufficient

Table 29. Comparative effectiveness of combined drug and CBT-I versus CBT-I: overview and strength of evidence (continued)

Study Type	Outcome Type	Comparison Outcome Measure	# Trials (n)	Combined % (n/N)	CBT % (n/N)	Results and Magnitude of Effect [95% CI]	Strength of Evidence (Rationale)
Older adults Combined Temazepam/CBT-I therapy vs. CBT-I (1 RCTs; N=38)	Global Outcomes	Not reported					Insufficient
	Sleep Outcomes	Sleep onset latency, self-report, minutes	0				Insufficient
		Total sleep time, self-report, minutes	1 (37)	332	352	NS, MD = -20.1 [-58.2 to 18.0]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Wake time after sleep onset, self-report, minutes	1 (37)	21	22	NS, MD = -1.5 [-24.6 to 21.6]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Sleep efficiency, %	1 (37)	85	85	NS, MD = 0.06 [-6.1 to 6.3]	Insufficient (moderate study limitations, imprecise, and unknown consistency)
	Adverse Effects	Overall withdrawals	1 (38)	5 (1/20)	0 (0/18)	NS, RR 2.71 [0.12 to 62.70]	Insufficient (moderate study limitations, very imprecise, and unknown consistency)
		Withdrawals due to adverse events	1 (38)	0 (0/20)	0 (0/18)	NA	Insufficient (moderate study limitations, imprecise, and unknown consistency)
		Participants with ≥1 adverse event	NR				Insufficient

AR = absolute risk reduction; CI = confidence intervals; ER = extended release; MD = mean difference; ND = No statistically significant difference; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; RR = risk ratio;
SL = sublingual; WMD = weighted mean difference

Combined Zolpidem/CBT-I Therapy Versus CBT-I

Two RCTs compared combined zolpidem and CBT-I therapy to CBT-I therapy alone [60,163] Morin et al. randomized 160 adults, 80 to combined CBT-I with 10 mg of zolpidem taken daily at bedtime and 80 to CBT-I alone.[163] Zolpidem was taken during the initial 6 weeks of therapy. Mean age was 50 years and 61 percent were female. The mean duration of insomnia was 16 years. The baseline ISI score was 17, indicating moderate severity. The trial was conducted in Canada. Morin et al. had moderate risk of bias. The 8-week trial by Jacobs et al. randomized 18 adults to combined CBT-I with 10 mg of zolpidem taken daily and 15 adults CBT-I alone.[60] Mean age was 48 years, and 69 percent were female. Mean duration of insomnia was 10 years. The trial was conducted in the United States and received support from industry. Jacobs et al. had moderate risk of bias.

At week 6, the proportions of participants who responded to treatment, defined as an ≥8 point reduction in ISI scores, did not differ between groups (61% for combined vs. 60% for CBT-I alone. Proportions of participants who remitted to treatment, defined as an ISI score <8 points, did not differ between the combined and CBT-I alone groups (44% vs. 39%).

The mean difference in ISI scores at 6 weeks of was -0.50 points (95% CI, -1.58 to 0.58) between groups. Mean reductions in ISI scores were 8.8 and 8.3 points for the combined and CBT-I alone groups, respectively. Strength of evidence for global outcomes was insufficient. Patients rated moderately or markedly improved by an independent assessor also did not differ between groups, 83 percent (60/72) versus 89 percent (66/74) in the combined and CBT alone groups, respectively. Jacobs et al. did not report global outcomes.

Overall, combined therapy was not better than CBT-I alone in improving sleep onset latency, TST, or sleep efficiency. Strength of evidence was low to insufficient. Morin et al. reported combined therapy significantly improved WASO by 14 minutes compared with CBT-I alone. Morin et al reported 11 withdrawals during the initial 6 weeks of therapy, six in the combined arm and five in the CBT-I alone arm. No adverse effects were reported. Jacobs et al. reported five withdrawals in the combined therapy group (28%) and one CBT-I participant (7%). None of the withdrawals were attributed to adverse effects. Specific adverse effects were not reported.

Combined Temazepam/CBT-I Therapy Versus CBT-I

Two RCTs compared combined temazepam and CBT-I therapy with CBT-I alone.[72,74]

Wu et al. randomized 38 participants, 19 each in the combined therapy and CBT-I arms. Demographic information was not reported for the temazepam, CBT-I, or combined therapy arms separately, but among the four treatment arms, the mean age was 38 years, and 53 percent were female. Temazepam 7.5 mg nightly was initially administered with gradual increases up to 30 mg and then a decrease to 15 mg in the last treatment week for a total of 8 weeks. The trial was conducted in China and had government funding. Wu et al. had moderate risk of bias. Global outcomes were not reported. Post-treatment, combined therapy was better than CBT-I in reducing sleep onset latency. There was no difference in TST and sleep efficiency between the two groups. Evidence was insufficient for all outcomes. Post-treatment, the proportions of participants who met normal sleep criteria, based on a sleep-onset latency ≤30 minutes and sleep efficiency ≥85 percent, were not significantly different between the combined and CBT-I groups (50% vs. 36%). There were no differences among the groups in the daytime dysfunction component of the PSQI. Only one withdrawal was reported in the combined group, none in the CBT-I arm. There were no withdrawals due to adverse effects. Specific adverse effects were not reported. Strength of evidence was insufficient for withdrawals and adverse effects.

Morin et al. randomized 38 older adults, 20 in the combined temazepam and CBT-I arm and 18 in the CBT-I arm.[74] The mean age was 65 years and most participants were female (68%) and white. The mean duration of insomnia was 18 years. Temazepam was initially administered at 7.5 mg nightly with gradual increases up to 30 mg as needed (participants were to use sleep medication at least 2 to 3 nights per week, but medication was made available all 7 nights) for a total of 8 weeks. The trial was conducted in the United States and had government sponsorship. Morin et al. had moderate risk of bias. There were no differences in sleep outcomes between the combined and CBT-I groups. Strength of evidence was insufficient for all outcomes. One withdrawal was reported in the combined therapy group, none in the CBT-I group. Specific adverse effects were not reported within this publication. Strength of evidence was insufficient for withdrawals and adverse effects.

Comparative Effectiveness and Combination Treatments: Unique Comparisons

Key Points

- Evidence was insufficient to draw conclusions regarding the efficacy or comparative effectiveness of CBT-I versus Tai Chi, acupuncture versus estazolam, or the adjunctive efficacy of a traditional Chinese medicine approach combined with sleep medication.

Overview of Included Studies

Wang et al. randomized 90 insomnia disorder patients to an intervention based upon traditional Chinese medicine called Low Resistance Thought Induction Sleep-regulating Technique combined with 1-2 mg estazolam nightly or estazolam alone.[164]

Guo et al. randomized 180 patients with insomnia disorder to three arms, verum acupuncture plus placebo, estazolam plus sham acupuncture, or sham acupuncture plus placebo.[165]

Irwin et al randomized 123 older adults to CBT-I, Tai Chi Chih, or a sleep seminar education control.[76]

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, ezopiclone 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, pharmacologic, and all CAM interventions was limited. Evidence was insufficient to draw conclusions about the 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 across a variety of delivery modes delivered to the general adult population, older adults, and adults with pain. 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), waitlist control, and placebo (sham treatments or pills). Relative risk ranged from 2.95 to 8.95 across measures of remission and response. The rate of remission or response ranged from between 50 and 80 percent in CBT-I groups and between 0 and 50 percent in passive control groups. Some trials showed a large placebo effect; sham treatment controls did not have the largest placebo effect. The largest placebo effects were reported in trials with waitlist controls. Trials for which we were unable to conduct remitter or responder analysis show 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 was clear that these populations also gain important benefits from CBT-I. Low strength evidence shows that CBT-I improves global and several sleep outcomes in older adults. Moderate strength evidence shows 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 shows that CBT-I improves global and most sleep outcome 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 with 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 be low-physical harm to individuals, but few trials reported withdrawals and often reported withdrawals in the overall population as opposed to withdrawals by group. Withdrawals in psychological intervention trials may reflect intervention feasibility (i.e., requires too much time or the inconvenience of

attending weekly sessions) than to physical or psychological harms, but reporting this information would improve understanding of these interventions in practice.

Nonbenzodiazepine hypnotics, eszopiclone and zolpidem and the orexin receptor antagonist, suvorexant, improved short-term global and sleep outcomes in general adult populations. The relative risk of remission or response with these drugs ranged from 1.3 for suvorexant to 2.7 for eszopiclone. Remitter or response rate ranged between 50 and 85 percent in the treatment groups and between 19 and 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 general populations and for most pharmacologic interventions in older adults was generally insufficient. Comparative effectiveness evidence was limited to a few small, short-term studies. This precluded meaningful comparisons between and across categories of pharmacologic agents as well as comparisons versus cognitive behavioral therapy. 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). 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 is similar to placebo when compared to 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). 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 and short duration of the trials included in our review are not sufficient to capture them. Eligible observational studies suggest 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. Dose reduction is 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.

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 et al. found increased incidence of depression[166] and skin cancer[167] with nonbenzodiazepine hypnotics and ramelteon compared with placebo. Using pooled analyses of RCT data submitted to the FDA and published RCT data, Carson et al.[34] 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 five-fold increase in memory loss, confusion, and disorientation; a three-fold increase in dizziness, loss of balance, or falls; and a four-fold increase in residual morning sedation, though absolute rates were low.[168] Weich et al 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.[169]

Applicability

The applicability of the conclusions of this review to practice deserves discussion. Participants in general adult population trials were middle-aged, primarily free of comorbid conditions, predominantly 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 individual has insomnia disorder according to authoritative diagnostic criteria. This review does not address episodic insomnia or insomnia symptoms, but insomnia disorder.

However, 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 are 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 having a 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 was more common in trials of psychological interventions than in drug trials. Insomnia disorder requires select 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 have been used (i.e., 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 more recently FDA approved drugs. 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. Other systematic reviews aiming to assess the efficacy of very short duration of these medications are available.

Eligible drug trials rarely lasted longer than 6 weeks. We believe that excluding studies of very short duration is 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 (Table 30):

- Conceptual research to establish MIDs for instruments measuring global outcomes; 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 (versus 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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Table 30. Future research needs

Key Question	Results of Literature Review	Types of Studies; Needed to Answer Question	Future Research Recommendations
KQ1. What are the efficacy and comparative effectiveness of treatments for insomnia disorder in adults?	Moderate strength evidence shows that global outcomes improve with CBT-I and certain medications. Little information was available to assess combination treatments and head to head comparisons.	RCTs	RCTs should be conducted that capture global outcomes and compare combination treatments and head to head comparisons.
a. What are the long-term efficacy and comparative effectiveness of treatments for insomnia disorder in older adults?	A very limited number of trials had long term outcomes; more research is needed.	RCTs	Additional long-term trials on the efficacy of evidence-based treatments to investigate factors associated with sustained improvements from psychological interventions.
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?	Few trials were identified to analyze combination treatments (across intervention classes).	RCTs	RCTs that assess the efficacy and comparative effectiveness of short-term drug therapy combined with long-term CBT-I.
c. What are the long-term efficacy and comparative effectiveness of treatments for insomnia disorder in adults?	Few trials were identified. One systematic review concluded that CBT-I was superior to drug treatment for insomnia disorder.	RCTs	RCTs that compare various delivery modes of CBT-I to drug treatments.
KQ2. What are the harms of treatments for insomnia disorder in adults?	Harms were not always reported, especially in psychological and CAM trials.	Cohort studies	Cohort studies that reflect actual drug usage and systematically collect data on all harms.
a. What are the harms of treatments for insomnia disorder in older adults?	Evidence on long term harms was limited.	Systematic review of observational studies and open label RCTs.	A comprehensive assessment of medication harms that reflects actual use.
b. What are the harms of combined treatments (e.g., cognitive behavioral therapy and drug therapy) for insomnia disorder in adults?	Limited data.	RCTs	RCTs that systematically collect harms data.
c. What are the long-term harms of treatments for insomnia disorder in adults?	Very limited data.	Systematic review of observational studies and open label RCTs.	A comprehensive assessment of medication harms that reflects actual use.

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Abbreviations

AASM	American Academy of Sleep Medicine
AHRQ	Agency for Healthcare Research and Quality
ARR	Absolute risk reduction
BBT	Brief behavioral therapy
BDI	Beck Depression Inventory
CAM	Complementary and alternative medicine
CBT	Cognitive behavioral therapy
CBT-I	Cognitive behavioral therapy for insomnia
CGI	Clinical Global Impression
CI	Confidence interval
DSM	Diagnostic and Statistical Manual
ESS	Epworth sleepiness scale
FSS	Fatigue Severity Scale
HR	Hazard ratio
ICSD	International Classification of Sleep Disorders
ISI	Insomnia Severity Index
MBT	Multicomponent behavioral therapies
MD	Mean difference
MID	Minimum important difference
MOS	Medical Outcomes Sleep questionnaire
OR	Odds ratio
PGI	Patient Global Impression
PICOTS	Population, intervention, comparators, outcomes, timing, settings
PR	Prolonged release
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomized controlled trial
RD	Risk difference
RR	Risk ratio
SF-36	Short-form Health Survey
SIP	Scientific Information Packet
SMD	Standardized mean difference
SOL	Sleep onset latency
SR	Sleep restriction
STAI	State-Trait Anxiety Inventory
TST	Total sleep time
WHOQOL	World Health Organization Quality of Life
WASO	Wake after sleep onset
WMD	Weighted mean difference

Appendix A. Search Strategies

Key Question Trials Searches

1	exp *"Sleep Initiation and Maintenance Disorders"/ 2	insomnia.ti.
3	1 or 2	
4	exp Review Literature as Topic/	
5	Meta-Analysis/	
6	Meta-Analysis as Topic/	
7	Randomized Controlled Trials as Topic/	
8	randomized controlled trial/	
9	Random Allocation/	
10	clinical trial/	
11	clinical trial, phase i.pt.	
12	clinical trial, phase ii.pt.	
13	clinical trial, phase iii.pt.	
14	clinical trial, phase iv.pt.	
15	controlled clinical trial.pt.	
16	randomized controlled trial.pt.	
17	multicenter study.pt.	
18	clinical trial.pt.	
19	exp Clinical Trials as topic/	
20	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	
21	3 and 20	

