

Combination Treatment for Chronic Insomnia Disorder in Adults:

An American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment.

Introduction: This systematic review provides supporting evidence for the accompanying clinical practice guideline on combination treatment for chronic insomnia disorder in adults.

Methods: The American Academy of Sleep Medicine (AASM) commissioned a task force (TF) of sleep medicine experts. A systematic review was conducted to identify studies that compared the use of combination treatment (behavioral-psychological treatment used concurrently with pharmacological treatment) to therapy with behavioral-psychological or pharmacological treatments. Statistical analyses were performed to determine the clinical meaningfulness of using various interventions to treat chronic insomnia in adults. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process was used to assess the evidence for making recommendations.

Results: The literature search resulted in 1134 articles, out of which 14 articles provided data suitable for meta-analyses. The TF provided a detailed summary of the evidence along with the quality of evidence, the balance of benefits and harms, patient values and preferences, and resource use considerations.

Keywords: chronic insomnia disorder, behavioral treatments, psychological treatments, pharmacologic treatments, combination therapy

INTRODUCTION

Insomnia is the most common sleep disorder encountered in the general population and clinical settings. Insomnia causes significant distress, functional impairment, and increases health care costs and risk for other disorders. Current clinical practice guidelines (CPG) recommend behavioral-psychological treatment and medications as single treatment modalities for insomnia. However, in clinical practice these two types of treatments are often used in combination, either simultaneously or sequentially. Despite this practice, important knowledge gaps remain: Is combined behavioral-psychological treatment and medication for insomnia more efficacious than either treatment alone? Is the potential harm greater with combined treatment than with either treatment alone? This systematic review addresses these important questions.

BACKGROUND

Chronic insomnia disorder is defined by persistent difficulties with sleep initiation and/or maintenance that are associated with daytime symptoms such as fatigue, sleepiness, cognitive difficulties (e.g., deficits in attention, concentration, or memory), and mood disturbances (e.g., depression, anxiety, or irritability).¹ The sleep disturbances and associated daytime consequences must be present at least 3 days/week for 3 months or longer and cannot be explained by inadequate sleep opportunity (i.e., insufficient time allotted for sleep) or sleep circumstances (e.g., inappropriate sleep environment).¹ Chronic insomnia disorder can occur in isolation but is more commonly comorbid with other medical (e.g., chronic pain disorder), mental health (mood or anxiety disorders), or sleep disorders (e.g., obstructive sleep apnea).

Insomnia symptoms are highly prevalent, with about one-third of adults reporting at least one insomnia symptom at any given moment.²⁻⁴ Estimates of chronic insomnia disorder prevalence range from 5-15%, clustering around 5-10% when stringent International Classification of Sleep Disorders (ICSD) or Diagnostic and Statistical Manual of

Mental Disorders (DSM) diagnostic criteria are applied.²⁻⁵ Epidemiological studies consistently show that chronic insomnia disorder is more common among women, middle-aged to older adults, individuals who regularly engage in shift work, and those with co-occurring medical and mental health disorders.⁴ Over a 5-year period, more than 10% of individuals who initially sleep well will develop insomnia. Among those already experiencing insomnia, nearly 60% will continue to have symptoms over the same period. Furthermore, individuals with insomnia are more likely to report persistence of their symptoms one year later than to report remission.⁶

Chronic insomnia disorder has been linked to reduced quality of life,⁷ decrements in perceived health,⁵ impaired role functioning,⁸ increased risk of cardiovascular disease,⁹⁻¹⁰ obesity,¹¹ hypertension and diabetes,^{12, 13} mental health and substance use disorders,^{14, 15-16} and suicidal thoughts and behaviors.¹⁷⁻¹⁸ In addition to its wide-ranging adverse effects on the individual, the economic impact of chronic insomnia is substantial. For example, the average 6-month total costs for adults with untreated insomnia are estimated to be at least \$1100 greater than for adults without insomnia,¹⁹ with direct and indirect costs estimated at more than \$150 billion in the US annually.²⁰

Treatment options for chronic insomnia disorder include both behavioral-psychological treatment and pharmacological treatment. Pharmacological therapies, which include over-the-counter sleep aids and prescription sleep-promoting medications, are widely available, easy to use, and generally well-tolerated. As a result, they are the most common treatments for chronic insomnia disorder. Over-the-counter sleep aids include antihistamines like diphenhydramine and doxylamine, melatonin, as well as herbal remedies such as valerian and chamomile. Increasingly, cannabis is also being used by adults with chronic insomnia disorder. However, most over-the-counter remedies are not regulated by the U.S. Food and Drug Administration (FDA) in the same way as prescription drugs. Additionally, there are limited data to support their short-term or long-term efficacy and safety.^{21-22, 23}

Table 1 summarizes medications commonly used to treat insomnia. Note that this table is not limited to medications recommended in the 2017 American Academy of Sleep Medicine (AASM) CPG, nor to medications with FDA approval for treatment of insomnia. Rather, it is intended to reflect common clinical practice. Over the past 20 years, prescriptions for FDA-approved benzodiazepine receptor agonists have steadily decreased, while prescriptions for trazodone have risen, despite the fact that this medication is not FDA-approved for treatment of insomnia, and has limited evidence of efficacy and safety for insomnia.²⁴ The newest class of FDA-approved medications are orexin/hypocretin receptor antagonists, which were introduced in 2014. Orexin/hypocretin is a peptide neurotransmitter that plays a role in regulating arousal. Prescriptions for sleep-promoting medications are most common among women, older adults, and non-Hispanic White adults.²⁵ Placebo-controlled studies generally support the efficacy and safety of prescription sleep-promoting medications for short-term use,^{26, 27} though evidence is more limited for their long-term use and safety concerns exist regarding the use of specific medications in certain subgroups. For instance, older adults may be particularly vulnerable to the risk of cognitive impairment and falls associated with benzodiazepine receptor agonists.

Among the behavioral-psychological treatment options, several single-component treatments exist that target specific behavioral (e.g., maladaptive sleep habits, irregular sleep scheduling) or cognitive factors (e.g., worry, dysfunctional beliefs, apprehension about sleep) that contribute to chronic insomnia. Cognitive-behavioral therapy for insomnia (CBT-I) describes a multicomponent intervention that integrates these single-component therapies to comprehensively target factors that may perpetuate insomnia. While the specific CBT-I components may vary, core components of CBT-I generally include both behavioral strategies (e.g., sleep restriction therapy, stimulus control therapy, relaxation) and cognitive strategies (e.g., cognitive restructuring, constructive worry). The most common

core components of CBT-I are described in Table 2. Complementary and alternative medicine therapies (e.g., acupuncture, yoga) and third-wave psychotherapy treatments (e.g., mindfulness-based practices, Acceptance and Commitment Therapy) have more recently been explored as treatments for chronic insomnia disorder. Limited randomized trial data characterizing their efficacy and safety exist.

Multiple systematic reviews and meta-analyses support the efficacy and safety of CBT-I in adults with chronic insomnia with and without comorbid medical and mental health disorders.²⁸⁻³⁵ CBT-I has demonstrated benefit in patients with insomnia and various common co-occurring conditions, including depression and other mental health disorders,^{36, 37} chronic pain,³⁸⁻⁴⁰ breast cancer,^{41, 42} and hypnotic dependence.⁴³ Overall, studies suggest that roughly 70-80% of patients receiving CBT-I experience a treatment response²⁸ and 40-50% achieve remission from insomnia post-treatment.^{44, 45} Initial treatment gains are additionally well-maintained over time, with post-treatment follow-up periods as long as 2-3 years.^{46, 47}

Existing CPGs issued by the AASM address behavioral-psychological and pharmacologic treatments separately. In 2017, the AASM issued its first CPG⁴⁸ for the pharmacological treatment of chronic insomnia, recognizing that pharmacotherapy was the most widely used therapy approach. Based on a systematic review and meta-analyses, the AASM task force (TF) provided conditional recommendations for medications appropriate for patients with sleep onset insomnia (triazolam, ramelteon, zaleplon), sleep maintenance insomnia (doxepin, suvorexant), and combined sleep onset and maintenance insomnia (temazepam, zolpidem, eszopiclone) compared to no treatment. The TF acknowledged that most of the studies included in support of these recommendations assessed only short-term use of medications. In addition, the TF provided conditional recommendations *against* the use of the following non-prescription and prescription medications for patients with either sleep onset or maintenance insomnia: trazodone, tiagabine, diphenhydramine, melatonin, tryptophan, and valerian. In short, recommendations in the AASM CPG generally align with the presence or absence of an FDA indication for treatment of insomnia among drugs available at the time. The most recent CPG by the AASM, issued in 2020, strongly recommended the use of multicomponent CBT-I for chronic insomnia in adults and provided conditional recommendations for multicomponent therapies for insomnia and the single-component therapies stimulus control, sleep restriction therapy, and relaxation therapy.⁴⁹ Importantly, sleep hygiene therapy received a conditional recommendation *against* its use as a single-component treatment for chronic insomnia, despite its widespread use in clinical practice.

The existing AASM CPGs do not explicitly address the relative benefits of behavioral-psychological versus pharmacological treatment in chronic insomnia disorder, nor the benefits and harms of combined pharmacologic and behavioral-psychological treatment. Recognizing this major gap in knowledge, the AASM commissioned the Combination Treatment for Insomnia in Adults TF. Combination treatment for chronic insomnia, whether used simultaneously or sequentially, is highly clinically relevant. Patients may receive medications while waiting for CBT-I in specialty clinics; others may be on medication for years before being recommended CBT-I; still others may initiate CBT-I or medication after experiencing only a partial therapeutic response with the other type of treatment. Thus, evidence-based guidance on this approach is critically needed. While sequences of treatment with behavioral-psychological treatments and pharmacotherapy may be most *clinically* relevant, most *research* evidence on combination treatment addresses the concurrent initiation of both treatment approaches, perhaps because such approaches are more amenable to traditional randomized controlled trials (RCTs). Accordingly, throughout this systematic review and accompanying CPG,⁵⁰ we use the term “combination treatment” to refer to behavioral-psychological treatments initiated concurrently with pharmacological treatments.

The aim of this review is to assess the efficacy of combination treatment (behavioral-psychological treatment used concurrently with pharmacological treatment) relative to treatment with either modality alone in adults with chronic insomnia disorder, evaluate the potential for treatment side effects, and identify gaps in the current literature to offer recommendations for future research. This systematic review provides supporting evidence for the accompanying CPG for combination treatment for chronic insomnia disorder in adults.⁵⁰

Table 1. Prescription and non-prescription medications commonly used to treat insomnia

Medication Class	Examples	Comments
Benzodiazepine receptor agonists (BzRA)	benzodiazepines: triazolam ^{1,2} , temazepam ^{1,2} , clonazepam non-benzodiazepines (Z-drugs): zolpidem ^{1,2} , zaleplon ^{1,2} , eszopiclone ^{1,2}	Pros: Widely available; range of pharmacokinetic properties (e.g., onset of action, half-life) to address different insomnia symptoms; established short-term efficacy. Cons: Risk of tolerance, dependence, and abuse; side effects including sedation, cognitive impairment, delirium, motor incoordination, falls, hip fractures, and parasomnias, next-morning impairment; caution in older adults.
Dual orexin receptor antagonists (DORA)	suvorexant ^{1,2} , lemborexant ^{1,3} , daridorexant ^{1,3}	Pros: Established short-term efficacy; lower risk for cognitive and psychomotor impairment vs. BzRA; low potential for abuse, dependence Cons: Potential for sedation, impaired alertness, motor incoordination, vivid dreams, sleep paralysis, next-morning impairment; higher cost.
Sedating antidepressants	doxepin ^{1,2} , trazodone, mirtazapine, amitriptyline	Pros: Short-term efficacy for sleep maintenance symptoms; generally well-tolerated; minimal risk for abuse Cons: Efficacy not well established except for doxepin 3-6 mg; side effects including sedation, cognitive and psychomotor impairment, anticholinergic effects.
Sedating antihistamines	diphenhydramine ¹ , doxylamine, hydroxyzine	Pros: Available over the counter Cons: Limited efficacy data; side effects including sedation, cognitive and psychomotor impairment, anticholinergic effects, e.g., dry mouth, confusion in older adults.
Melatonin, melatonin receptor agonists	melatonin, ramelteon ^{1,2}	Pros: Melatonin available over the counter; Ramelteon -efficacious for sleep onset insomnia Cons: Not efficacious for sleep maintenance insomnia; side effects include sedation, fatigue, dizziness, nausea, abnormal dreams
Sedating antipsychotics	quetiapine, olanzapine	Pros: May be useful for patients with comorbid mental disorders Cons: Limited efficacy data for insomnia disorder Side effects include sedation, cognitive and psychomotor impairment,

		hypotension, glucose and lipid dysmetabolism, weight gain.
Gabapentinoids	gabapentin, pregabalin	Pros: May be useful for comorbid insomnia and chronic pain Cons: Side effects include sedation, dizziness, cognitive and psychomotor impairment, depression.

Note: This table summarizes drugs commonly used in clinical practice for treatment of insomnia and does not represent AASM recommendations. Adapted from Morin and Buysse (2024)⁵¹; ¹FDA approved for insomnia. ²Weak recommendation for use in insomnia per 2017 AASM Clinical Practice Guideline. ³FDA approval after 2017 AASM Clinical Practice Guideline.

Table 2. Core components of CBT-I

Behavioral strategies	
Stimulus Control Therapy (SCT) ^a	Instructions designed to (1) extinguish the association between the bed/bedroom and wakefulness to restore the association of bed/bedroom with sleep, and (2) establish a consistent wake-time. Stimulus control instructions: (1) go to bed only when sleepy; (2) get out of bed when unable to sleep; (3) use the bed/bedroom for sleep and sex only (e.g., no reading or watching television in bed); (4) wake up at the same time every morning; and (5) refrain from daytime napping.
Sleep Restriction Therapy (SRT) ^a	A method to enhance sleep drive and consolidate sleep by limiting time in bed equal to the patient’s sleep duration, typically estimated from daily diaries. Time in bed is initially limited to the average sleep duration and is subsequently increased or decreased based on sleep efficiency thresholds until sufficient sleep duration and overall sleep satisfaction are achieved.
Relaxation Training ^a	Structured exercises designed to reduce somatic tension (e.g., abdominal breathing, progressive muscle relaxation, autogenic training) and cognitive arousal (e.g., guided imagery training, meditation) .
Cognitive strategies	
Cognitive restructuring	A structured therapeutic process designed to identify and modify unhelpful beliefs about sleep that may support sleep-disruptive habits and/or raise performance anxiety about sleeping. This process may include structured psychoeducation, use of thought records, Socratic questioning, and behavioral experiments.
Constructive worry	A method to reduce pre-sleep cognitive arousal and sleep-related worry by scheduling a time (about 15-30 minutes) to jot down concerns (worries, preoccupations, next-day tasks) and potential solution (problem-solving component) about two hours before bedtime .
Multicomponent behavioral and cognitive strategies ^a	CBT-I combines one or more of the cognitive therapy strategies with education about sleep regulation plus stimulus control and sleep restriction therapy. CBT-I also often includes sleep hygiene education, relaxation training, and other counter-arousal methods. Treatment progresses using information typically gathered with sleep diaries completed by the patient throughout the course of treatment (typically 4–8 sessions).