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1 retracted article/ (6992)
2 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
3 (animal$ not human$).sh,hw.
4 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
5 1 or 2
6 5 not (3 or 4)
7 exp cohort analysis/
8 exp longitudinal study/
9 exp prospective study/
10 exp follow up/
11 cohort$.tw.
12 7 or 8 or 9 or 10 or 11
13 exp case-control study/
14 (case$ and control$).tw.
15 13 or 14 (455401)
16 (case$ and series).tw.
17 exp review/
18 (literature adj3 review$).ti,ab.
19 exp meta analysis/
20 exp "Systematic Review"/
21 17 or 18 or 19 or 20
22 (medline or embase or pubmed or cinahl or amed or psychlit or psychinfo or scisearch or cochrane).ti,ab.
23 retracted article/
24 22 or 23
25 21 and 24
26 (systematic$ adj2 (review$ or overview)).ti,ab.
27 (meta?anal$ or meta anal$ or metaanal$ or metanal$).ti,ab.
28 25 or 26 or 27
29 (ae or si or to or co).fs.
30 (safe or safety).ti,ab.
31 side effect$.ti,ab.
32 ((adverse or undesireable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
33 exp adverse drug reaction/
34 exp drug toxicity/
35 exp intoxication/
36 exp drug safety/
37 exp drug monitoring/
38 exp drug hypersensitivity/
39 exp postmarketing surveillance/
40 exp phase iv clinical trial/
41 (toxicity or complication$ or noxious or tolerability).ti,ab.
42 exp postoperative complication/
43 exp peroperative complication/
44 or/29-43
45 6 or 12 or 28 or 44
46 insomnia.ti.
47 exp *insomnia/
48 46 or 47
49 45 and 48
50 limit 49 to (book or book series or conference abstract or conference proceeding or "conference review" or editorial or erratum or letter or note or short survey or trade journal)
51 49 not 50

52 limit 51 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
53 limit 52 to (adult <18 to 64 years> or aged <65+ years>)
54 51 not 52
55 54 or 53
56 55 and 28
57 55 and 6

Long-Term Medication Harms Searches

Database: Ovid MEDLINE(R) <1946 to March Week 2 2015>

Search Strategy:

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1 exp Clinical Trials as Topic/
2 (clinical adj trial$).tw.
3 1 not 2
4 meta analysis as topic/
5 meta-analy$.tw.
6 metaanaly$.tw.
7 meta-analysis/
8 (systematic adj (review$1 or overview$1)).tw.
9 exp Review Literature as Topic/
10 or/4-9
11 cochrane.ab.
12 embase.ab.
13 (psychlit or psyclit).ab.
14 (psychinfor or psycinfo).ab. (5040)
15 or/11-14 (42476)
16 reference list$.ab. (9440)
17 bibliograph$.ab. (11111)
18 hand search.ab. (887)
19 relevant journals.ab. (691)
20 manual search$.ab. (2245)
21 or/16-20 (22763)
22 selection criteria.ab. (19411)
23 data extraction.ab. (9426)
24 22 or 23 (27261)
25 review/ (1926349)
26 24 and 25 (19412)
27 comment/ (565762)
28 letter/ (835600)
29 editorial/ (350592)
30 animal/ (5406976)
31 human/ (13760465)
32 30 not (31 and 30) (3907576)
33 or/27-29,32 (5153078)
34 10 or 15 or 21 or 26 (143690)
35 34 not 33 (134448)
36 randomized controlled trials as topic/ (96124)
37 randomized controlled trial/ (386752)
38 random allocation/ (82288)
39 double blind method/ (128148)
40 single blind method/ (19993)
41 clinical trial/ (490498)
42 clinical trial, phase i.pt. (14748)
43 clinical trial, phase ii.pt. (23750)
44 clinical trial, phase iii.pt. (9599)
45 clinical trial, phase iv.pt. (992)
46 controlled clinical trial.pt. (88805)
47 randomized controlled trial.pt. (386752)
48 multicenter study.pt. (180963)
49 clinical trial.pt. (490498)
50 exp Clinical trials as topic/ (285725)

51 or/36-50 (1058015)
52 (clinical adj trial$).tw. (207442)
53 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (125720)
54 placebos/ (32653)
55 placebo$.tw. (154289)
56 randomly allocated.tw. (16322)
57 (allocated adj2 random$).tw. (18819)
58 52 or 53 or 54 or 55 or 56 or 57 (406887)
59 51 or 58 (1183418)
60 case report.tw. (187940)
61 case report.tw. (187940)
62 letter/ (835600)
63 historical article/ (311107)
64 60 or 61 or 62 or 63 (1322985)
65 59 not 64 (1153190)
66 exp cohort studies/ (1406571)
67 cohort$.tw. (272112)
68 controlled clinical trial.pt. (88805)
69 epidemiologic methods/ (29742)
70 limit 69 to yr=1971-1983 (5327)
71 66 or 67 or 68 or 70 (1582264)
72 exp case-control study/ (699307)
73 (case$ and control$).tw. (316249)
74 72 or 73 (924604)
75 epidemiologic studies/ (6119)
76 (follow up adj stud$).tw. (36662)
77 longitudinal.tw. (134534)
78 (observational adj stud$).tw. (43357)
79 retrospective.tw. (268500)
80 cross sectional.tw. (161660)
81 cross-sectional studies/ (187634)
82 or/75-81 (691126)
83 (ae or to or po or co).fs. (3197420)
84 side effect$.ti,ab. (168868)
85 side effect$.ti,ab. (168868)
86 ((adverse or undesireable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab. (297311)
87 exp product surveillance, postmarketing/ (11496)
88 exp adverse drug reaction reporting systems/ (5749)
89 exp clinical trials, phase iv/ (228)
90 exp poisoning/ (132641)
91 exp substance-related disorders/ (228432)
92 exp drug toxicity/ (89990)
93 exp abnormalities, drug induced/ (13846)
94 exp drug monitoring/ (14781)
95 exp drug hypersensitivity/ (38543)
96 (toxicity or complication$ or noxious or tolerability).ti,ab. (851249)
97 exp postoperative complications/ (427475)
98 exp intraoperative complications/ (41135)
99 or/83-98 (4237092)
100 *"Sleep Initiation and Maintenance Disorders"/ (6315)
101 insomnia.ti. (4019)
102 100 or 101 (6593)
103 71 or 74 or 82 or 59 (3009212)
104 99 and 102 and 103 (1277)
105 104 not 64 (1266)

Ovid Technologies, Inc. Email Service

Search for: limit 59 to "therapy (best balance of sensitivity and specificity)"
Results: 1

Database: Embase <1996 to 2015 Week 10>
Search Strategy:

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1 retracted article/ (6901)
2 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. (877999)
3 (animal$ not human$).sh,hw. (1904432)
4 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/ (2984829)
5 1 or 2 (884739)
6 5 not (3 or 4) (718148)
7 exp cohort analysis/ (186637)
8 exp longitudinal study/ (66854)
9 exp prospective study/ (256709)
10 exp follow up/ (800168)
11 cohort$.tw. (432168)
12 7 or 8 or 9 or 10 or 11 (1370176)
13 exp case-control study/ (90471)
14 (case$ and control$).tw. (376130)
15 13 or 14 (406263)
16 (case$ and series).tw. (132675)
17 exp review/ (1547793)
18 (literature adj3 review$).ti,ab. (171736)
19 exp meta analysis/ (84624)
20 exp "Systematic Review"/ (85413)
21 17 or 18 or 19 or 20 (1719840)
22 (medline or embase or pubmed or cinahl or amed or psychlit or psychinfo or scisearch or cochrane).ti,ab. (117574)
23 retracted article/ (6901)
24 22 or 23 (124427)
25 21 and 24 (93190)
26 (systematic$ adj2 (review$ or overview)).ti,ab. (83997)
27 (meta?anal$ or meta anal$ or metaanal$ or metanal$).ti,ab. (90946)
28 25 or 26 or 27 (187187)
29 (ae or si or to or co).fs. (2034152)
30 (safe or safety).ti,ab. (590943)
31 side effect$.ti,ab. (183018)
32 ((adverse or undesireable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab. (390625)
33 exp adverse drug reaction/ (233079)
34 exp drug toxicity/ (32803)
35 exp intoxication/ (129263)
36 exp drug safety/ (227450)
37 exp drug monitoring/ (25776)
38 exp drug hypersensitivity/ (33281)
39 exp postmarketing surveillance/ (23924)
40 exp phase iv clinical trial/ (1503)
41 (toxicity or complication$ or noxious or tolerability).ti,ab. (963851)

42 exp postoperative complication/ (375284)
43 exp peroperative complication/ (18843)
44 or/29-43 (3299871)
45 6 or 12 or 28 or 44 (4626578)
46 insomnia.ti. (5521)
47 exp *insomnia/ (7012)
48 46 or 47 (7156)
49 limit 48 to child <unspecified age> (201)
50 limit 49 to (adult <18 to 64 years> or aged <65+ years>) (64)
51 48 not 49 (6955)
52 48 or 50 (7156)
53 52 and 28 (231)
54 limit 53 to yr="2013 -Current" (48)
55 52 and 6 (1243)
56 limit 55 to yr="2013 -Current" (279)
57 52 and 44 (2095)
58 limit 57 to conference abstract (189)
59 57 not 58 (1906)
60 limit 59 to "therapy (best balance of sensitivity and specificity)" (631)

Appendix B. Risk of Bias Assessment Instrument and Instructions

Selection Bias	
Did method of randomization create biased allocation to interventions (inadequate randomization)?	
Were all randomized participants analyzed in the group to which they were allocated?	
Were the groups similar at baseline regarding the most important prognostic indicators?	
Did method of allocation create a biased allocation to interventions (inadequate allocation concealment)?	
Risk of selection bias (inadequate randomization or allocation concealment):	**[Low, Unclear, High]**
Performance Bias	
Was the care provider blinded to the intervention?	
Were the participants blinded to the intervention?	
Psych/Behavioral Interventions: Were interventions adequately defined (i.e., theory-based, manualized)?	
Psych/Behavioral Interventions: Were fidelity checks conducted to ensure proper implementation?	
Risk of performance bias due to lack of participant and personnel blinding, intervention definition & fidelity?	**[Low, Unclear, High]**
Detection Bias	
Were the outcome assessors blinded to the intervention?	
Questionnaire Derived Outcomes: Was the scale used to measure outcomes validated, reliable?	
Were outcomes measured in clinically meaningful ways?	
Were co-interventions avoided or similar?	
Was the timing of the outcome assessment similar in all groups?	
Were estimates appropriately corrected for multiple comparisons?	
If *NOT* pooling with other studies: Was study adequately powered to detect differences?	
Risk of detection bias due to lack of outcome assessor blinding, outcomes measurement, statistical analysis, power?	**[Low, Unclear, High]**

Attrition Bias	
Was attrition lower than 20%?	
Reasons for incomplete/missing data adequately explained?	
Incomplete data handled appropriately?	
Risk of attrition bias due to amount, nature, or handling of incomplete outcome data?	**[Low, Unclear, High]**
Reporting Bias	
Was a select group of outcomes reported (compared to methods section, protocol)?	
What is the risk of reporting bias due to selective outcome reporting? [Low, Unclear, High]	
Other Sources of Bias	
Are there other risks of bias? If yes, describe them in the Notes.	
Overall Risk of Bias Assessment by outcome(s)	**[Low, Moderate, High] and explanation (1-2 sentences)**

Appendix C. Excluded Studies

Excluded References[1--439]

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Appendix D. Supporting Tables: Efficacy of Psychological Interventions for Insomnia Disorder

Table D1. Psychological studies for insomnia disorder: risk of bias assessments

Study	Overall Risk of Bias Assessment
Smith 2015[1]	Moderate - Double blind study; Not ITT analysis; no blinding; no multiple comparisons correction; small sample size but did power analyses, found significant results.
Harvey 2014[2]	Moderate – Unblinded; low attrition; ITT analysis.
Ho 2014[3]	High - Investigaters not blinded and high attrition rate over 30% in all categories; ITT analysis.
Holmqvist, 2014[4]	Moderate - did state that no blinding but this most likely due to nature of treatment, attrition was 33% in one treatment group but this is the one major weakness.
Irwin 2014[5]	Moderate - Assessors unaware of patient treatment assignment Unclear participant blinding. Outcome assessors blinded. Low attrition. ITT analysis.
Ong 2014[6]	High - unblinded; non-standard randomization procedure; small sample size; unclear how missing data were handled.
Taylor, 2014[7]	Moderate - Not ITT analysis; no blinding; no multiple comparisons correction; small sample size but did power analyses, found significant results.
Van Straten 2014[8]	Moderate-High - Patients informed of allocation to group (unblinded). High attrition. ITT analysis with multiple imputation, but this is a very small sample so should be cautious with this.
Arnedt, 2013[9]	Low-moderate: no ITT analysis; low attrition; multiple comparisons correction unclear; blinding, randomization method NR
Bothelius 2013[10]	Moderate - Block randomization. Unblinded. Did not include several in final analyses who didn't complete baseline assessment.
Fernando 2013[11]	Low - Double blind study ITT analysis; Low attrition; Multiple comparison correction unnecessary.
Lancee 2013;[12] Lancee 2014[13]	Moderate/High - No blinding; High attrition for some groups/time points. ITT analysis.
Pech, 2013[14]	Moderate: ITT analysis; multiple comparisons correction unclear.
Vitiello, 2013;[15] McCurry, 2014[16]	Low-moderate: Participants and assessors blinded; modified ITT analysis; low attrition; no adjustment for multiple comparisons; did not discuss treatment fidelity.
Epstein, 2012[17]	Low-moderate: no blinding; high attrition for 3-month and 1-year F/U.