^a These components were previously described in AASM’s Behavioral and Psychological Treatments for Chronic Insomnia Disorder in Adults Systematic Review⁵²

METHODOLOGY

Expert Task Force

The AASM commissioned a TF of sleep medicine clinicians with expertise in the treatment of adults with chronic insomnia disorder to develop this systematic review. The TF was required to disclose all potential conflicts of

interest (COI) per the AASM's COI policy prior to being appointed to the TF and throughout the research and writing of these documents. In accordance with the AASM's COI policy, TF members with a Level 1 conflict were not allowed to participate. TF members with a Level 2 conflict were required to recuse themselves from any related discussion or writing responsibilities. All relevant conflicts of interest are listed in the Disclosures section.

PICO Questions

PICO (Patient, Intervention, Comparison, and Outcomes) questions were developed to assess the efficacy of combination treatment relative to treatment with either modality alone in adults with chronic insomnia disorder. The PICO questions were based on existing AASM practice parameters, systematic reviews, and other guidelines. The AASM Board of Directors approved the final list of PICO questions presented in **Table 3** before the literature searches were conducted. Through consensus, the TF then developed a list of patient-centered, clinically relevant outcomes to determine the efficacy of the interventions. The TF rated the relative importance of each outcome to determine which outcomes were *critical* versus *important* for decision making. A summary of these outcomes by PICO is presented in **Table 4**.

The TF identified a relatively large number of insomnia-related outcomes, several of which appeared to represent conceptually similar domains. Therefore, the TF grouped outcomes to assess the effect of combination treatment in adults with insomnia. Critical outcome domains included: *global insomnia severity* measures (Insomnia Severity Index [ISI], Pittsburgh Sleep Quality Index [PSQI]); *sleep continuity* (sleep efficiency [SE], sleep onset latency [SOL], wake after sleep onset [WASO]); and *daytime outcomes* (patient-reported fatigue, depression, anxiety, quality of life). Important outcomes included total sleep time (TST) and treatment side effects. Self-reported sleep continuity and total sleep time outcomes from sleep diary were prioritized by the TF for deriving recommendations.

The TF set a clinically meaningful threshold (CMT) for each outcome to determine whether the mean differences between treatment and comparator were clinically meaningful. The CMT was defined as the minimum level of improvement in the outcome of interest that would be considered clinically relevant to clinicians and patients. CMTs were determined based on a TF literature review of commonly used thresholds.⁵² When no clearly established threshold values could be determined, the TF used their clinical judgment and experience to establish a CMT based on consensus. A summary of the CMTs for the clinical outcome measures is presented in **Table 4**. In developing CMTs for these analyses, the TF first considered the thresholds previously established for differentiating any single treatment (i.e., behavioral-psychological treatment *or* medication) from placebo (or other control condition). We examined prior CPGs and meta-analyses for these values. Since we did not know *a priori* whether combination treatment yields larger effects than single treatments in comparison to placebo, we adopted the same CMTs established for single treatments in our comparison of combination treatment to placebo. These values are presented in the second column of **Table 4**. Next, in the absence of direct evidence to develop CMTs for combination treatment, the TF estimated after extensive deliberation, that CMTs for any comparison of combination treatment to single, active treatments would yield CMTs about half as large as comparisons to placebo. These CMT values are presented in the third column of **Table 4**.

Table 3. PICO questions

1	<p>In adults with chronic insomnia disorder, what are the benefits and harms of combination treatment compared to pharmacological treatment alone?</p> <p>Population: Adults with chronic insomnia disorder</p> <p>Intervention:</p>
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	<p>Behavioral-psychological - biofeedback; brief therapies for insomnia; cognitive behavioral therapy-insomnia (CBT-I); cognitive therapy; intensive sleep retraining; mindfulness; paradoxical intention therapy; relaxation therapy (e.g., abdominal breathing, imagery training, autogenic training); sleep hygiene education; sleep restriction therapy; stimulus control therapy</p> <p>Pharmacological - benzodiazepine receptor agonists (benzodiazepine and non-benzodiazepine agents); dual orexin receptor antagonists (DORA); sedating antidepressants (e.g., trazodone, doxepin, amitriptyline); sedating antihistamines (e.g., diphenhydramine, doxylamine); melatonin; melatonin receptor agonists; other drugs used to treat insomnia (e.g., gabapentin, pregabalin, sedating antipsychotics); other pharmacologically active agents used to treat insomnia (e.g., cannabis, herbal and naturopathic agents)</p> <p>Comparison: Pharmacological treatments alone, placebo</p> <p>Outcomes: Insomnia symptom severity, sleep quality, sleep continuity (sleep efficiency [SE], sleep onset latency [SOL], wake after sleep onset [WASO]), total sleep time (TST), daytime function (cognitive symptoms, mood symptoms, physical symptoms (e.g., fatigue, pain, headaches), quality of life, daytime sleepiness, treatment side effects</p>
2	<p>In adults with chronic insomnia disorder, what are the benefits and harms of combination treatment compared to behavioral-psychological treatment alone?</p> <p>Population: Adults with chronic insomnia disorder</p> <p>Intervention: Behavioral-psychological - biofeedback; brief therapies for insomnia; cognitive behavioral therapy-insomnia (CBT-I); cognitive therapy; intensive sleep retraining; mindfulness; paradoxical intention therapy; relaxation therapy (e.g., abdominal breathing, imagery training, autogenic training); sleep hygiene education; sleep restriction therapy; stimulus control therapy</p> <p>Pharmacological - benzodiazepine receptor agonists (benzodiazepine and non-benzodiazepine agents); dual orexin receptor antagonists (DORA); sedating antidepressants (e.g., trazodone, doxepin, amitriptyline); sedating antihistamines (e.g., diphenhydramine, doxylamine); melatonin; melatonin receptor agonists; other drugs used to treat insomnia (e.g., gabapentin, pregabalin, sedating antipsychotics); other pharmacologically active agents used to treat insomnia (e.g., cannabis, herbal and naturopathic agents)</p> <p>Comparison: Behavioral-psychological treatments alone, sham behavioral-psychological</p> <p>Outcomes: Insomnia symptom severity, sleep quality, sleep continuity (SE, SOL, WASO), TST, daytime function (cognitive symptoms, mood symptoms, physical symptoms (e.g., fatigue, pain, headaches), quality of life, daytime sleepiness, treatment side effects</p>

184

185

Table 4. Summary of clinically meaningful thresholds for individual outcome measures by PICO question

Outcome Measure(s)	Combination vs. placebo CMT	Combination vs single treatment CMT	# studies reporting measure PICO 1	# studies reporting measure PICO 2
Critical outcomes				
Insomnia severity ISI	- 4 points	- 2 points	1	4
Sleep quality PSQI	- 2 points	- 1 point	3	--
Sleep efficiency Diary	+ 7%	+ 3.5%	4	4

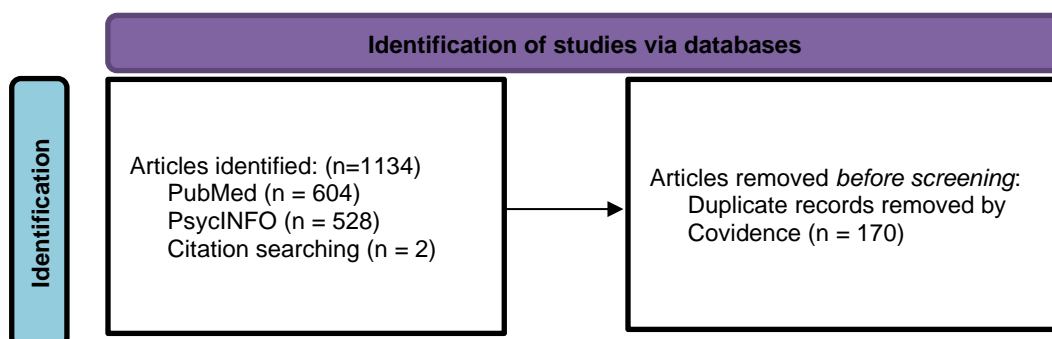
Outcome Measure(s)	Combination vs. placebo CMT	Combination vs single treatment CMT	# studies reporting measure PICO 1	# studies reporting measure PICO 2
Sleep onset latency Diary	- 15 minutes	- 7 minutes	2	3
WASO Diary	-15 minutes	- 7 minutes	3	2
Daytime function				
BAI	- 4 points	- 2 points	--	1
BDI	- 5 points	- 2.5 points	1	2
PSWQ	- 10 points	- 5 points	--	1
PHQ-9	- 2.5 points	- 1.25 points	1	--
PHQ-15	- 2.5 points	- 1.25 points	1	--
MFI	- 7 points	- 3.5 points	--	1
SF-36 ^a	+ 3 points	+ 1.5 points	--	1
ESS	- 2 points	- 1 point	--	1
Important outcomes				
Total sleep time Diary	+ 20 minutes	+ 10 minutes	6	5
Treatment side effects				
Adverse event tool	--	--	2	--
Narrative	--	--	3	--

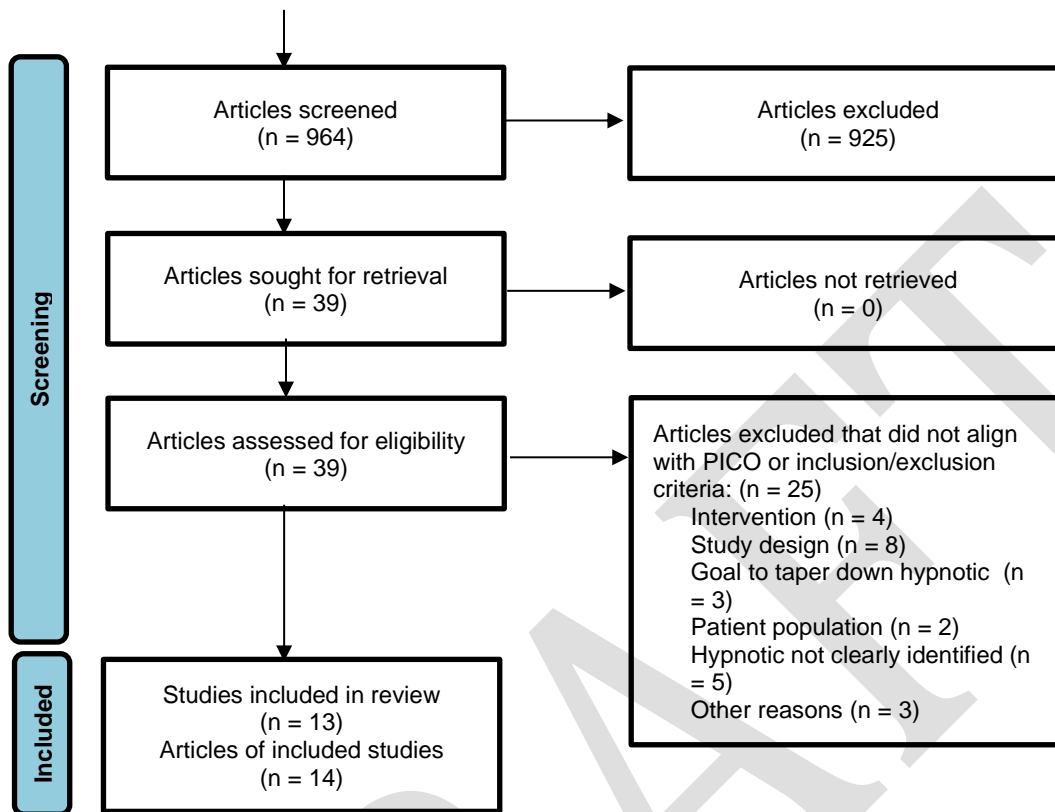
PICO – population intervention comparator outcome; CMT – clinically meaningful threshold; ISI – Insomnia Severity Index; PSQI – Pittsburgh Sleep Quality Index; WASO – wake after sleep onset; BAI – Beck Anxiety Inventory; BDI – Beck Depression Inventory; PSWQ – Penn State Worry Questionnaire; PHQ – Patient Health Questionnaire; MFI – Multidimensional Fatigue Inventory; SF-36 – 36-Item Short Form Survey (SF-36) Short form 36; ^a SF-36 physical and mental scores.
 -- Not reported

Literature Searches, Evidence Review and Data Extraction

The TF performed a review of the scientific literature to retrieve articles that addressed the PICO questions. The databases PubMed and PsycINFO were searched in October and November 2023, respectively (see Figure 1).⁵³ Index and free text terms reflective of the PICO questions such as insomnia disorder, behavioral treatments, psychological treatments, and pharmacologic treatments, as well as inclusion and exclusion criteria, are detailed in the supplemental materials (see Figures S1 – S36). The search was updated in October 2024. In addition, the references of included studies, relevant guidelines on the treatment of insomnia, systematic reviews, and meta-analyses were screened. Studies were reviewed based on inclusion/exclusion criteria by two TF members using Covidence (Melbourne, Australia). Discrepancies between reviewers were discussed and resolved by a third TF member. A total of 14 articles were included.

Figure 1. PRISMA flow diagram





Statistical and Meta-analysis and Interpretation of Clinically Meaningful Thresholds

Meta-analysis was performed on outcomes of interest for each PICO question (Table 3). Studies were excluded from the meta-analysis if missing data could not be calculated, imputed, or obtained from authors. Combination treatment was compared to single active treatment interventions. Medications were grouped together in the meta-analyses to increase statistical precision. The TF judged that comparisons of combination treatment to single active treatments were most relevant to clinical practice; clinicians are most likely to weigh combination treatment against either pharmacotherapy or behavioral-psychological therapy alone, rather than against no treatment or placebo. Therefore, results from the comparison of combination treatment to placebo are presented only at the end of the Supplemental materials. The results of these analyses indicated that, compared to placebo, combination treatment produced clinically meaningful improvements in the critical outcomes global insomnia severity and diary sleep continuity and in the important outcome diary total sleep time (Figures S34-S36).

Analyses were performed using Review Manager 5.3 software by pooling data across studies for each outcome measure. Immediate post-treatment data from each arm were used for meta-analysis of the RCTs. The pooled results for each continuous outcome measure were usually expressed as the mean difference (MD) between the intervention and comparator for RCTs. However, for some outcomes where different scales were pooled, a standardized mean difference (SMD) was determined. To guide interpretation of the SMD, we re-expressed the SMD by multiplying it by an estimate of the standard deviation (SD) associated with the most widely used instrument. The SD was calculated with a weighted average across all intervention groups of all studies that used the selected instrument (post-intervention SD). The summary effect was re-expressed in the original scale-specific units of the familiar instrument for clinical relevance and impact of the intervention effect. When pooling across instruments in a single

meta-analysis where some scales increase while other scales decrease, we multiplied the mean values from one set of studies by -1 to ensure that all the scales pointed in the same direction.⁵⁴ The pooled results for dichotomous outcome measures were expressed as the risk ratio or risk difference between the intervention and comparator. The relative risk data were converted to an absolute risk estimate expressed as the number of events/100 patients treated. Analyses were performed using either a fixed effects model or a random effects model with results displayed as a forest plot. Interpretation of clinically meaningful for the outcomes of interest was conducted by comparing the mean difference in effect size, or the risk difference for dichotomous outcomes, of each treatment approach to the CMT (Table 3).