Study	Overall Risk of Bias Assessment
Espie, 2012;[18] Espie 2014[19]	Low: controlled for unequal baseline values in analyses; ITT analysis
Harris 2012[20]	Low - Participant and personnel blinding unclear; Raters blinded; ITT analysis for main outcomes; Low attrition.
Jansson-Frojmark, 2012a[21]	Low-moderate: ITT analysis; multiple comparisons correction unclear; randomization method unclear; analysis blinded.
Jansson-Frojmark, 2012b[22]	Low-Moderate: ITT analysis (one exception, a randomized participant who was excluded due to unstable medication use); Multiple comparisons correction unclear; randomization method unclear; analysis blinded.
Jernelov 2012[23]	Moderate - Double blind placebo controlled study; High attrition rate; Randomization process not well described.
Lancee 2012[24]	High - Not blinded, very high attrition (>30 % at 4 weeks). Large sample (n=623)
Morgan, 2012[25]	Moderate: Very high attrition; No mention of correcting for multiple comparisons for reported outcomes (only for exploratory analyses).
Pigeon, 2012[26]	Low-moderate: Blinding unclear; no attrition.
Tang, 2012[27]	Moderate - Difference on baseline insomnia severity between groups controlled for in analysis; completer analysis; small sample size; no blinding; multiple comparisons correction unclear.
Tegeler 2012[28]	High - mainly small sample size and no power, no blinding, wait-list control Blinding unclear; Multiple comparisons correction unclear.
Bjorvatn, 2011[29]	Moderate: ITT analysis; blinding unclear; did not describe randomization process or compare baseline characteristics; attrition higher 20% for control group and did not explain missing data
Buysee, 2011[30]	Moderate: Blinding unclear; multiple comparisons correction unclear; no sample size calculation
Hammer 2011[31]	High – first author interviewed potential participants and conducted all treatments ; small sample size (n=8), no smaple size/power calculation; Did not analyze sleep log or actigraphy data underpowered comparative effectiveness study with sample size of 10; attrition of 20%.
Passos 2011[32]	High - lack of statistical power and high attrition - 30%; ITT analysis. Blinding unclear. Multiple comparisons correction unclear.
Rybarczyk, 2011[33]	Low: Participants recruited at the same time as another study and were basically those who chose not to participate in that study. ITT analysis for 8 week analysis only, completers only for 1 year analysis. Multiple comparisons correction unclear.

Study	Overall Risk of Bias Assessment
Cortoos 2010[34]	Moderate - method of randomization was unclear but attrition was low at 6%. small n, no sample size calculation; no between-group comparisons; no numerical data for PSG results.
Jungqvist 2010;[35] Jungqvist 2012[36]	Moderate. Randomization procedure description unclear for last third of participants. Unsure if randomized or not. Unblinded. ITT analysis; High. Randomization procedure description unclear for last third of participants. Unsure if randomized or not. Unblinded. Very high attrition (nearly 50% in one group, high still in the other). Not ITT analysis.
Riley, 2010[37]	Moderate: No ITT analysis; two groups of intervention participants were combined for analyses; research assistants not blinded; did not adjust for multiple comparisons.no fidelity checks
Edinger, 2009[38]	Low/moderate: Not ITT analysis; unclear about multiple comparisons corrections
Ritterband 2009;[39] Thorndike 2014[40]	Low-moderate: ITT analysis; multiple comparisons correction unclear; no fidelity checks
van Straten, 2009[41]	Low: ITT analysis; blinding, multiple comparisons adjustment, and fidelity checks unclear.
Vincent, 2009[42]	Low-moderate: Multiple comparisons correction unclear; high attrition
Vitiello, 2009[43]	Moderate: Not ITT analysis; multiple comparisons correction unclear; did not discuss attrition or compare completers to non-completers
Soeffing, 2008[44]	Moderate-high: Discussed fidelity checks and treatment fidelity, but not attrition; did not report all scale outcomes; did not report methods for analyzing missing data
Espie, 2007[45]	Low-moderate: High attrition
McCrae, 2007[46]	Moderate: Reporting bias, small n; one participant not included in analyses due to withdrawal; unclear blinding and multiple comparisons correction
Germain, 2006;[47] Buysee 2011[30]	Moderate: Unclear whether all participants analyzed, missing data, and multiple comparisons; no between-group analysis.
Wu, 2006	Moderate: Blinding only for medications; not ITT analysis; multiple comparisons correction unclear; low statistical power
Jansson, 2005[48]	Moderate: Did not mention blinding; few details about intervention; did not appear to correct for multiple comparisons; no explanation of attrition, completer analysis

Study	Overall Risk of Bias Assessment
Morin, 2005[49]	Low-moderate: Says ITT analysis, but how drop-outs were handled NR; low attrition; randomization concealed; no sample size calculation; multiple comparisons correction unclear. Confusing as some "good sleepers" included despite requiring insomnia
Rybarczyk, 2005[50]	Low-moderate: Multiple comparisons correction unclear; didn't discuss who was delivering interventions or fidelity checks
Bastien, 2004[51]	Low-moderate: Data was missing for blinding, randomization process; attrition high at 6 months, unclear how missing data were handled
Jacobs 2004	Moderate
Strom, 2004[52]	Moderate: attrition over 20%, mostly in the treatment group; completer analysis; multiple comparisons correction unclear.
Edinger, 2003[53]	Low-moderate: Low attrition; ITT analysis; did not adjust for multiple comparisons
Morgan, 2003[54]	Moderate: high attrition but reasonably powered and well randomized.
Pallesen 2003[55]	High - due to lack of stat power and unclear exclusion of possible confounders (hypnotics); Attrition - 16.7% with extra 14.5% lost to followup at 6 months.
Edinger, 2001[56]	Low: ITT analyses, though placebo group not included in 6 month analyses as they were re-randomized after first follow-up; otherwise low risk in all categories
Espie, 2001[57]	Moderate/-high: Unclear about differences at baseline, blinding, multiple comparisons correction; no ITT analysis; no comparison of baseline characteristics
Lichstein, 2001[58]	Moderate: Completer-only analysis, reasonable sample size; multiple comparisons problem
Mimeault, 1999[59]	Moderate: Small sample size; no justification for clinical significance; completer-only analysis; While authors describe 4 LTFs during treatment, they do not describe the 9 they lost before follow-up (3 months).
Morin, 1999[60]	Moderate: Analyses do not include drop outs. Blinding for PCT and PCT part of combined. No mention of correcting for multiple comparisons. Select outcomes reported, but justified. Placebo group has treatment after 3 months.
Jacobs 1993[61]	High – underpowered for CE study; no other similar comparisons. ITT analysis. Blinding unclear. Multiple comparisons correction unclear.
Morin, 1993[62]	Low-moderate: Efficacy of randomization unclear; seemingly ITT analysis: multiple comparisons correction unclear: low attrition

Study	Overall Risk of Bias Assessment
Espie, 1989[63]	Moderate-high: No sample size calculation and 4 treatment groups; unclear analysis, whether participants were analyzed per ITT, multiple comparisons, and what "experimental drop outs" means. Care provider for all groups was senior author
Morin, 1988[64]	Moderate: Blinding unclear; attrition unclear; ITT analysis unclear; possibly underpowered
Morin, 1987[65]	High: High dropouts, small n, possible reporting bias

Table D2. Efficacy of psychological interventions in the general adult population: strength of evidence assessments

Outcome	Intervention	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
Remission	CBT-I	4 (179)	RR = 2.95 [1.78 to 4.87]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	MCT/BBT								Insufficient
	Stimulus Control	NR							
	Sleep Restriction								Insufficient
	Relaxation	NR							Insufficient
Responder (ISI score change of 7/8)	CBT	2 (123)	RR = 2.59 [0.45 to 14.99]	Medium	Direct	Imprecise	Consistent	Undetected	Insufficient
	MCT/BBT	NR	NA						Insufficient
	Stimulus Control	NR	NA						Insufficient
	Relaxation	NR	NA						Insufficient
ISI score	CBT	6 (537)	WMD = -4.48 [-6.59 to -2.38]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	MCT/BBT	NR							Insufficient
	Stimulus Control	NR							Insufficient
	Relaxation	NR							Insufficient
PSQI score	Individual CBT	7 (430)	WMD = -2.14 [-2.92 to -1.37]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	MCT/BBT	1 (40)	MD = NR Favors MCT P<1.001	Medium	Direct	Unclear	Consistent	Undetected	Insufficient
	Stimulus Control	1 (40)	WMD = -2.40 [-4.07 to -0.74]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	Relaxation	NR							Insufficient
CGI=very much improved	CBT	1 (60)	RR= 8.08 [1.13 to 57.73]	Medium	Direct	Precise	Unknown	Undetected	Low
	MCT/BBT	NR	NA						Insufficient
	Stimulus Control	NR	NA						Insufficient
	Relaxation	NR	NA						Insufficient
Sleep									
Subjective sleep onset	CBT	15 (1246)	WMD = -12.70 [-18.23 to -7.18]	Medium	Direct	Precise	Inconsistent	Undetected	Moderate

Outcome	Intervention	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
latency (minutes)*	MCT/BBT	1 (40)	MD = NR Favors MCT P<1.001	Medium	Direct	Unclear	Consistent	Undetected	Insufficient
	Stimulus Control	2 (68)	WMD= -31.24 [-45.26 to 17.22]	Medium	Direct	Precise	Consistent	Undetected	Low
	Relaxation	1 (28)	MD = -6.10 [-19.64 to 40.11]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Subjective total sleep time (minutes)*	CBT	15 (1233)	Favors CBT-I WMD = 14.24 [2.08 to 26.39]	Medium	Direct	Precise	Consistent	Detected	Moderate
	MCT/BBT	1 (40)	MD = NR Favors MCT P<1.001	Medium	Direct	Unclear	Unknown	Undetected	Insufficient
	Stimulus Control	2 (67)	WMD= 43.54 [12.67 to 74.42]	Medium	Direct	Precise	Consistent	Undetected	Low
	Relaxation	2 (77)	WMD= 10.23 [-19.64 to 40.11]	Medium	Direct	Imprecise	Inconsistent	Undetected	Insufficient
Wake time after sleep onset	CBT	11 (832)	WMD = -22.33 [-37.44 to -7.21]	Medium	Direct	Precise	Inconsistent	Undetected	Moderate
	MCT/BBT	1 (40)	MD = NR Favors MCT P<1.001	Medium	Direct	Unclear	Unknown	Undetected	Insufficient
	Stimulus Control	1 (40)	WMD= -37.60 [-67.65 to 7.55]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	Relaxation	1 (50)	WMD = -2.70 [-14.34 to 8.94]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Sleep efficiency	CBT	15 (1230)	Favors CBT-I WMD = 7.20 [4.57 to 9.82]	Medium	Direct	Precise	Consistent	Detected	Moderate
	MCT/BBT	NR	NA	NA	NA	NA	NA	NA	Insufficient
	Stimulus Control	1 (40)	WMD= 13.40 [6.44 to 20.36]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	Relaxation	1 (50)	WMD = -1.90 [-2.53 to 6.33]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Sleep quality	CBT	10 (809)	SMD = 0.40 [0.18 to 0.595]	Medium	Direct	Precise	Consistent	Detected	Moderate
	MCT/BBT	NR	NA	NA	NA	NA	NA	NA	Insufficient

Outcome	Intervention	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
	Stimulus Control								
	Relaxation	NR	NA	NA	NA	NA	NA	NA	Insufficient

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org)*

Table D3. Sustainability of psychological interventions in the general adult population (outcomes assessed at 6 to 24 months after treatment initiation): strength of evidence assessments

Outcome	Intervention	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
PSQI score	CBT	2 (241)	WMD = -2.71 [-3.67 to -1.75]	Medium	Direct	Precise	Consistent	Undetected	Low
Sleep									
Subjective sleep onset latency (minutes)*	CBT	4 (413)	WMD = -15.69 [-32.67 to 1.29]	Medium	Direct	Imprecise	Inconsistent	Undetected	Insufficient
Subjective total sleep time (minutes)*	CBT	4 (413)	WMD = 17.30 [-4.28 to 38.87]	Medium	Direct	Imprecise	Inconsistent	Undetected	Insufficient
Wake time after sleep onset	CBT	3 (377)	WMD = -15.20 [-26.28 to -4.12]	Medium	Direct	Precise	Consistent	Undetected	Low
Sleep efficiency	CBT	4 (413)	WMD = 5.00 [1.71 to 8.29]	Medium	Direct	Precise	Consistent	Undetected	Low
Sleep quality	CBT	1 (136)	MD = 0.54 [0.20 to 0.89]	Medium	Direct	Precise	Unknown	Undetected	Low

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio

Table D4. Efficacy of psychological interventions in older adults: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Remission (ISI≤7)	CBT	NR							Insufficient
	MCT/BBT	NR							Insufficient
	Sleep restriction	1 (94)	RR = 5.68 [1.32 to 24.54]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	Stimulus Control	1 (94)	RR = 7.39 [1.76 to 30.94]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Responder (ISI score change of 7/8)	CBT	NR							Insufficient
	MCT/BBT	NR							Insufficient
	Sleep restriction	1 (73)	RR = 3.25 [1.45 to 7.30]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	Stimulus Control	1 (94)	RR = 3.69 [1.68 to 8.11]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
ISI score	CBT	NR							Insufficient
	MCT/BBT	NR							Insufficient
	Sleep restriction	Epstein 2012							Insufficient
	Stimulus Control	Epstein 2012							Insufficient
ISI mean change	CBT	1 (125)	MD= 3.60 [2.13 to 5.07]**	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	MCT/BBT	NR	NA	NA	NA	NA	NA	NA	Insufficient
	Sleep restriction	1 (94)	MD= -5.00 [-6.94 to -3.06]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Stimulus Control	1 (94)	MD= -5.10 [-7.02 to -3.18]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
PSQI score	CBT	2 (162)	WMD = -2.98 [-4.01 to -1.95]	Medium	Direct	Precise	Consistent	Undetected	Low
	MCT/BBT	1 (79)	WMD = -2.90 [-4.22 to -1.58]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	Sleep restriction	NR	NA	NA	NA	NA	NA	NA	Insufficient
	Stimulus Control	NR	NA	NA	NA	NA	NA	NA	Insufficient
PSQI mean change	CBT	1 (113)	MD=-2.20 [-3.39 to -1.01]	Medium	Direct	Precise	Unknown	Undetected	Low
	MCT/BBT	1 (79)	WMD = -3.36	Medium	Direct	Precise	Unknown	Undetected	Insufficient