GRADE Assessment for Developing Recommendations

The quality of the evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.^{55, 56} The TF considered the following four GRADE domains: certainty of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use, as described below:

1. **Certainty of evidence:** The TF rated their confidence that the estimate of the effect for each outcome was correct based on an assessment of the overall risk of bias (randomization, blinding, allocation concealment, selective reporting), imprecision (95% confidence interval crosses the CMT and/or sample size < 200 participants), inconsistency ($I^2 \geq 50\%$), indirectness (study population vs target patient population), and risk of publication bias. The overall certainty of the evidence is a combined rating based on all outcomes that the TF deemed critical for decision making. GRADE classifies the certainty of the evidence in one of four grades: high, moderate, low, or very low. Important outcomes are not considered when determining the overall certainty of evidence.
2. **Benefits vs. harms:** The TF assessed the balance of beneficial outcomes against any harms based on the best estimates of the desirable effects and the undesirable effects reported in the literature and on the clinical expertise of the TF.
3. **Patient values and preferences:** Based on the clinical expertise of the TF members and any data published on the topic relevant to patient preferences, the TF determined if patient values and preferences would be generally consistent across most patients, and if patients would use the intervention based on the relative harms and benefits identified.
4. **Resource use:** Based on the clinical expertise of the TF members, the TF judged whether the accessibility and costs associated with each treatment approach compared favorably to those associated with alternative treatments. Information on costs to patients and the health care system, impact on health equity, acceptability, and feasibility to implement the treatments were considered.

A summary of each GRADE domain is provided after the detailed evidence review for each PICO question.

Public Comment and Final Approval

Drafts of the systematic review and accompanying guideline were made available for public comment for a four-week period on the AASM website. AASM members, relevant interest holders (formerly referred to as stakeholders), and the general public were invited to provide feedback on the drafts. The TF took into consideration all the comments received and made decisions about whether to revise the draft based on the scope and feasibility

of comments. The public comments and revised documents were submitted to the AASM Board of Directors who subsequently approved the final documents for publication.

The AASM expects this systematic review to have an impact on professional behavior, patient outcomes, and possibly, health care costs. This review reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available.

RESULTS

The systematic review and data analyses address the two PICO questions regarding the efficacy of combination treatment interventions to treat chronic insomnia in adults. Detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF are shown below. Each evidence summary is accompanied by a discussion of the certainty of evidence, balance of benefits and harms, patient values and preferences, and resource use considerations that contributed to the development of the clinical practice recommendations; these recommendations are provided in the accompanying CPG.⁵⁰

PICO 1: Combination treatment compared to pharmacological treatment alone

Cognitive behavioral therapy for insomnia (CBT-I) plus pharmacological treatment vs pharmacological treatment alone

Six RCTs published in seven articles^{47, 57-62} investigated the use of CBT-I plus pharmacological treatment compared to pharmacologic treatment alone in adults with chronic insomnia disorder. Outcomes included one or more of the following: global insomnia severity measures, diary sleep continuity, daytime outcomes, diary TST, and/or treatment side effects. Study participants' mean age ranged from 38 to 65 years old with a majority female participants. Mean insomnia duration ranged from six months to 25 years. Five studies used in-person CBT-I and one study used a self-help CBT program. Treatment duration ranged from six to 16 weeks. Insomnia medications included lormetazepam 2 mg; temazepam 7.5 mg – 30 mg; zolpidem 10 mg; and zopiclone 3.75 mg – 7.5 mg. The meta-analyses are provided in the supplemental material, Figures S1 – S11 along with the summary of findings table, Table S1. A summary of the evidence for each outcome is provided below.

Critical Outcomes

GLOBAL INSOMNIA SEVERITY MEASURES: Four RCTs^{47, 58, 59, 61} were included in the meta-analysis of global insomnia severity measures. Insomnia medications included lormetazepam, temazepam, zolpidem, and zopiclone. Two studies reported global insomnia severity measured by the PSQI, one study used the ISI, and one study used the SII. The meta-analysis showed a clinically meaningful improvement in global insomnia severity in the combination treatment group compared to pharmacological treatment alone (SMD -0.67, 95% CI -0.97 to 0.36; n=178). When re-expressed in the units of the PSQI scale, the mean posttreatment PSQI score in the combination group was 2.5 points lower (95% CI -3.64 to -1.35; CMT -1 points) compared to pharmacological treatment alone; see supplemental material, Figure S1). The certainty of evidence was low due to risk of bias and imprecision.

DIARY SLEEP CONTINUITY: Four RCTs^{47, 57, 58, 62} were included in the meta-analysis of diary sleep continuity. Insomnia medications included lormetazepam, temazepam and zolpidem. Three studies reported SE and SOL, and two studies reported WASO. The meta-analysis showed a clinically meaningful improvement in sleep continuity in the combination group compared to pharmacological treatment alone (SMD -0.31, 95% CI -0.61 to -0.02; n=177). When re-expressed in SE units, the mean post-treatment SE in the combination group was 3.5% higher

(95% CI 0.23 to 6.89; CMT +3.5%) compared to pharmacological treatment alone. Re-expressed as SOL, the combination group fell asleep on average 7.6 minutes faster (95% CI -15.01 to -0.49; CMT -7 minutes) compared to the pharmacological treatment alone group. Re-expressed as WASO, the combination group was awake for 13.9 minutes less during the night (95% CI -27.4 to -0.9; CMT -7 minutes) compared to pharmacological treatment alone; see supplemental material, Figure S2). The certainty of evidence was low due to risk of bias and imprecision.

DAYTIME OUTCOMES: Three RCTs^{58, 59, 61} were included in the meta-analysis of daytime outcomes. Insomnia medications included lormetazepam, zolpidem, and zopiclone. Various questionnaires were used to measure daytime outcomes including the Beck Depression Index (BDI), Patient Health Questionnaire (PHQ-9), PHQ-15, and Penn State Worry Questionnaire (PSWQ). The meta-analysis did not show a clinically meaningful improvement in daytime outcomes in the combination group compared to pharmacological treatment alone (SMD -0.31, 95% CI -0.64 to 0.03; n=143). Re-expressed in the units of the BDI scale, the mean post-treatment BDI score in the combination group was 1.5 points lower (95% CI -3.16 to 0.15; CMT -2.5 points) compared to pharmacological treatment alone (see supplemental material, Figure S3). Thus, post-treatment depression symptom scores were lower in the combination group compared to the CBT-I alone group, but this difference was not clinically meaningful. The certainty of the evidence was low due to risk of bias and imprecision.

Important Outcomes

DIARY TOTAL SLEEP TIME: Four RCTs^{47, 57, 58, 62} measured TST via diary. Insomnia medications included lormetazepam, temazepam, and zolpidem. The meta-analysis did not show a clinically meaningful improvement in TST in the combination group compared to pharmacological treatment alone (MD -15.48, 95% CI -43.63 to 12.67; n=177; CMT +10 minutes; see supplemental material, Figure S4). The certainty of evidence was low due to risk of bias and imprecision.

TREATMENT SIDE EFFECTS: One study⁶⁰ measured reports of morning sleepiness with an adverse event questionnaire. Study participants were treated with temazepam. The analysis did not show an improvement in reports of morning sleepiness in the combination group compared to pharmacological treatment alone (RR 2.68, 95% CI 0.62 to 11.56; n=36). The absolute risk difference was 20 more reports per 100 (6 fewer to 46 more reports) participants in the combination group, i.e., more reports of sleepiness in the combination group. This outcome had no a priori CMT (see supplemental material, Figures S5-S9). The certainty of evidence was very low due to risk of bias and imprecision.

The supplement material describes additional data from the objectively measured outcomes using PSG (Figures S10 and S11). The analyses showed that combination treatment may have an increased effect on objectively measured sleep continuity and TST when compared to pharmacological treatment alone in adults with insomnia.

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of the evidence for PICO 1 was low. The quality of evidence was downgraded due to the risk of bias and imprecision (see supplemental material, Table S1).