Outcome	Type	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
			[-4.59 to -2.13]						
	Sleep restriction	NR	NA	NA	NA	NA	NA	NA	Insufficient
	Stimulus Control	NR	NA	NA	NA	NA	NA	NA	Insufficient
Subjective sleep onset latency (minutes)*	CBT	3 (191)	WMD = -9.98 [-16.48 to -3.48]	Medium	Direct	Precise	Consistent	Undetected	Low
	MCT/BBT	3 (146)	WMD = -10.36 [-16.31 to -4.55]	Low	Direct	Precise	Consistent	Undetected	Low
	Sleep restriction	2 (141)	WMD = -11.38 [-27.74 to 4.99]	Medium	Direct	Imprecise	Inconsistent	Undetected	Insufficient
	Stimulus Control	2 (113)	WMD= -10.36 [-44.50 to 23.79]	Medium	Direct	Imprecise	Inconsistent	Undetected	Insufficient
Subjective total sleep time (minutes)*	CBT	4 (220)	WMD = 3.14 [-15.90 to 22.18]	Medium	Direct	Imprecise	Consistent	Undetected	Low
	MCT/BBT	3 (146)	WMD = -18.61 [-46.82 to 9.60]	Medium	Direct	Imprecise	Inconsistent	Undetected	Insufficient
	Sleep restriction	2 (141)	WMD = -17.57 [-102.36 to 67.21]	Medium	Direct	Imprecise	Inconsistent	Undetected	Insufficient
	Stimulus Control	2 (113)	WMD= 40.37 [23.47 to 57.27]	Medium	Direct	Precise	Consistent	Undetected	Low
Wake time after sleep onset	CBT	4 (220)	WMD = -26.96 [-35.73 to -18.19]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	MCT/BBT	3 (146)	WMD = -14.90 [-22.66 to -7.14]	Medium	Direct	Precise	Consistent	Undetected	Low
	Sleep restriction	1 (94)	MD= -24.47 [-40.98 to -7.96]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	Stimulus Control	1 (94)	MD= -26.60 [-38.11 to -15.09]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Sleep efficiency	CBT	3 (196)	WMD = 9.18 [5.76 to 12.62]	Medium	Direct	Precise	Consistent	Undetected	Low
	MCT/BBT	3 (146)	WMD = 6.33 [3.38 to 9.29]	Medium	Direct	Precise	Consistent	Undetected	Low
	Sleep restriction	1 (94)	MD = -24.47 [-40.98 to -7.96]	Moderate	Direct	Precise	Unknown	Undetected	Insufficient
	Stimulus Control	1 (94)	MD= 13.20 [9.92 to 16.48]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Sleep efficiency,	CBT		WMD = 7.75 [1.49 to 14.01]	Medium	Direct	Precise	Consistent	Undetected	Low

Outcome	Type	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
long term	MCT/BBT								
Sleep efficiency-mean change	CBT	1 (123)	WMD= 11.20 [6.25 to 16.15]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	MCT/BBT	NR							Insufficient
	Sleep restriction	NR							Insufficient
	Stimulus Control	NR							Insufficient
Sleep quality	CBT	NR							Insufficient
	MCT/BBT	NR							Insufficient
	Sleep restriction	1 (94)	SMD= 0.74 [0.32 to 1.16]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	Stimulus Control	1 (94)	SMD= 0.99 [0.56 to 1.42]	Medium	Direct	Precise	Unknown	Undetected	Insufficient

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio

* As a rule of thumb, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org)*

Table D5. Efficacy of psychological interventions in adults with pain: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
ISI score	CBT	4 (130)	WMD = -7.10 [-12.87 to -1.32]	Medium	Direct	Precise	Inconsistent	Undetected	Low
ISI score, long term	CBT	1 (74)	MD = -3.40 [-6.25 to -0.55]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Sleep									
Subjective sleep onset latency (minutes)*	CBT	3 (122)	WMD = -26.50 [-43.25 to -9.75]	Medium	Direct	Precise	Consistent	Undetected	Low
Subjective sleep onset latency (minutes)*, long term	CBT	1 (70)	WMD = -6.30 [-16.28 to 3.68]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Subjective total sleep time (minutes)*	CBT	4 (132)	WMD = 23.52 [-12.05 to 59.09]	Medium	Direct	Imprecise	Consistent	Undetected	Insufficient
Subjective total sleep time (minutes)*, long term	CBT	1 (70)	WMD = -6.00 [-36.22 to 24.22]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Wake time after sleep	CBT	3 (122)	WMD = -38.18 [-65.57 to -10.78]	Medium	Direct	Precise	Consistent	Undetected	Low
Wake time after sleep onset, long term	CBT	1 (70)	WMD = -6.00 [-19.66 to 7.66]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Sleep efficiency	CBT	4 (132)	WMD = 13.22 [5.07 to 21.38]	Medium	Direct	Precise	Consistent	Undetected	Low

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio

* As a rule of thumb, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org)*

Appendix E. Supporting Tables: Efficacy of Pharmacologic Interventions for Chronic Insomnia

Table E1. Pharmacologic interventions for insomnia disorder: risk of bias assessments

Study	Risk of Bias Assessment
Michelson, 2014[66]	Low: computer-generated randomization; concealment through interactive voice response system and masked throughout study; .Double-blinded and groups similar at baseline
From Kuriyama[67] NCT00237497	Moderate - Double blind placebo controlled study. However had a high discontinued rate – study not published individually; data obtained for previous systematic review; assessed as acceptable risk of bias by systematic review investigators.
From Kuriyama[67] NCT00671567	Unclear – study not published individually; data obtained for previous systematic review; assessed as acceptable risk of bias by systematic review investigators.
Goforth, 2014[68]	Low. Double blind study and with a low attrition rate.
Roth 2013;[69] Roth 2014[70]	Low Adjusted for multiple comparisons using hierarchy; 20/294 (7%) attrition; reporting bias, i.e., data only for TST; outcomes for NOW, SL must be estimated from figure; no data for WASO
Herring 2014;[71] Herring 2012[72]	Low. Computer-generated randomization schedule based on input from a blinded Merck statistician. Assignment was implemented through an interactive voice response system.Double-blinded and a low attrition rate
Lankford, 2012[73] Antidepressants	Low Computer-generated randomization; large enough sample size for adequate power ; 7% (17/254) attrition; Unclear if adjusted for multiple comparisons; Data for LSO and NAASO NR
Randall, 2012[74]	Moderate. Double blind placebo controlled study. High attrition rate. Randomization process not well described; high attrition; completer only analysis.
Krystal, 2011[75] Antidepressants	Low/moderate 229 randomized; 11% attrition; ITT analysis; double-blinded, PSG scorer blinded; unclear if adjusted for multiple comparisons; some outcome data NR.
Uchimura, 2011[76] Ramelteon	Moderate No sample size calculation, but large populations; 1-ary outcome adjusted for 2-point comparison; primary outcome analyzed on randomized and per-protocol population; 362/1443 (25%) attrition; data for SOL after week 2, for TST for week 1; no data for NAW, sleep quality, or PGI; forced escalation study
Wade, 2011[77] Ramelteon	Low/Moderate 5% attrition for 3 weeks, 22% 26 week extension, reasons described; reports data for SL only; re-analysis of data from Wade 2010 by total cohort and different age subgroups
Ancoli-Israel, 2010[78] Non-benzodiazepine hypnotics	Low/moderate Internet-based randomization system; achieved sample size based on power calculation; addressed multiple comparisons using sequential comparisons; 26% attrition, similar between groups; reporting bias, i.e., no data for NOW, quality, depth of sleep; data for TST, SL, WASO must be estimated from figures
Krystal, 2010[79] Antidepressants	Moderate Allocation concealment unclear; Double-blinded, PSG scorer blinded; 11% attrition; ITT analysis; no mention of adjustment for multiple comparisons
Wade, 2010[80] Ramelteon	Low - Achieved desired sample size for primary outcome; 5% attrition for 3 weeks, 22% 26 week extension
Fava, 2009[81] Zolpidem	High Patient population and attrition not described (only abstract states number of subjects (n=383), n does not appear anywhere else, or how many in each arm; power statement states that total of 260 subjects needed for 90% power but enrolled more; ITT and per-protocol analyses; no adjustment for multiple comparisons -despite making 200 secondary

Study	Risk of Bias Assessment
	efficacy comparison; Most outcome data must be estimated from figures and are shown as change from baseline; no data for SDS or SIS, or MGH-CPFQ; no outcomes for Q-LES-Q or HRU
Mayer, 2009[82] Ramelteon	Low No sample size calculation but large population; 116/451 (26%) discontinued over 6 months (reasons described), but all who were randomized were analyzed, using last observation carried forward
Krysta,l 2008[83] Nonbenzodiazepine hypnotic	Low/Moderate Achieved sample size based on power calculation; 405/1018 (40%) attrition (over 24 weeks), reasons described; ITT analysis using last observation carried forward; no adjustment for multiple comparisons; outcome data must be estimated from figures
Pollack, 2008[84]	Low/Moderate - 123/595 (21%) attrition; used last-observation-carried forward for ITT analysis; reporting bias: no outcome data for sleep quality.
Walsh, 2007[85] Nonbenzodiazepine hypnotic	Low Achieved sample size, having assumed 42% attrition in power calculations; 350/828 (42%) attrition over 6 months; attrition 52% among placebo, 37% among active drug; used last-observation-carried forward for missing values; results refer to 2 tables as online supplements, which could not be found
Zammit, 2007[86] Ramelteon	Low/Moderate Achieved sample size based on power calculation; 405/1018 (40%) attrition (over 24 weeks), reasons described; ITT analysis using last observation carried forward; no adjustment for multiple comparisons; outcome data must be estimated from figures
Reynolds, 2006[87] Antidepressants	High - 26% (7/27) attrition; Analysis does not appear to be ITT although unclear; No adjustment for multiple comparisons; small sample size small n (27 started, 20 completed; no sample size calculation/power statement; all data must be derived from figures, which are impossible to read; data for sleep efficiency by PSG NR
Roth, 2006;[88] Roth, 2014[70] Ramelteon	Moderate No sample size/power calculation, but large sample; 128/829 (15%) attrition, reasons described; no mention of how non-completers were handled, no n's in results; reporting bias (no outcome data for NOW, ease of falling back to sleep, sleep quality)
Wu, 2006[89]	Moderate Small sample size, no small sample/ power calculation; moderate attrition rate; completer analysis
Jacobs, 2004[90]	Moderate: placebo for active medication, but not for CBT; fidelity to meds based on self-report.
Perlis, 2004[91]	Low/Moderate No power calculation or adjustment for multiple comparisons; 39/199 (20%) attrition (over 12 weeks), reasons described; ITT analysis using last observation carried forward
Voshaar, 2004[92] Head to head	Moderate - had sample size calculation based on withdrawal symptoms, but did not achieve that size; 64/223=29% attrition, greater from zolpiden group; study objectve was rebound symptoms after stopping drug
Zammit, 2004[93]	Low Achieved sample size based on power calculation; addressed multiple comparisons using hierarchy; 16/308 (5%) attrition, between-group differences described; ITT analysis; consistent reporting
Krystal, 2003[94] Nonbenzodiazepine hypnotic	Low Achieved sample size based on power calculation (which assumed 50% attrition); adjusted for multiple comparison using Bonferroni correction; 320/791 (40%) attrition (over 6 month study), but lower than assumed in sample size calculation, reasons described; however, attrition twice as high in placebo group than active drug group; analyses: ITT (using last observation carried forward), observed cases, and completers
Walsh, 2002[95]	Moderate/High

Study	Risk of Bias Assessment
Nonbenzodiazepine hypnotic	No sample size calculation or adjustment for multiple comparisons; 28/163 (17%) attrition, reasons described; many outcomes in methods are not in results; other outcome data must be estimated from figures; very poorly reported methods, e.g., no patient inclusion/exclusion criteria (questions at end of report suggest this was transcribed from an oral presentation)
Allain, 2001[96] Nonbenzodiazepine hypnotics	Low No sample size calculation, but found many significant differences; no adjustment for multiple comparisons; non-standard daytime outcome measures; attrition 10/245 (4%) unbalanced: more patients withdrew from the placebo arm than from the active treatment arm (5% vs 0%), citing lack of efficacy; ITT analysis with "observed cases procedure" and LOCF
Hajak, 2001[97] Antidepressant	Moderate 47 subjects total; 15% attrition; outcome analysis by completers only, AEs by ITT; no sample size calculation; did adjust for multiple comparisons
Fry, 2000[98] Nonbenzodiazepine hypnotic	Low More women in Zaleplon 5 mg group; adjusted for multiple comparisons between zaleplon doses & placebo using Dunnett distribution; no sample size calculation, but fairly large n; data for SOL must be estimated from figure; 9/595 (2%) attrition; reasons described; consistent reporting
Asnis, 1999[99] Nonbenzodiazepine hypnotic	High No sample-size calculation, no adjustment for multiple comparisons; completer-only analysis; non-standard scales for daytime outcomes; 37/193 (19%) attrition; reporting bias, i.e., no outcomes for ease of falling asleep, daytime concentration, activities, alertness, mood, concentration, or creativity, GIT, or QoL; much data must be estimated from figures
Elie, 1999[100] Nonbenzodiazepine hypnotic	Low Adjusted for multiple comparisons using Dunnett distribution; no sample size calculation, but fairly large n; 41/615 (7%) not in efficacy analysis; reasons for attrition and attritions by treatment group NR (except for AEs); data for SOL must be estimated from figure; consistent reporting
Morin, 1999[60] Benzodiazepine	Low –Moderate: Analyses do not include drop outs. Incomplete blinding; no mention of correcting for multiple comparisons. Select outcomes reported, but justified: low attrition.
Lahmeyer, 1997[101] Non-benzodiazepine hypnotic	Moderate: no adjustment for multiple comparisons; moderate attrition; possible reporting bias.
Leppik, 1997[102] Head to head	Low-Moderate: low attrition during active treatment; no ITT analyses; possible reporting bias;
Scharf, 1994[103] Nonbenzodiazepine hypnotic	Low/Moderate Double-blinded, PSG scoring blinded; some nonstandard scales: no details on components of Morning or Evening Questionnaire or Global Impression; no data for "refreshing" or number of awakenings ; no correction for multiple comparisons
Minnekeer, 1988[104] Benzodiazepine	High - 25.9% drop out rate, largest in placebo group; not ITT for efficacy; no adjustment for multiple comparisons; no standard outcomes scales; outcome data displayed in figures only; scales in figure 1 and 2 unclear; little correlation between outcomes in methods and in results
Mitler, 1984[105] Benzodiazepine	High - Small sample size, n=21; no sample size/ power calculation; attrition NR; no mention of adjustment for multiple comparisons; non-standard scales; non-standard scales.
Reeves, 1977[106] Benzodiazepine	High - Small sample size (n=41), 15% attrition; no small sample size/ power calculation; completer analysis; no adjustment for multiple comparisons; non-standard scales
Monti, 1996[107]	High - Only participant was blinded in PSG lab (single blinded); n=12, no sample size/power calculation; non-standard scales; attrition NR

Table E2. Efficacy of nonbenzodiazepines for insomnia disorder in the general adult population: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
Clinical global outcome	Eszopiclone	1 (825)	RR 2.7 [2.1, 3.4]	Medium	Direct	Precise	Unknown	Undetected	Low
	Zaleplon	NR							Insufficient
	Zolpidem	NR							Insufficient
	Zolpidem "as needed"	1 (243)	RR 2.2 [1.6, 3.2]	Medium	Direct	Precise	Unknown	Undetected	Low
	Zolpidem SL	NR							Insufficient
	Zolpidem ER	1 (1016)	RR 1.8 [1.6, 2.0]	Medium	Direct	Precise	Unknown	Undetected	Low
ISI scores	Eszopiclone	1 (828)	MD -4.6 [-5.3, -3.9]	Medium	Direct	Precise	Unknown	Undetected	Low
Sleep									
Subjective sleep onset latency (minutes)	Eszopiclone	3 (1820)	WMD -19.1 [-24.1, -14.1]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	Zaleplon 10mg	1 (209)	MD -9.9 [-19.5, -0.4]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Zaleplon 5 mg	1 (208)	MD 2.5 [-9.0, 14.3]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Zolpidem	4 (373)	WMD -15 [-22.1, -7.8]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	Zolpidem "as needed"	2 (355)	WMD -14.8 [-23.4, -6.2]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	Zolpidem SL	1 (295)	MD -18 [CI NR].	Medium	Direct	Precise	Unknown	Undetected	Low
	Zolpidem ER	1 (1018)	Greater with zolpidem ER (approx.. 9 minutes, graphically displayed)	Medium	Direct	Precise	Unknown	Undetected	Low
Subjective total sleep time (minutes)	Eszopiclone	3 (1820)	WMD 44.8 [35.4, 54.2]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	Zaleplon	2 (930)	NA, not pooled NS versus placebo	Medium	Direct	Unclear	Consistent	Suspected	Low
	Zolpidem	3 (167)	WMD = 23 [2.0, 43.9]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	Zolpidem "as needed"	2 (355)	WMD 48.1 [34.8, 61.5]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	Zolpidem SL	1 (295)	NS versus placebo, data NR	Medium	Direct	Imprecise	Unknown	Suspected	Insufficient
	Zolpidem ER	1 (1018)	Greater with zolpidem ER (approx.. 25 minutes, graphically displayed)	Medium	Direct	Precise	Unknown	Undetected	Low
Wake time after sleep onset	Eszopiclone	3 (1820)	WMD -10.8 [-19.8, -1.70];	Medium	Direct	Precise	Inconsistent	Undetected	Low
	Zaleplon	NR							Insufficient
	Zolpidem	NR							Insufficient
	Zolpidem "as needed"	2 (437)	*Score at endpoint* (1 trial) MD -22.8 [-37.0, -8.6] *Mean change* (1 trial) MD -1.4 [-10.8, 8.0]	Medium	Direct	Imprecise	Inconsistent	Undetected	Low
	Zolpidem SL	1 (295)		Medium	Direct	Imprecise	Unknown	Undetected	Insufficient

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
	Zolpidem ER	1 (1018)	Greater with zolpidem ER (approx.. 16 minutes, graphically displayed)	Medium	Direct	Precise	Unknown	Undetected	Low
Sleep efficiency	Eszopiclone	NR							Insufficient
	Zaleplon	NR							Insufficient
	Zolpidem	NR							Insufficient
	Zolpidem "as needed"	NR							Insufficient
	Zolpidem SL	NR							Insufficient
	Zolpidem ER	NR							Insufficient
Sleep quality	Eszopiclone	2 (992)	SMD 0.47 [0.32, 0.61]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	Zaleplon	2 (879)	RR 1.19 [1.02, 1.38]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	Zolpidem	3 (557)	RR 1.40 [1.20, 1.65]	Medium	Direct	Imprecise	Consistent	Undetected	Moderate
	Zolpidem "as needed"	2 (408)	Not pooled. *Mean change* (1 trial) SMD 0.32 [0.07 to 0.58]; "significant improvement vs. placebo (data not shown) (1 trial)	Medium	Direct	Precise	Consistent	Suspected	Low
	Zolpidem SL	1 (295)	SMD 0.38 [0.15, 0.61]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Zolpidem ER	NR							Insufficient
Adverse Effects									
Study withdrawals	Eszopiclone	3 (1927)	RR 0.8 [0.7, 1.00]	Medium	Direct	Imprecise	Inconsistent	Undetected	Low
	Zaleplon	2 (971)	RR 1.4 [0.9, 2.3]	Medium	Direct	Imprecise	Consistent	Undetected	Low
	Zolpidem	6 (859)	RR 1.2 [0.8, 1.7]	Medium	Direct	Imprecise	Consistent	Undetected	Low
	Zolpidem "as needed"	3 (607)	RR 1.0 [0.5, 2.0]	Medium	Direct	Imprecise	Inconsistent	Undetected	Low
	Zolpidem SL	1 (295)	RR 1.4 [0.6, 3.4]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Zolpidem ER	1 (1018)	RR 0.7 [0.6, 0.9]	Medium	Direct	Precise	Unknown	Undetected	Low
Study withdrawals due to an adverse effect	Eszopiclone	3 (1927)	RR 1.4 [0.97, 2.0]	Medium	Direct	Imprecise	Consistent	Undetected	Low
	Zaleplon	2 (965)	RR 1.6 [0.7, 3.9]	Medium	Direct	Imprecise	Consistent	Undetected	Low
	Zolpidem	5 (828)	RR 2.8 [1.2, 6.4]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	Zolpidem "as needed"	3 (607)	RR 2.8 [0.95, 8.0]	Medium	Direct	Imprecise	Consistent	Undetected	Insufficient
	Zolpidem SL	1 (295)	RR 0.3 [0.01, 7.8]	Medium	Direct	Imprecise	Unknown t	Undetected	Insufficient
	Zolpidem ER	1 (1018)	RR 1.8 [1.0, 3.1]	Medium	Direct	Precise	Unknown	Undetected	Low
Patients with ≥1 adverse effect	Eszopiclone	2 (1616)	RR 1.2 [1.1, 1.4]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	Zaleplon	2 (688)	RR 0.96 [0.89, 1.05]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	Zolpidem	4 (698)	RR 1.05 [0.91, 1.21]	Medium	Direct	Precise	Consistent	Undetected	Moderate
	Zolpidem "as	1 (245)	RR 1.3 [0.7, 2.2]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
	needed"								
	Zolpidem SL	NR							Insufficient
	Zolpidem ER	1 (1018)	RR 1.23 [1.10, 1.39]	Medium	Direct	Precise	Unknown	Undetected	Low

ER=extended release; MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; SL=sublingual

Table E3. Efficacy of nonbenzodiazepines for insomnia disorder in adults with low back pain: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
Clinical global outcome	Eszopiclone	NR							Insufficient
Sleep									
Subjective sleep onset latency (minutes)	Eszopiclone	1 (52)	MD -4.90 [-15.32 to 5.52]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Subjective total sleep time (minutes)	Eszopiclone	1 (52)	MD 23.14 [-18.26 to 64.54]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Wake time after sleep onset	Eszopiclone	1 (52)	MD -39.44 [-69.79 to -9.09]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Sleep efficiency	Eszopiclone		NR						Insufficient
Sleep quality	Eszopiclone	1 (52)	SMD 0.60 [0.03 to 1.17]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Adverse Effects									
Study withdrawals	Eszopiclone	1 (58)	RR 0.30 [0.11 to 0.85]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Study withdrawals due to an adverse effect	Eszopiclone	1 (58)	RR NA, 0 events	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Patients with ≥1 adverse effect	Eszopiclone	1 (58)	RR 1.52 [0.15 to 15.78]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

Table E4. Efficacy of nonbenzodiazepines for insomnia disorder in older adults: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
Clinical global outcome	Eszopiclone	1 (386)	RR 1.51 [1.11, 2.06]	Medium	Direct	Precise	Unknown	Undetected	Low
	Zolpidem	NR							Insufficient
ISI	Eszopiclone	1 (362)	MD -2.30 [-3.30 to -1.30]	Medium	Direct	Precise	Unknown	Undetected	Low
Sleep									
Subjective sleep onset latency (minutes)	Eszopiclone	1 (382)	MD -4.90 [-15.32, 5.52]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Zolpidem	1 (152)	MD -18.3 [-31.2, -5.4]	Medium	Direct	Precise	Unknown	Undetected	Low
Subjective total sleep time (minutes)	Eszopiclone	1 (382)	MD 30.0 [19.7, 40.3]	Medium	Direct	Precise	Unknown	Undetected	Low
	Zolpidem	1 (152)	MD 18.20 [-3.16, 39.56]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Wake time after sleep onset	Eszopiclone	1 (380)	MD -21.6 [-29.6, -13.6]	Medium	Direct	Precise	Unknown	Undetected	Low
	Zolpidem	NR							Insufficient
Sleep efficiency	Eszopiclone	NR							Insufficient
	Zolpidem	NR							Insufficient
Sleep quality	Eszopiclone	1 (388)	SMD 0.24 [0.04, 0.44]	Medium	Direct	Precise	Unknown	Undetected	Low
	Zolpidem	NR							Insufficient
Adverse Effects									
Study withdrawals	Eszopiclone	1 (388)	RR 1.02 [0.72, 1.46]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Zolpidem	1 (166)	RR 0.61 [0.23, 1.61]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Study withdrawals due to an adverse effect	Eszopiclone	1 (388)	RR 1.56 [0.69, 3.51]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Zolpidem	1 (166)	RR 0.34 [0.07, 1.64]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Patients with ≥1 adverse effect	Eszopiclone	1 (388)	RR 1.17 [0.98, 1.41]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Zolpidem	1 (166)	RR 1.13 [0.88, 1.46]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

Table E5. Efficacy of melatonin and ramelteon for insomnia disorder in the general adult population: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
Clinical global outcome	Melatonin	1 (700)	MD -0.39 [-0.71, -0.08]	Medium	Direct	Precise	Unknown	Suspected	Insufficient
	Ramelteon	NR							Insufficient
Sleep									
Subjective sleep onset latency (minutes)	Melatonin	1 (700)	MD -6 [-10, -2]	Medium	Direct	Precise	Unknown	Suspected	Insufficient
	Ramelteon	5 (2972)	WMD -3.1 [-7.4, 1.2]	Medium	Direct	Imprecise	Consistent	Undetected	Low
Subjective total sleep time (minutes)	Melatonin	NR							Insufficient
	Ramelteon	5 (2781)	WMD 0.08 [-10, 10.1]	Medium	Direct	Imprecise	Inconsistent	Undetected	Low
Wake time after sleep onset	Melatonin	NR							Insufficient
	Ramelteon	2 (721)	WMD 5.9 [-6.1, 17.9]	Medium	Direct	Imprecise	Consistent	Undetected	Low
Sleep efficiency	Melatonin	NR							Insufficient
	Ramelteon	NR							Insufficient
Sleep quality	Melatonin	NR							Insufficient
	Ramelteon	5 (2973)	SMD -0.08 [-0.16, -0.01]	Medium	Direct	Precise	Inconsistent	Undetected	Low
Adverse Effects									
Study withdrawals	Melatonin	1 (711)	RR 0.87 [0.64, 1.18]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Ramelteon	2 (1594)	RR 1.47 [1.11, 1.94] RD 0.05 [-0.02, 0.12]	Medium	Direct	Imprecise	Consistent	Undetected	Low
Study withdrawals due to an adverse effect	Melatonin	1 (711)	RR 0.86 [0.42, 1.75]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Ramelteon	3 (1999)	RR 1.23 [0.47, 3.25]	Medium	Direct	Imprecise	Consistent	Undetected	Low
Patients with ≥1 adverse effect	Melatonin	1 (711)	RR 0.77 [0.49, 1.21]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Ramelteon	3 (1999)	RR 1.03 [0.93, 1.13]	Medium	Direct	Precise	Consistent	Undetected	Moderate

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

Table E6. Efficacy of ramelteon for insomnia disorder in older adults: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
Clinical global outcome	Ramelteon	NR							Insufficient
Sleep									
Subjective sleep onset latency (minutes)	Ramelteon	1 (826)	MD -10.1 [-15.6, -4.6]	Medium	Direct	Precise	Unknown	Undetected	Low
Subjective total sleep time (minutes)	Ramelteon	1 (825)	MD 5.90 [-1.95, 13.75]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Wake time after sleep onset	Ramelteon	NR							Insufficient
Sleep efficiency	Ramelteon	NR							Insufficient
Sleep quality	Ramelteon	1 (826)	SMD -0.10 [-0.27, 0.07]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Adverse Effects									
Study withdrawals	Ramelteon	1 (829)	RR 0.88 [0.63, 1.23]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Study withdrawals due to an adverse effect	Ramelteon	1 (829)	RR 0.93 [0.40, 2.16]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Patients with ≥1 adverse effect	Ramelteon	1 (829)	RR 1.10 [0.96, 1.26]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

Table E7. Efficacy of benzodiazepines for insomnia disorder in the general adult population: strength of evidence assessments

Outcome	Benzodiazepine Type	Number of Trials	n	Summary Statistics, WMD or MD [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global										
Clinical global outcome	Temazepam	NR								Insufficient
Sleep										
Subjective sleep latency (minutes)	Temazepam	1	34	MD -30.9 -51.2, -10.6]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Subjective total sleep time (minutes)	Temazepam	1	34	MD 93.5 [45.84, 141.16]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Sleep efficiency	Temazepam	1	34	MD 14.10 [5.83, 22.37]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Adverse Effects										
Study withdrawals	Temazepam	1	39	RR 1.43 [0.27, 7.61]	Medium	Direct	Imprecise	Consistent	Undetected	Insufficient
Study withdrawals due to an adverse effect	Temazepam	1	39	RR 6.67 [0.37, 121.07]	Medium	Direct	Imprecise	Consistent	Undetected	Insufficient
Patients with ≥ 1 adverse effect	Temazepam	NR								Insufficient