BENEFITS VS. HARMS: The benefits of combination treatment compared to pharmacological treatment alone included clinically meaningful improvements in global insomnia severity measures and sleep continuity. The improvement in daytime outcomes was not considered clinically meaningful. The TF judged these desirable effects (benefits) as small. TST and morning sleepiness analyses did not show better outcomes for combination treatment

compared to pharmacotherapy alone, and the meta-analysis of TST could not exclude a beneficial effect for pharmacological treatment alone. Only one study compared side effects, finding more frequent reports of morning sleepiness in the combination group. The TF judged these undesirable effects (harms) as minimal. Based on these findings and the TF's clinical experience, they judged that the potential benefits of combination treatment outweigh the potential harms.

RESOURCE USE: The estimated cost for CBT-I is \$100 - \$200 per session.⁶³ When evaluating resource use, the cost of insomnia medication was not considered since it is included in both the intervention and the comparator groups. The TF judged the additional costs of CBT-I in the combination treatment as moderate.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is possibly important uncertainty and/or variability in how much patients value the efficacy outcomes. Given that two critical outcomes reached the CMT, the TF judged that most adults with chronic insomnia would generally select combination treatment over pharmacological treatment alone.

PICO 2: Combination treatment compared to behavioral-psychological treatment alone

Cognitive behavioral therapy for insomnia (CBT-I) plus pharmacological treatment vs CBT-I alone

Six RCTs published in seven articles^{45, 47, 57, 61, 62, 64, 65} investigated the use of CBT-I plus pharmacological treatment compared to CBT-I alone in adults with chronic insomnia disorder to improve one or more of the following: global insomnia severity measures, diary sleep continuity, daytime outcomes, and/or diary TST. Study participants' mean age ranged from 38 to 65 years old, with a majority female participants across studies arms. Mean insomnia duration ranged from six months to 20 years. All studies used in-person CBT-I and treatment duration ranged from six to 10 weeks. Insomnia medications included temazepam 7.5 mg – 30 mg; trazodone 100 mg; zolpidem 10 mg; and zopiclone 3.75 mg – 7.5 mg. The meta-analyses are provided in the supplemental material, Figures S12 – S17 along with the summary of findings table, Table S2. A summary of the evidence for each outcome is below.

Critical Outcomes

GLOBAL INSOMNIA SEVERITY MEASURES: Four RCTs^{45, 47, 61, 65} were included in the meta-analysis of global insomnia severity measures. Insomnia medications included temazepam, trazodone, zolpidem, and zopiclone. Three studies reported global insomnia severity measured by the ISI and one study used the Sleep Impairment Index (SII). For one study⁶¹ the posttreatment data for the combination arm were extracted at five weeks while the posttreatment data for the CBT-I arm were extracted at 10 weeks. This approach ensured that the analysis compared the groups after receiving the same number of CBT-I sessions albeit over different durations. The meta-analysis showed little to no difference in global insomnia severity measures for combination treatment group compared to the CBT-I group (SMD 0.10, 95% CI -0.17 to 0.37; n=228). When re-expressed in the units of the ISI scale, the mean post-treatment ISI score in the combination group was 0.45 points higher (95% CI -0.77 to 1.67; CMT -2 points) compared to the CBT-I alone group. See supplemental material, Figure S12. The certainty of evidence was moderate due to risk of bias.

DIARY SLEEP CONTINUITY: Four RCTs^{45, 47, 57, 62} were included in the meta-analysis of sleep continuity. Insomnia medications included temazepam and zolpidem. Four studies reported SE, three studies reported SOL, and two studies reported WASO. The meta-analysis did not show a clinically meaningful improvement in sleep continuity in the combination group compared to the CBT-I alone group (SMD -0.11, 95% CI -0.35 to 0.13; n=261). When re-expressed in SE units, the mean post-treatment SE in the combination group was 1.28% higher

(95% CI -1.51 to 4.06; CMT +3.5%) compared to CBT-I alone. Re-expressed as SOL, combination treatment participants fell asleep on average 2.63 minutes faster (95% CI -8.37 to 3.11; CMT -7 minutes) compared to CBT-I alone participants. Re-expressed as WASO, the combination group was awake for 4.48 minutes less (95% CI -14.25 to 5.29; CMT -7 minutes) during the night compared to the CBT-I alone group (see supplemental material, Figure S13). None of these differences met the pre-specified CMT. The certainty of the evidence was low due to risk of bias and imprecision.

DAYTIME OUTCOMES: Three RCTs^{61, 64, 65} were included in the meta-analysis of daytime outcomes. Insomnia medications included trazodone, zolpidem, and zopiclone. Various questionnaires were used to measure daytime outcomes, including the Beck Anxiety Index (BAI), BDI, Epworth Sleepiness Scale (ESS), Multidimensional Fatigue Inventory (MFI), PSWQ, and the 36-item Short Form Survey (SF-36) physical and mental components. The meta-analysis did not show a clinically meaningful improvement in daytime outcomes in the combination group compared to the CBT-I alone group (SMD 0.39, 95% CI 0.10 to 0.68; n=191). Re-expressed in the units of the BDI scale, the mean post-treatment BDI score in the combination group was 2.1 points higher (95% CI 0.54 to 3.67; CMT -2.5 points) compared to the CBT-I alone group (see supplemental material, Figure S14). In other words, post-treatment depression symptom scores were higher in the combination group compared to the CBT-I alone group. The certainty of the evidence was moderate due to risk of bias.

Important Outcomes

The TF determined total sleep time to be an important (but not critical) outcome for evaluating the efficacy of CBT-I plus pharmacological treatments.

DIARY TOTAL SLEEP TIME: Four RCTs^{45, 47, 57, 62} measured TST via sleep diary. Insomnia medications included temazepam and zolpidem. The meta-analysis showed a clinically meaningful improvement in TST in the combination group compared to CBT-I alone (MD 13.81 minutes, 95% CI -6.78 to 34.41; n=261; CMT +10 minutes; see supplemental material, Figure S15). The certainty of evidence was low due to risk of bias and imprecision.

TREATMENT SIDE EFFECTS: None of the studies identified in our literature review reported data for treatment side effects for PICO 2.

The supplement material describes additional data from the objectively measured outcomes using PSG (Figures S5 and S6). The analyses showed that combination treatment had little to no effect on objectively measured sleep continuity or total sleep time when compared to CBT-I alone in adults with insomnia.

OVERALL CERTAINTY OF EVIDENCE: The TF determined that the overall certainty of the evidence for PICO 2 was low. The certainty of evidence was downgraded due to the risk of bias and imprecision (see supplemental material, Table S2).

BENEFITS VS HARMS: The potential desirable effects (benefits) of combination treatment were deemed minimal when compared to CBT-I alone. This decision was based on the fact that only one meta-analysis (diary TST) found a clinically meaningful improvement for combination treatment compared to CBT-I alone. The treatment-related improvement in daytime symptoms was smaller in the combination group than the CBT-I alone group. However, this potential benefit in favor of CBT-I (which is also considered a "harm" related to combination treatment) did

not reach the clinical meaningfulness threshold. No study included measures of undesirable effects (harms), such as treatment side effects. Based on their clinical experience, the TF rated harms of combination treatment as minimal relative to CBT-I alone. Overall, the TF judged that the potential benefits of combination treatment do not outweigh the potential harms.

RESOURCE USE: The current unit cost of temazepam is \$0.07 for a 15 mg capsule and \$0.09 for a 30 mg capsule; trazodone costs \$0.06 for a 100 mg tablet; and zolpidem costs \$0.04 for a 10 mg tablet.⁶⁶ Brand name drugs may augment these costs. When evaluating resource use, the cost of CBT-I was not considered since it is included in both the intervention and the comparator groups. The TF judged the added costs of medications in combination treatment to be negligible, assuming generic hypnotic medications are used.

PATIENTS' VALUES AND PREFERENCES: The TF judged that there is possibly important uncertainty and/or variability in how much patients value the main outcomes. Given that none of the critical outcomes reached the CMT, the TF judged that most adults with chronic insomnia would generally not select combination treatment over CBT-I alone.

OTHER INTERVENTIONS

The TF also identified studies reporting evidence for interventions in which the GRADE process was not applied. These interventions were not considered for recommendations in the accompanying clinical practice guideline because they had limited data on critical or important outcomes. The interventions, in alphabetical order, included: combination treatment of behavioral therapy plus triazolam compared to triazolam alone⁶⁷; combination treatment of biofeedback plus zolpidem compared to zolpidem alone⁶⁸; combination treatment of psychotherapy plus estazolam compared to estazolam alone⁶⁹; and combination treatment of relaxation therapy plus estazolam compared to estazolam alone.⁷⁰ Generally, the analyses showed improvements in sleep outcomes for the combination group compared to pharmacological treatment alone, similar to those described in PICO 1 analyses that included CBT-I plus pharmacological treatment (see supplemental material, Figures S18-S33).

DISCUSSION & FUTURE DIRECTIONS

This systematic review and meta-analysis evaluated evidence regarding the efficacy of combination treatment for insomnia compared to pharmacological treatment alone (PICO1) or behavioral-psychological treatment alone (PICO2). The target population was adults with chronic insomnia disorder. Overall, the evidence for critical outcomes (i.e., global insomnia symptoms, sleep continuity, daytime symptoms) does not support the use of combination treatment over behavioral-psychological (e.g., CBT-I) alone (PICO 2). However, patients who prioritize increasing TST (an important, but not critical, outcome in our analyses) may reasonably choose combination treatment over CBT-I alone. The evidence for critical outcomes supports the use of combination treatment over pharmacologic treatment alone. However, the additional costs of CBT-I may be a barrier for certain patients. The review is a comprehensive summary of the evidence to date and is intended to provide clinicians and researchers with a resource to guide their treatment of insomnia and to guide future research. The conclusions drawn by this review are limited by our selection criteria, the small number of studies included, and the associated limitations of these studies, reviewed below.

The findings from our systematic review are broadly consistent with other recent studies evaluating the efficacy of combination treatment. A systematic review and network meta-analysis (NMA) by Zhang et al.,⁷¹ for example,

examined 23 randomized controlled trials (RCTs) that compared various psychotherapies for insomnia (e.g., CBT-I, sleep restriction, and stimulus control) to pharmacotherapy. The review also included studies comparing the combination of psychotherapy and pharmacotherapy to either treatment alone. NMA allows comparison of multiple interventions or treatments, even if they were not directly compared in head-to-head trials. Our analysis, by contrast, used more traditional meta-analysis methods that are considered standard in the development of clinical practice guidelines, focusing only on studies with direct comparisons. Of the 10 publications included in the current systematic review and meta-analysis, six^{45, 47, 57, 61, 62, 65} were also reviewed by Zhang et al.⁷¹ Consistent with the findings from the present review, Zhang and colleagues found that combination treatment (psychotherapy plus pharmacotherapy) was more effective than pharmacotherapy alone for improving insomnia severity, increasing SE, and decreasing subjective WASO and SOL (subjective and objective). However, combination treatment was not superior to psychotherapy treatment (specifically CBT-I) alone on any outcome measures. Thus, despite differences in study methods, our findings closely resemble those of Zhang et al. and lend confidence to our conclusions.

A more recent systematic review and NMA by Furukawa et al.⁷² of 13 RCTs also included six of the same studies reviewed in the current analysis.^{45, 47, 57, 61, 62, 65} The primary outcome of Furukawa et al.⁷² was treatment remission, assessed by a validated self-report measure (e.g., ISI ≤ 7), at post-treatment and at long-term follow-up (3 to 12 months). Subjective sleep continuity metrics (SE, TST, SOL, WASO) were secondary outcomes. Consistent with the findings of our review, Furukawa and colleagues found no evidence that combination treatment was superior to CBT-I at post-treatment. However, combination treatment was superior to pharmacotherapy alone at post-treatment in terms of remission rates and subjective WASO. Taken together, the efficacy findings of these two NMAs and our systematic review suggest a consistent pattern: combination treatment is not superior to CBT-I alone for improving critical insomnia outcomes but, when compared to pharmacotherapy alone, combination treatment produces clinically meaningful improvements in remission, sleep quality, and sleep continuity measures.

Several factors beyond efficacy are considered in the GRADE process and may represent barriers or facilitators to the use of the treatments reviewed in this systematic review and meta-analysis. An individual patient's values or clinician's judgment of specific sleep-related outcomes as clinically important may drive treatment selection. For instance, the evidence in this systematic review indicates that combination treatment may have a larger effect on sleep duration than CBT-I alone. Therefore, patients or clinicians who consider longer sleep duration a particularly important clinical outcome may prefer combination treatment to CBT-I alone. The evidence also suggests situations when a patient or clinician's values and preferences may lead to the choice of pharmacotherapy alone. For example, a patient may value the lower cost and time commitment of pharmacotherapy alone over combination treatment.⁴⁸

Translating the findings of this systematic review and meta-analysis to clinical practice also requires an appreciation of "clinically meaningful" thresholds. The GRADE process used to evaluate evidence requires that the TF establish "clinically meaningful" thresholds representing a meaningful difference between treatments for the critical and important outcomes. These thresholds were established by consensus based on prior meta-analyses^{48, 52} as well as the TF's expertise and clinical experience, because there are no empirically validated thresholds in the literature for many of the outcomes evaluated. The TF defined thresholds that were considered reasonable given what is known about combination treatment and each therapy alone at this time. The TF recognizes that these thresholds may evolve with information from future research on patient-centered outcomes of combination treatment.

Limitations

Limitations in the available evidence from published studies in this systematic review affected the TFs ability to draw definitive conclusions. Most notably, a total of 10 publications comprised the entirety of the data informing

the guideline documents. This low number reflects both the dearth of published literature on this important topic as well as the TF's specific definition of combination treatment: concurrent initiation of behavioral-psychological and pharmacological treatment. Thus, studies that focused on sequential combination treatments (e.g., starting with CBT-I followed by pharmacotherapy, or vice versa) were excluded from this systematic review. Sequential intervention studies can use a variety of study designs that are difficult to evaluate in meta-analyses. For instance, some sequential studies do not include randomized treatment assignment, add a second treatment only to treatment non-responders, do not report pre-treatment data prior to the first treatment, or vary with regard to maintaining the first treatment after addition of the second. Nevertheless, excluding such studies limits the applicability of the findings to real-world clinical scenarios, where sequential combination treatment may often be employed. Sequential strategies might yield different outcomes compared to concurrent treatments, particularly in terms of patient adherence, timing of effects, and long-term efficacy.

Specific limitations from our systematic review include the following:

1. Studies from a single academic medical center: Multiple studies in our review originated from a single academic medical center. While this demonstrates the institution's commitment to advancing insomnia research, it may raise concerns about the generalizability of the findings. The demographic, cultural, and healthcare system-related factors specific to that center's patient population may not reflect broader, more diverse populations. This limitation underscores the need for research conducted across multiple settings to ensure that recommendations are broadly applicable.

2. Small sample sizes. All but one of the studies in the final analytic sample were smaller than 100; the remaining study had a sample size of N=160. Small sample sizes may increase sampling error and cause biased results. Thus, the certainty of evidence is affected.