MD=mean difference; NR=not reported; WMD-weighted mean difference

Table E8. Efficacy of benzodiazepines for insomnia disorder in the older adult population: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
Clinical global outcome	Temazepam	NR							Insufficient
Sleep									
Subjective sleep onset latency (minutes)	Temazepam	NR							Insufficient
Subjective total sleep time (minutes)	Temazepam	1 (35)	MD 33.2 [-7.1, 73.5]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Wake time after sleep onset	Temazepam	1 (35)	MD -22.3 [-36.3, -8.3]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Sleep efficiency	Temazepam	1 (35)	MD 9.2 [2.8, 15.6]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Sleep quality	Temazepam	NR							Insufficient
Adverse Effects									
Study withdrawals	Temazepam	1 (40)	RR 1.50 [0.28, 8.04]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Study withdrawals due to an adverse effect	Temazepam	1 (40)	RR 7.00 [0.38, 127.32]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Patients with ≥1 adverse effect	Temazepam	NR							Insufficient

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

Table E9. Efficacy of antidepressants for insomnia disorder in the general adult population: strength of evidence assessments

Outcome	Anti-depressant	Number of Trials	n	Summary statistics, [95% CI] [a]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global										
Clinical Global Impression responders: (much-very much improved) or ISI score "clinically reduced" (percent reporting)	Doxepin	1	40	MD -0.58 [-1.05, -0.12]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Insomnia Severity Index (score)	Doxepin	NR								Insufficient
Sleep										
Subjective sleep latency (minutes)	Doxepin	NR								Insufficient
Subjective total sleep time (minutes)	Doxepin	1	221	3 mg: MD 11.9 [NR] 6 mg: MD 17.3 [NR]	Medium	Direct	Precise	Unknown	Suspected	Low
Wake time after sleep onset	Doxepin	1	221	3 mg: MD -10.2 [NR] 6 mg: MD -14.2 [NR]	Medium	Direct	Precise	Unknown	Suspected	Low
Adverse Effects										
Study withdrawals	Doxepin	2	276	RR 1.01 [0.52, 1.96]	Medium	Direct	Precise	Consistent	Undetected	Insufficient
Study withdrawals due to an adverse event	Doxepin	2	276	RR 1.19 [0.36, 3.93]	Medium	Direct	Precise	Consistent	Undetected	Insufficient
Patients with ≥1 adverse event	Doxepin	2	268	RR 1.11 [0.96, 1.27]	Medium	Direct	Precise	Consistent	Undetected	Low

CI=confidence interval; MD=mean difference; n=number of participants; RR = relative risk; SE=standard error

Table E10. Efficacy of antidepressants for insomnia disorder in older adults: strength of evidence assessments

Outcome	Anti-depressant Age	Number of Trials	n	Summary Statistics, [95% CI] [a]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global										
Insomnia Severity Index (score), mean change from baseline	Doxepin	2	494	WMD -1.93 [-2.89, -0.98]	Medium	Direct	Precise	Consistent	Undetected	Moderate
Sleep Outcomes										
Subjective sleep latency (minutes), mean change from baseline	Doxepin	1	240	MD -14.7 [-24.0, -5.4]	Medium	Direct	Precise	Unknown	Undetected	Low
Subjective total sleep time (minutes), mean change from baseline	Doxepin	2	494	WMD 23.9 [12.0, 35.7]	Medium	Direct	Precise	Consistent	Undetected	Moderate
Wake time after sleep onset (minutes), mean change from baseline	Doxepin	1	254	MD -17.0 [-29.3, -4.7]	Low	Direct	Precise	Unknown	Undetected	Low
Sleep quality	Doxepin	2	494	Significant improvements vs. placebo in both trials	Medium	Direct	Precise	Consistent	Undetected	Low
Adverse Effects										
Study withdrawals	Doxepin	2	495	RR 0.63 [0.36, 1.12]	Medium	Direct	Imprecise	Consistent	Undetected	Low
Study withdrawals due to an adverse event	Doxepin	2	495	RR 0.73 [0.20, 2.69]	Medium	Direct	Imprecise	Consistent	Undetected	Insufficient
Patients with ≥1 adverse event	Doxepin	2	494	RR 0.87[0.60, 1.26]	Medium	Direct	Imprecise	Consistent	Undetected	Low

CI=confidence interval; MD=mean difference; n=number of participants; RR = relative risk; SMD = standardized mean difference; WMD = weighted mean difference

[a] Analyses based on outcome measures only. In some cases, significance of outcomes differs from that reported in RCT, which incorporated baseline values and/or center in analysis.

Table E11. Efficacy of orexin receptor antagonist for insomnia disorder in mixed general and older adult population: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
Clinical global outcome – Responders (≥6-point improvement from baseline	Suvorexant 20/15 mg	2 (1049)	RR 1.32 [1.16,1.50]	Medium	Direct	Precise	Consistent	Undetected	Moderate
Insomnia Severity Index (score)	Suvorexant 20/15 mg	2 (1084)	WMD -1.2 [-1.8, -0.6]	Medium	Direct	Precise	Consistent	Undetected	Moderate
Sleep									
Subjective sleep onset latency (minutes)*	Suvorexant 20/15 mg	2 (1089)	WMD -5.97 [-10.01, -1.92]	Medium	Direct	Precise	Consistent	Undetected	Moderate
Subjective total sleep time (minutes)*	Suvorexant 20/15 mg	2 (1089)	WMD 15.97 [4.73, 27.22]	Medium	Direct	Precise	Consistent	Undetected	Moderate
Wake time after sleep onset	Suvorexant 20/15 mg	2 (1089)	WMD -4.67 [-8.86, -0.47]	Medium	Direct	Precise	Consistent	Undetected	Moderate
Sleep efficiency	Suvorexant 20/15 mg	NR							Insufficient
Sleep quality	Suvorexant 20/15 mg	2 (1089)	SMD 0.20 [0.08, 0.32]	Medium	Direct	Precise	Consistent	Undetected	Moderate
Adverse Effects									
Study withdrawals	Suvorexant 20/15 mg	2 (1266)	RR 0.95 [0.70, 1.29]	Medium	Direct	Imprecise	Consistent	Undetected	Low
Study withdrawals due to an adverse effect	Suvorexant 20/15 mg	2 (1266)	RR 0.66 [0.31, 1.42]	Medium	Direct	Imprecise	Consistent	Undetected	Low
Patients with ≥1 adverse effect	Suvorexant 20/15 mg	2 (1266)	RR 0.99 [0.88, 1.12]	Medium	Direct	Precise	Consistent	Undetected	Moderate

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

Table E12. Comparative effectiveness of pharmaceutical treatments for insomnia disorder: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
Clinical global outcome	Zolpidem vs. Temazapam	1 (157)		Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Zaleplon vs. Zolpidem	NR							Insufficient
Sleep									
Subjective sleep onset latency (minutes)*	Zolpidem vs. Temazapam	1 (159)	MD 0.00 [-10.43, 10.43]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Zaleplon vs. Zolpidem	1 (301)	MD -13.7 [-25.1, -2.3] favoring zolpidem 10 mg vs. zaleplon 5 mg NS zolpidem 10 mg versus zaleplon 10 mg	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Subjective total sleep time (minutes)*	Zolpidem vs. Temazapam	1 (159)	MD 27.0 [2.1, 51.9] favoring zolpidem	Medium	Direct	Precise	Unknown	Undetected	Low
	Zaleplon vs. Zolpidem	2 (965)	No direct comparison and reported data does not allow analysis					Suspected	Insufficient
Wake time after sleep onset	Zolpidem vs. Temazapam	1 (159)	MD 1.00 [-10.51, 12.51]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Zaleplon vs. Zolpidem	NR							Insufficient
Sleep efficiency	Zolpidem vs. Temazapam	NR							Insufficient
	Zaleplon vs. Zolpidem	NR							Insufficient
Sleep quality	Zolpidem vs. Temazapam	NR							Insufficient
	Zaleplon vs. Zolpidem	2 (870)	RR 0.90 [0.80, 1.01]	Medium	Direct	Precise	Consistent	Undetected	Moderate
Adverse Effects									
Study withdrawals	Zolpidem vs. Temazapam	NR							Insufficient
	Zaleplon vs. Zolpidem	2 (965)	RR 0.98 [0.66, 1.46]	Medium	Direct	Imprecise	Consistent	Undetected	Low
Study withdrawals due	Zolpidem vs. Temazapam	NR							Insufficient

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
to an adverse effect	Zaleplon vs. Zolpidem	2 (958)	RR 0.68 [0.36, 1.27]	Medium	Direct	Imprecise	Consistent	Undetected	Low
Patients with ≥1 adverse effect	Zolpidem vs. Temazapam	NR							Insufficient
	Zaleplon vs. Zolpidem	2 (958)	RR 0.95 [0.87, 1.03]	Medium	Direct	Precise	Consistent	Undetected	Moderate

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

Table E13. Comparative effectiveness of pharmaceutical treatments versus CBT for insomnia disorder: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
Clinical global outcome	Zolpidem vs. CBT	NR							Insufficient
	Temazapam vs. CBT	NR							Insufficient
	Temazapam vs. CBT, older adults	NR							
Sleep									
Subjective sleep onset latency (minutes)*	Zolpidem vs. CBT	1 (27)	MD = 24.6 [-3.1, 52.3]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazapam vs. CBT	1 (36)	MD = -12.0 [-20.9, -3.1]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	Temazapam vs. CBT, older adults	NR							Insufficient
Subjective total sleep time (minutes)*	Zolpidem vs. CBT	1 (27)	MD = 17.7 [-33.4, 68.8]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazapam vs. CBT	1 (36)	MD = 42.6 [6.3, 79.0]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	Temazapam vs. CBT, older adults	1 (35)	MD = 31.9 [-4.4, 68.2]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Wake time after sleep onset	Zolpidem vs. CBT	NR							Insufficient
	Temazapam vs. CBT	NR							Insufficient
	Temazapam vs. CBT, older adults	1 (35)	MD = 7.2 [-5.0, 19.3]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Sleep efficiency	Zolpidem vs. CBT	1 (27)	MD = -16.3 [-28.9, -3.7]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	Temazapam vs. CBT	1 (36)	MD = 5.1 [-2.3, 12.5]						
	Temazapam vs. CBT, older adults	1 (35)	MD = -2.1 [-6.6, 2.4]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Sleep quality	Zolpidem vs. CBT	NR							Insufficient

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
	Temazapam vs. CBT	NR							Insufficient
	Temazapam vs. CBT, older adults	NR							Insufficient
Adverse Effects									
Study withdrawals	Zolpidem vs. CBT	1 (30)	RR 2.00 [0.20, 19.78]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazapam vs. CBT	1 (39)	RR 6.7 [0.4, 121.1]	Medium	Direct	Imprecise	Unknown	Undetected	
	Temazapam vs. CBT, older adults	1 (35)	RR 6.3 [0.4 to 114.8]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Study withdrawals due to an adverse effect	Zolpidem vs. CBT	1 (30)	NA						Insufficient
	Temazapam vs. CBT	1 (39)	RR 6.7 [0.4, 121.1]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazapam vs. CBT, older adults	1 (35)	RR 6.3 [0.4, 114.8]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Patients with ≥1 adverse effect	Zolpidem vs. CBT	NR							Insufficient
	Temazapam vs. CBT	NR							Insufficient
	Temazapam vs. CBT-I, older adults	NR							Insufficient

CBT-I = Cognitive Behavioral Therapy for insomnia; MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

Table E14. Comparative effectiveness of pharmaceutical treatment versus combined pharmaceutical treatment and CBT for insomnia disorder: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
Clinical global outcome	Zolpidem/ vs. Combined	NR							Insufficient
	Temazepam/ vs. Combined	NR							Insufficient
	Temazapam vs. CBT, older adults	NR							Insufficient
Sleep									
Subjective sleep onset latency (minutes)*	Zolpidem/ vs. Combined	1 (24)	MD 20.2 [-17.0, 57.4]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazepam/ vs. Combined	1 (35)	MD 2.3 [-5.1, 9.7]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazapam vs. CBT, older adults	NR							Insufficient
Subjective total sleep time (minutes)*	Zolpidem/ vs. Combined	1 (24)	MD 6.0 [-57.1, 69.1]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazepam/ vs. Combined	1 (35)	MD 9.4 [-30.0, 49.3]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazapam vs. CBT, older adults	1 (36)	MD 52.0 [12.1, 91.9]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
Wake time after sleep onset	Zolpidem/ vs. Combined	NR							Insufficient
	Temazepam/ vs. Combined	NR							Insufficient
	Temazapam vs. CBT, older adults	1 (36)	MD 8.7 [-4.3, 21.7]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Sleep efficiency	Zolpidem/ vs. Combined	1 (24)	MD -13.2 [-27.9, 1.5]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazepam/ vs. Combined	1 (35)	MD -1.6 [-7.7, 4.5]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazapam vs. CBT, older adults	1 (36)	MD -2.2 [-8.2, 3.9]						
Sleep quality	Zolpidem/	NR							Insufficient

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
	vs. Combined								
	Temazepam/ vs. Combined	NR							Insufficient
	Temazapam vs. CBT, older adults								
Adverse Effects									
Study withdrawals	Zolpidem/ vs. Combined	1 (33)	RR 0.5 [0.1, 2.1]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazepam/ vs. Combined	1 (39)	RR 2.9 [0.3, 25.1]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazapam vs. CBT, older adults	1 (40)	RR 3.0 [0.3, 26.5]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Study withdrawals due to an adverse effect	Zolpidem/ vs. Combined	1 (33)	NA (0 events)	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazepam/ vs. Combined	1 (39)	RR 2.9 [0.3, 25.1]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazapam vs. CBT, older adults	1 (40)	RR 7.0 [0.4 to 127.3]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Patients with ≥1 adverse effect	Zolpidem/ vs. Combined	NR							Insufficient
	Temazepam/ vs. Combined	NR							Insufficient
	Temazapam vs. CBT, older adults	NR							Insufficient