3. Limited study of subpopulations. Although insomnia disorder affects a broad spectrum of individuals across demographic and mental and physical health-related variables, these characteristics were not specifically addressed in the reviewed literature. Thus, we caution against extrapolating findings to important subpopulations that a clinician may treat. For instance, the race/ethnicity of study participants was only reported by a single study, which reported that 100% of participants were White. Furthermore, studies often excluded participants with health comorbidities (e.g., depression, other sleep disorders) or if they were taking medications that might affect sleep (e.g., steroids, psychotropics). Patients with insomnia in clinical practice often have comorbid medical and mental health conditions and medications.

4. Limited pharmacological treatments studied. While a number of pharmacological agents are used in the treatment of insomnia in practice, benzodiazepine receptor agonists were studied in more than half of the publications analyzed in the guideline documents. Our review included studies using pharmacological agents that are not available in the US (e.g., nitrazepam). However, these medications are benzodiazepines and have sleep effects similar to other benzodiazepines that are available in the United States. Our review did not include several common drug classes (e.g., DORAs, melatonin receptor agonists) as there were no data available regarding the efficacy of combination therapy involving these medications. Given the small number of studies overall, insomnia medications were grouped together in meta-analyses. Such grouping could, however, decrease precision if different medications have different effects. Combining medication classes limits the ability to draw conclusions about whether benefits and harms differ across hypnotic medications with different mechanisms of action.

5. *Behavioral/psychological treatment limitations.* Four RCTs included behavioral-psychological treatments other than CBT-I but none included sufficient data on critical or important outcomes to inform the systematic review. In addition, the specific content and modality of CBT-I varied across the included studies. For example, while educational, behavioral, and cognitive treatment components appeared in all RCTs, relaxation was included in only three studies. Similarly, CBT-I was delivered individually, in small groups, and via a self-help manual. As a result, the TF could only draw conclusions regarding CBT-I as the behavioral-psychological treatment and could not comment on the relative benefits and risks of different constituent treatment components or delivery modalities. The combination treatment studies in this systematic review included only behavioral-psychological and pharmacological treatments that have evidence for efficacy as single treatments. Thus, we did not consider studies that used “sleep hygiene” instructions as the behavioral-psychological intervention. Although “sleep hygiene” is commonly used with medications in clinical practice,⁷³ it has not been shown to be efficacious in the treatment of chronic insomnia.⁴⁹ Consequently, our systematic review does not address its efficacy as a combination therapy.

6. *Lack of data on adverse effects.* Although the guideline emphasizes the potential benefits of combination treatment, information on potential short-term side effects and long-term adverse outcomes of these therapies remains sparse. Given that the risk-benefit profile of combination therapy is crucial in clinical decision-making, this absence of detailed adverse effect data leaves a critical gap. The lack of robust safety data affects the TF’s ability to comprehensively evaluate whether the benefits of combination therapy outweigh potential risks, which is essential for clinicians to make fully informed recommendations to patients.

7. *Lack of long-term follow-up data.* We only considered post-treatment outcomes in our meta-analysis. Therefore, we cannot comment on the durability of any benefits with combination treatment, or the relative benefits and harms of combination therapy compared with psychological/behavioral or pharmacological treatment alone long-term.

In light of these limitations, caution is warranted in interpreting the data in this analysis and in applying our findings. The findings also highlight the importance of individualized patient assessment, shared decision-making, and the need for further research to address knowledge gaps and strengthen the evidence base for combination therapy in chronic insomnia disorder.

Future Research

The current systematic review and meta-analysis identified several knowledge gaps to be addressed in future clinical trials of combination treatment for insomnia in adults. Future clinical trials should:

1. Determine the heterogeneity of treatment effects for combination compared to single-component therapies in different patient subgroups. Relevant subgroups could include (but are not limited to) different racial/ethnic minority groups, different cultural groups, patients with low health literacy, neurodivergent patients, patients who require assistance with activities of daily living, or patients living in institutional settings (e.g., nursing homes).
2. Be conducted with patients presenting with comorbidities³¹ such as depression,⁷⁴ pain,^{75, 76} substance misuse,⁷⁷ or sleep apnea.⁷⁸ Incorporating patient-centered approaches and interest holders in the design of combination trials to determine patient uptake and preferences would also be useful.

3. Test additional medications, such as orexin receptor antagonists (e.g., suvorexant, daridorexant, lemborexant) and sedating antidepressants (e.g., trazodone, doxepin, mirtazapine) given their distinct mechanisms of action, effects on sleep, and side effect profiles compared to benzodiazepine receptor agonists. These medications may also have distinct effects in some of the specific patient populations described above.
4. Evaluate other behavioral-psychological therapies combined with pharmacotherapy beyond those included in the meta-analyses. For example, it would be helpful to evaluate outcomes in combination therapy trials involving brief behavioral therapy for insomnia (BBT-I), mindfulness-based behavioral therapy for insomnia (MBT-I) or single-component behavioral-psychological treatments (e.g., combination of stimulus control therapy plus pharmacotherapy compared to sleep restriction therapy plus pharmacotherapy).
5. Include direct and systematic assessments of adverse effects and harms associated treatment. Methods to mitigate potential risks associated with combination treatment also need to be systematically evaluated, such as using alternatives to sleep restriction therapy or using other methods to attenuate its potential synergistic effect on undesired daytime symptoms (e.g., sleepiness) when combined with pharmacotherapy.
6. Include long-term follow-ups to establish whether any clinically meaningful differences between combination treatment and single treatments are maintained.
7. Include simultaneous assessments of subjective and objective sleep parameters. In line with prior research recommendations,⁵² such studies should evaluate the utility of objective sleep monitoring, including novel methods for conducting and analyzing PSG, research actigraphy, and consumer sleep devices. Such studies could contribute to understanding heterogeneity of treatment effects and treatment-relevant phenotypes based on objective measures.
8. Systematically incorporate assessments of daytime symptoms, functional impairment, and quality of life, as different pharmacotherapies combined with different behavioral-psychological therapies may produce varying daytime functioning effects (e.g., fatigue, functional impairment).^{79, 80} Future combination trials should also incorporate cardiovascular, metabolic or brain health outcomes, such as blood pressure or cognition.
9. Address design issues such as randomization based on specific insomnia phenotypes or therapies matched to phenotypes. For example, the clinically meaningful impact of combination treatment compared to CBT-I alone on TST should be carefully tested among insomnia phenotypes based on objective short sleep duration.⁸¹⁻⁸³
10. Seek to improve our understanding of the moderators and mediators of response to combination treatment compared to either therapy alone.
11. Address important clinical implementation issues such as whether sequential (CBT-I followed by pharmacotherapy or vice-versa) compared to simultaneous (CBT-I plus pharmacotherapy) forms of delivery of combination treatment produce differential benefits and harms.⁸⁴ Trial designs that involve sequential randomizations, such as a sequential, multiple assignment, randomized trial (SMART),⁸⁵ micro-randomized trial (MRT)⁸⁶ and the hybrid experimental design (HED)⁸⁷ may help to empirically optimize the sequencing and adaptation of interventions.

12. Include placebo arms and appropriate sham-controls. Placebo pharmacotherapy conditions are relatively straightforward, but future combination trials should also consider behavioral-psychological comparators that are inactive yet credible.

Summary

Despite its apparent widespread clinical use, this systematic review and meta-analysis found relatively few studies that empirically addressed the efficacy and harms of combined behavioral-psychological treatment and pharmacotherapy for insomnia compared to either treatment alone. On the basis of critical and important clinical outcomes and clinically meaningful thresholds, we did not find evidence that combination therapy had better outcomes than CBT-I alone. We did, however, find evidence for better outcomes for combination therapy compared to medication alone. The findings in this review are limited by the relatively small number of eligible studies; by small numbers of participants; by relatively homogenous participant samples; by limited range of pharmacological agents; and by short follow-up intervals. Our findings highlight the need for additional studies that address these limitations, and that include study designs and populations more closely reflecting clinical practice.

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