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

Table E15. Comparative effectiveness of combined pharmaceutical treatment and CBT versus CBT for insomnia disorder: strength of evidence assessments

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Global									
Clinical global outcome	Zolpidem/ CBT vs. CBT	1 (149)	Remitters RR 1.2 [0.8, 1.7]; Responders RR 1.0 [0.8, 1.3] ISI MD -0.5 [-1.6, 0.6]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazepam/ CBT vs. CBT	NR							Insufficient
	Temazepam/ CBT vs. CBT Older adults	NR							Insufficient
Sleep									
Subjective sleep onset latency (minutes)*	Zolpidem/ CBT vs. CBT	2 (187)	WMD 7.1 [-1.4, 15.6]	Medium	Direct	Imprecise	Consistent	Undetected	Low
	Temazepam/ CBT vs. CBT	1 (37)	MD -14.3 [-23.5, -5.1]	Medium	Direct	Precise	Unknown	Undetected	Insufficient
	Temazepam/ CBT vs. CBT Older adults	NR							Insufficient
Subjective total sleep time (minutes)*	Zolpidem/ CBT vs. CBT	2 (187)	WMD 4.5 [-30.5, 39.4]	Medium	Direct	Imprecise	Inconsistent	Undetected	Insufficient
	Temazepam/ CBT vs. CBT	1 (37)	MD 33.2 [-3.1, 69.5]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazepam/ CBT vs. CBT Older adults	1 (37)	MD -20.1 [-58.2, 18.0]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Wake time after sleep onset	Zolpidem/ CBT vs. CBT	1 (160)	MD -14.2 [-25.1, -3.4]	Medium	Direct	Precise	Unknown	Undetected	Low
	Temazepam/ CBT vs. CBT	NR							Insufficient
	Temazepam/ CBT vs. CBT Older adults	1 (37)	MD -1.5 [-24.6, 21.6]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Sleep efficiency	Zolpidem/ CBT vs. CBT	2 (187)	WMD -1.2 [-8.5, 6.2]	Medium	Direct	Imprecise	Inconsistent	Undetected	Insufficient
	Temazepam/ CBT vs. CBT	1 (37)	MD 6.7 [-1.1, 14.5]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazepam/	1 (37)	MD 0.06 [-6.1, 6.3]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient

Outcome	Type	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
	CBT vs. CBT Older adults								
Sleep quality	Zolpidem/ CBT vs. CBT	NR							Insufficient
	Temazepam/ CBT vs. CBT	NR							Insufficient
	Temazepam/ CBT vs. CBT Older adults	NR							Insufficient
Adverse Effects									
Study withdrawals	Zolpidem/ CBT vs. CBT	2 (193)	RR 1.7 [0.7 to 4.6]	Medium	Direct	Imprecise	Consistent	Undetected	Insufficient
	Temazepam/ CBT vs. CBT	1 (38)	RR 3.0 [0.1 to 69.1]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazepam/ CBT vs. CBT Older adults	1 (38)	RR 2.7 [0.1 to 62.7]	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Study withdrawals due to an adverse effect	Zolpidem/ CBT vs. CBT	2 (193)	NA, no events	Medium	Direct	Imprecise	Consistent	Undetected	Insufficient
	Temazepam/ CBT vs. CBT	1 (38)	NA, no events	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
	Temazepam/ CBT vs. CBT Older adults	1 (38)	NA, no events	Medium	Direct	Imprecise	Unknown	Undetected	Insufficient
Patients with ≥1 adverse effect	Zolpidem/ CBT vs. CBT	NR							Insufficient
	Temazepam/ CBT vs. CBT	NR							Insufficient
	Temazepam/ CBT vs. CBT Older adults	NR							Insufficient

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

Table E16. Long-term harms of pharmaceutical treatments for insomnia disorder

Drug	Study (Year); Location	Design	Duration (Years)	Subjects	Adverse Effects/ Lack of Efficacy Leading to Withdrawal, % (n/N)	Serious Adverse Effects, % (n/N) or Estimates of Risk	Specific Adverse Effects, % (n/N)
Non BZDs							
Zolpidem	Lai, 2014{Lai, 2014 #2845} Taiwan	Retrospective cohort Adjusted for diabetes, sleep disorder, alcohol-related disorders, urinary incontinence, chronic arthritis, antihypertensive drugs, antidepressant drugs, and antipsychotic drugs	≥1 year or until hospitalization for head injury or fracture (major injury)	N=8188 who had received a first prescription for zolpidem between January 2000, and December 2009 N=32,752 patients, matched by age and sex, who had not used sedative-hypnotic agents Mean age 39 years Female 49%	NR	HRs [95% CI] for major injury for zolpidem users 1) Overall 1.67 (1.19 to 2.34) 2) Dosage groups a. ≤70 mg/year 0.48 (0.21 to 1.09) b. 71-800 mg/year 2.04 (1.32 to 3.13) c. 801-1600 mg/year 4.37 (2.12 to 9.01) d. >1600 mg/year 4.74 (2.38 to 9.42)	Major injury events Zolpidem user group: 49 (rate 60.1 per 10,000 person-years) Non-user control group: 120 (rate 36.7 per 10,000 person-years)

Drug	Study (Year); Location	Design	Duration (Years)	Subjects	Adverse Effects/ Lack of Efficacy Leading to Withdrawal, % (n/N)	Serious Adverse Effects, % (n/N) or Estimates of Risk	Specific Adverse Effects, % (n/N)
						3) younger cohort (aged 18-54 years) 1.70 (1.15 to 2.51) 4) older cohort (aged >55 years) was 1.57 (0.78 to 3.13).	
Non-BZD (use 49%): zopiclone, zolpidem, zaleplon BZD (use 34%): nordazepam, clonazepam, flurazepam Other (use ~17%): trazodone, melatonin agonist	Chen, 2012[108] Taiwan	Retrospective cohort Adjusted for the possible confounding factors of hypertension, type 2 DM, hyperlipidemia, and stroke.	3	n=5693 with chronic ("long-term") insomnia and with hypnotic use, n=28,465 without insomnia and no hypnotic use Patients aged 50 years or older; Female 56%	NR	HRs for dementia, hypnotic use vs. no hypnotic use All: 2.34[a] [95% CI 1.92 to 2.85]; Men: 2.28[a] [95% CI, 1.68 to 3.10]; Women: 2.39[a] [95% CI, 1.85 to 3.09]; Age, 50-65: 5.22[a] [95% CI, 2.62 to 10.41]; Age, >65: 2.33[a] [95% CI, 1.90 to	Dementia, hypnotic users: 4% (220/5693) Dementia, controls: 1.5% (424/28,041)

Drug	Study (Year); Location	Design	Duration (Years)	Subjects	Adverse Effects/ Lack of Efficacy Leading to Withdrawal, % (n/N)	Serious Adverse Effects, % (n/N) or Estimates of Risk	Specific Adverse Effects, % (n/N)
						2.88]; BZD vs. non-BZD: 1.01[a] [95% CI, 0.76 to 1.33];	
Zolpidem and BZDs	Kang, 2012[109] Korea	Retrospective case-crossover design, Hazard period exposures vs, Control period exposures Control period exposure defined as one day before each of 5 weeks, 10 weeks, 15 weeks, and 20 weeks from the hazard period, setting pairs as a ratio of 1:4 (1508/6032)	Control period was within 180 days before fracture	N=1508 cases who had a fracture, the hazard period exposure Older adults with insomnia, aged 65 years or older; Female 80% Osteoporosis 31% Note: Insomnia defined as patients who were mainly or partly diagnosed with insomnia and who were prescribed sleeping pills more	NR	Adjusted OR, hazard period exposure (n=1508) vs. control period exposures (n=6032) Zolpidem use: 1.72[a] [95% CI, 1.37 to 2.16];	Fractures, Hazard period exposure (236/1508)

Drug	Study (Year); Location	Design	Duration (Years)	Subjects	Adverse Effects/ Lack of Efficacy Leading to Withdrawal, % (n/N)	Serious Adverse Effects, % (n/N) or Estimates of Risk	Specific Adverse Effects, % (n/N)
				than once			
Zolpidem and other hypnotics	Kripke 2012{Kripke, 2012 #3032} US	Matched cohort study Data were adjusted for age, gender, smoking, body mass index, ethnicity, marital status, alcohol use and prior cancer.	2.5	N=10,531 hypnotic users (n=4338 zolpidem users) N=23,674 non-hypnotic users Mean age 54 years; Female 63%	NR	HRs [95%CI] for mortality <u>Any hypnotic use: doses/year tertiles</u> 1) 0.4-18 pills/year, mean 8, (n=3491); 3.60 (2.92- 4.44) 2) 18-132 pills/year, mean 57 (n=3548); 4.43 (3.67-5.36) 3) >132 pills/year, mean 469 (n=3490); 5.32 (4.50- 6.30) <u>Zolpidem only tertiles</u> 1) 5-130 mg/year, mean 60 (n=1453); 3.93 (2.98 to 5.17) 2) 130-800 mg/year,	HRs [95%CI] for incident major cancer <u>Any hypnotic use: doses/year tertiles</u> 1) 0.4-18 pills/year, mean 8, (n=3491); 0.86 (0.72-1.02) 2) 18-132 pills/year, mean 57 (n=3548); 1.20 (1.03-1.40) 3) >132 pills/year, mean 469 (n=3490); 1.35 (1.18-1.55) <u>Zolpidem only tertiles</u> 1) 5-130 mg/year, mean 60 (n=1453); 0.79 (0.60-1.04) 2) 130-800 mg/year, mean 360 (n=1456); 1.07 (0.83-1.39)

Drug	Study (Year); Location	Design	Duration (Years)	Subjects	Adverse Effects/ Lack of Efficacy Leading to Withdrawal, % (n/N)	Serious Adverse Effects, % (n/N) or Estimates of Risk	Specific Adverse Effects, % (n/N)
						mean 360 (n=1456); 4.54 (3.46-5.95) 3) >800 mg/year, mean 3600 (n=1427); 5.69 (4.58-7.07)	3) >800 mg/year, mean 3600 (n=1427); 1.28 (1.03- 1.59)
Zaleplon 5-10 mg	Ancoli-Israel, 2005[111] US and Europe	Open-label extensions to RCTs	1	N=576 older adults with chronic insomnia (mean age >70) No demographic information reported	Due to AEs: Pain 5% Somnolence or dizziness 4% GI changes 2% Cardiovascular changes 1% Lack of efficacy: NR	No deaths were noted	Headache 27% (155/576) Infection 13% (73/576) Backache 10% (58/576) Bronchitis/pharyngitis 11% (65/576) Dizziness 7% (43/576)
Eszopiclone 3 mg	Roth, 2005[112]	Open-label extensions to RCT	1	N=471 with chronic insomnia (360 who were on previously eszopiclone (ESZ-ESZ group) and 111 who were previously on placebo (PBO-ESZ group) in the	Due to AEs: Total 4% (18/471) ESZ-ESZ group 3% (11/360) PBO-ESZ group	Total 2% (11/471) Events were (number of participants) Chest pain 2 Accidental injury 2	Total, any AE 75% (325/471) Potentially treatment-related 31% (148/471) (ESZ-ESZ group

Drug	Study (Year); Location	Design	Duration (Years)	Subjects	Adverse Effects/ Lack of Efficacy Leading to Withdrawal, % (n/N)	Serious Adverse Effects, % (n/N) or Estimates of Risk	Specific Adverse Effects, % (n/N)
				RCT). Overall Mean age 46 Female 63%	6% (7/111) Most common reasons for withdrawal due to AEs were unpleasant taste and anxiety (2 patients each) Lack of efficacy: NR	Enlarged uterine fibroids 2 Anemia, atrial fibrillation, diabetes, joint disorder, and skin disorder (1 each). Two of these events resulted in withdrawal (By which effect not reported)	28% (99/360); PBO-ESZ group 44% (49/111)) Total, most common treatment-related Unpleasant taste 7% (32/471) Headache 5% (22/471) Somnolence 4% (18/471) Abnormal dreams 3% (14/471) Dizziness 2.5% (12/471)
Zolpidem, initial dose of 20 mg	Schlich, 1991[113] France	Open-label, prospective	0.5	N=107 with insomnia Mean age 63 Female 69%	Due to AEs: 5% during active treatment (5/107); 6.5% (7/107, including 2 patients during the placebo run-	NR	Total 43% (46/107) with 69 AEs 22% (24/107) had 42 events possibly treatment related,

Drug	Study (Year); Location	Design	Duration (Years)	Subjects	Adverse Effects/ Lack of Efficacy Leading to Withdrawal, % (n/N)	Serious Adverse Effects, % (n/N) or Estimates of Risk	Specific Adverse Effects, % (n/N)
					in phase)- Reasons not reported. Lack of efficacy: 2% (2/107)		including: Malaise 5 Vertigo 5 Anterograde amnesia 5 22 patients had 27 events which were considered unrelated to study drug (AEs not described)
BZDs							
Benzodiazepines and other	Jaussent, 2013[114] France	Prospective cohort	12 Median 8.9	n=1454 with hypnotic use (82% with ≥1 insomnia complaint) n=5242 without hypnotic use (70% with ≥1 insomnia complaint) Older adults, aged	NR	HRs for mortality, hypnotic use vs. no hypnotic use 1.03[a] [95% CI 0.84 to 1.28];	All-cause mortality With hypnotic use: 22% (326/1454) Without hypnotic use: 19% (981/5242) BZD use only:

Drug	Study (Year); Location	Design	Duration (Years)	Subjects	Adverse Effects/ Lack of Efficacy Leading to Withdrawal, % (n/N)	Serious Adverse Effects, % (n/N) or Estimates of Risk	Specific Adverse Effects, % (n/N)
				≥65 years; Female 59%			22% (238/1070) No BZD use: 19% (1069/5626)
Temazepam	Kripke 2012{Kripke, 2012 #3032} US	Matched cohort study Data were adjusted for age, gender, smoking, body mass index, ethnicity, marital status, alcohol use and prior cancer.	2.5	N=2076 temazepam users N=23,674 non-hypnotic users Mean age 54 years; Female 63%	NR	HRs [95%CI] for mortality <u>Temazepam only tertiles</u> 1) 1-240 mg/year, mean 98 (n=798); 3.71 (2.55-5.38) 2) 240-1640 mg/year, mean 683 (n=613); 4.15 (2.88-5.99) 3) >1640 mg/year, mean 7777 (n=665); 6.56 (5.03-8.55)	HRs [95%CI] for incident major cancer <u>Temazepam only tertiles</u> 1) 1-240 mg/year, mean 98 (n=798); 0.48 (0.30-0.77) 2) 240-1640 mg/year, mean 683 (n=613); 1.44 (1.05-1.98) 3) >1640 mg/year, mean 7777 (n=665); 1.99 (1.57-2.52)
Non-BZD (use 49%): zopiclone, zolpidem, zaleplon	Chen, 2012[108] Taiwan	Retrospective cohort	3	n=5693 with chronic ("long-term") insomnia and with hypnotic use, n=28,465 without	NR	HRs for dementia, hypnotic use vs. no hypnotic use All: 2.34[a] [95% CI	Dementia, hypnotic users: 4% (220/5693)

Drug	Study (Year); Location	Design	Duration (Years)	Subjects	Adverse Effects/ Lack of Efficacy Leading to Withdrawal, % (n/N)	Serious Adverse Effects, % (n/N) or Estimates of Risk	Specific Adverse Effects, % (n/N)
BZD (use 34%): nordazepam, clonazepam, flurazepam Other (use ~17%): trazodone, melatonin agonist				insomnia and no hypnotic use Patients aged 50 years or older; Female 56%		1.92 to 2.85]; Men: 2.28[a] [95% CI, 1.68 to 3.10]; Women: 2.39[a] [95% CI, 1.85 to 3.09]; Age, 50-65: 5.22[a] [95% CI, 2.62 to 10.41]; Age, >65: 2.33[a] [95% CI, 1.90 to 2.88]; BZD vs. non-BZD: 1.01[a] [95% CI, 0.76 to 1.33];	Dementia, controls: 1.5% (424/28,041)
Benzodiazepine and other hypnotics	Wang 2001{Wang, 2001 #3034} US	Case-control study Adjusted for age, gender, and several markers of frailty (comorbid disease severity, recent	Use of sedative-hypnotics was assessed in the 180 days before the index event	N=1222 cases who underwent surgical repair of a hip fracture N=4888 controls. (4-1 ratio)	NR	Adjusted odds ratio [95%CI] for hip fracture Benzodiazepine use 1.46 (1.21- 1.76)	NR

Drug	Study (Year); Location	Design	Duration (Years)	Subjects	Adverse Effects/ Lack of Efficacy Leading to Withdrawal, % (n/N)	Serious Adverse Effects, % (n/N) or Estimates of Risk	Specific Adverse Effects, % (n/N)
		hospitalizations, nursing home use, and use of other meds.)					
Melatonin agonists							
Ramelteon 4-16 mg	Uchiyama, 2011[115] Japan	Open-label, prospective	0.5 (includes two 1-week placebo run-in and out periods)	N=190 with chronic insomnia Mean age 47 Female 69%	Due to AEs: 4% (7/190). Types of AEs not indicated. Lack of efficacy: NR	Pyelonephritis and synovitis, 1 event each. Both required hospitalization.	Nasopharyngitis 24% (46/190) Headache 4% (7/190) Upper respiratory tract inflammation 6% (11/190) Eczema 6% (11/190)
Ramelteon 8-16 mg	Richardson, 2009[116] US	Open-label, prospective	1	N=1213 with chronic insomnia Adult group=965 (ages 18 to 64 years). Female 60%	Due to AEs: Adult group 12% (119/965) Older adult group 12% (29/248)	Overall: 3% (38/1213) Adult group (number of participants) Mortality: 2 (MVA) Prolactinoma 1 (possibly treatment	Ramelteon, 6 month use: Adult group Any AE: 81% (380/471) Nasopharyngitis 14% (67/471) Headache: 13%

Drug	Study (Year); Location	Design	Duration (Years)	Subjects	Adverse Effects/ Lack of Efficacy Leading to Withdrawal, % (n/N)	Serious Adverse Effects, % (n/N) or Estimates of Risk	Specific Adverse Effects, % (n/N)
				Older adult group=248 in older group (aged ≥65 years) Female 53%	Lack of efficacy: Adult group 18% (178/965) Older adult group 25% (61/248)	related) Chest pain 1 Cholelithiasis 1 Uterine fibroids 3 Older adult group (number of participants) Colon cancer 1 Bladder cancer 1 Chest pain 1 Cholelithiasis 1 Possibly treatment related (group not reported) Cerebrovascular accident Syncope	(63/471) Somnolence: 8% (36/471) Older Adult group Any AE: 83% (105/126) Nasopharyngitis 10% (13/126) Somnolence: 9% (11/126) Ramelteon, I year use: Adult group Any AE: 81% (300/370) Nasopharyngitis 15% (55/3700 Headache: 14% (50/370) Somnolence: 8%

Drug	Study (Year); Location	Design	Duration (Years)	Subjects	Adverse Effects/ Lack of Efficacy Leading to Withdrawal, % (n/N)	Serious Adverse Effects, % (n/N) or Estimates of Risk	Specific Adverse Effects, % (n/N)
							(30/370) <u>Older Adult group</u> Any AE: 89% (89/105) Nasopharyngitis 11% (11/105) Somnolence: 10% (10/105)

[a] adjusted for the possible confounding factors

AE = adverse effect; BZD = benzodiazepine; HR = hazard ratio; MVA = motor vehicle accident; non-BZD = non-benzodiazepine

Appendix F. Supporting Tables: Efficacy of Complementary and Alternative Medicine Interventions for Insomnia Disorder

Table F1. Complementary and alternative medicine interventions: Quality assessments of previous systematic reviews

Topic (Author, Year)	*A Priori* Design	Dual Review	Search Strategy	Inclusion Criteria	Included/ Excluded Identified	Study Charac-teristics	Study RoB	SoE	Statistical Analysis	Pub Bias	COI	Comments	Overall Assessment
Acupuncture Cheuk, 2012[117]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No		High
Homeopathy Cooper, 2010[118,119]	Yes	Can't answer	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No mention of how many independent data extractors	Fair
Valerian Taibi, 2007[120]	Yes	Can't answer	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No mention of how many independent extractors, how homogeneity assessed, assessment of publication bias	Fair

COI=conflict of interest; RoB=risk of bias; SoE=strength of evidence

Table F2. Complementary and alternative medicine interventions for insomnia disorder: risk of bias assessments

Study	Risk of Bias Assessment
Hachul, 2013[121]	Moderate-High: (if pooled)/High (if unpooled): Underpowered/no sample size calculation; possible Type II error; Attrition NR; Multiple comparisons correction unclear; Only PSG sleep values.
Harrison, 2013[122]	Moderate-High: Blocked randomization: one of a pair of matched participants "randomly selected" a bottle from box A or box B; the other of the pair got the bottle from the other box; may have low power due to small sample size; no power/sample size calculation; 6/34 (18%) attrition; completer-only analyses; most data for SOL is presented as 5-point categorical scale; no ITT analysis.
Huo, 2013[123]	Moderate: Randomized based on random number table; no power analysis and sample size/power calculation, but found significant differences; 0/60 (0%) attrition; blinding unclear.
Lin, 2013[124]	Low-Moderate: Not ITT analysis: computer-generated randomization; opaque envelopes; triple blinded with investigators, patients and statisticians blinded to treatment group; power analysis and sample size calculation; achieved desired sample size; 26/212 (12%) attrition; completer-only analyses
Abbasi, 2012[125]	Moderate: Assessor blinding unclear. Not ITT analysis. No correction for multiple comparisons; randomization suspect; possibly underpowered.
Afonso, 2012[126]	High: High attrition; No ITT analysis; Unblinded; no adjustment for multiple comparisons or 3-way comparisons
Hachul, 2011[127]	Moderate: Low attrition; no mention of how missing data were handled; possible reporting bias; no correction for multiple comparisons; possibly underpowered.
Zick, 2011[128]	Low-Moderate: Blinding and randomization adequate; possibly underpowered.
Naude 2010[129]	Included in Cooper 2010[118,119] SR.
Friedman, 2009[130]	Moderate: high attrition, no reporting of population characteristics by group.
Yeung 2009	Included in Cheuk 2012[117]
Morin 2005[131]	Included in Taibi, 2007[120]
Kirisoglu, 2004[132]	Low-moderate: low attrition; randomization method unclear.

ISI= Insomnia Sleep Index; NS= not significant; PSG= polysomnography; SE= sleep efficiency; SOL= sleep onset latency; TST= total sleep time

Table F3. Complementary and alternative medicine, placebo-controlled trials:[a] strength of evidence

Outcome	CAM Intervention	Number of Trials	n	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
PSQI Score	Acupuncture	8	364	WMD = -2.1 [-3.2 to -1.0]	High	Direct	Precise	Consistent	Undetected	Insufficient
	Adjunctive Acupuncture	4	206	WMD = -2.5 [-3.2 to -1.8]	High	Direct	Precise	Consistent	Undetected	Insufficient
	Magnesium	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Isoflavone	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Homeopathic complex	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Wuling capsule	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Simillimum	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Chamomile	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
Subjective sleep latency (minutes)	Acupuncture	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Adjunctive Acupuncture	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Magnesium	1	43	MD: -18 (-29.60 to -6.40)	Low	Direct	Imprecise	Unknown	Undetected	Insufficient
	Isoflavone	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Homeopathic complex	1	27	MD: -1.3[bc]	Moderate	Direct	Unknown	Unknown	Undetected	Insufficient
	Wuling capsule	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Simillimum	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Chamomile	1	34	MD: 1.3 (-2.59 to 5.19)	Low	Direct	Imprecise	Unknown	Undetected	Insufficient
Subjective total sleep time (minutes)	Acupuncture	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Adjunctive Acupuncture	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Magnesium	1	43	MD: 18 (-8.23 to 44.23)	Low	Direct	Imprecise	Unknown	Undetected	Insufficient
	Isoflavone	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Homeopathic complex	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Wuling capsule	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Simillimum	1	30	0.9[c]	High	Direct	Unknown	Unknown	Suspected	Insufficient
	Chamomile	1	34	MD" -24	Low	Direct	Imprecise	Unknown	Undetected	Insufficient

Outcome	CAM Intervention	Number of Trials	n	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
				(-70.30 to 22.30)						
Insomnia Severity Index (score)	Acupuncture	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Adjunctive Acupuncture	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Magnesium	1	43	MD: -1.63 (-3.06 to -.20)	Low	Direct	Precise	Unknown	Undetected	Insufficient
	Isoflavone	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Homeopathic complex	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Wuling capsule	0	NA	NA	NA	NA	NA	NA	NA	Insufficient
	Simillimum	0	NA	NA	NA	NA	NA	NA	Suspected	Insufficient
	Chamomile	1	34	MD: 0.3 (-2.91 to 3.51)	Low	Direct	Imprecise	Unknown	Undetected	Insufficient

CAM=complementary and alternative medicine; MD: mean difference; MP: mean proportion

[a] Other CAM studies did not have placebo control: Afonso et al 2012 compared passive stretching, yoga, and no treatment; Oliveira et al compared therapeutic massage, passive movement, and "control."

[b] On scale where 0 = 0-15 min; 1 = 15-30 min; 2 = 30-45 min; 3 = 45-60 min; and 4 = 60+ min; difference in medians reported as significant at 7.04 minutes.

[c] Measures of variance not reported and not calculable.

Appendix G. Supporting Tables: Comparative Effectiveness of Trials Across Intervention Types

Table G1. Head to head and comparison of intervention classes for insomnia disorder: risk of bias assessments

Study	Risk of Bias Assessment
Wang, 2014[133]	Moderate - Blinded, randomized, no attrition. Sleep diary measures are not valid for our purposes since they were started after only 3 weeks of treatment. Other (global) outcomes are okay to use.
Irwin, 2014[5]	Moderate. Assessors unaware of patient treatment assignment; Unclear participant blinding. Outcome assessors blinded. Low attrition. ITT analysis.
Guo, 2013[134]	Moderate - Personnel giving acupuncture unblinded. Participants and outcome assessors blinded. LOCF used for ITT analyses on patients who had at least one treatment, poor method. Okay attrition. Sleep outcomes basically unusable for data analysis purposes due to using only charts.
Tu, 2012[135]	High - Randomization procedure sounds like it may not have been random. Blinding mentioned, but unclear which part of the study was blinded. Only PSQI, no sleep outcomes reported.
Gross, 2011[136]	Moderate - Did not analyze with entire group due to a few drop-outs. Participants were not blinded. Did not appear to correct for multiple comparisons (unclear).
Guo, 2013[134]	Low – low attrition; outcomes and participants assessors blinded; allocation concealment.
Morin, 2009[137]	Moderate - Analyses do not include drop outs. Blinding for PCT and PCT part of combined, no blinding for CBT, etc. No mention of correcting for multiple comparisons. Select outcomes reported, but justified.
Huang, 2009[138]	High - Computer-generated randomization; unblinded; no mention of how many subjects in needle-rolling group were given clonazepam (possible cross-overs); subjects not described; used one-sided significance tests; low attrition.
Zavesicka, 2008[139]	High - subjects not blinded to treatment group (PSG scorer was blinded); may have low power due to small sample size; no power calculation; no blinding of trazodone; no attrition; cannot show effect of CBT, since there was not a group without CBT
Wu, 2006[89]	Moderate - Blinding only for medications; not ITT analysis; multiple comparisons correction unclear; low statistical power
Jacobs, 2004[90]	Moderate: placebo for active medication, but not for CBT; fidelity to meds based on self-report
Morin, 2003[140]	Moderate. Same study as a Morin 1999 study, reporting only on specific groups from the original trial. Blinding unclear. Low attrition, handling of missing data unclear. Only reporting on some groups from the original study.
Rosen, 2000[141]	High - Attrition over 20%. Blinding unclear. Handling of missing data unclear.
Morin, 1999[60]	Moderate - Analyses do not include drop outs. Blinding for PCT and PCT part of combined, no blinding for CBT, etc. No mention of correcting for multiple comparisons. Select outcomes reported, but justified. Placebo group has treatment after 3 months.
McClusky, 1991[142]	High: baseline characteristic NR; attrition NR; reporting bias(Carin)

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