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Abbreviations

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
BT	behavioural therapy
CAM	complementary and alternative medicine
CBT	cognitive behavioural therapy
CBT-I	cognitive behavioural therapy for insomnia
CI	confidence interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalography
EMG	electromyography
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICSD	International Classification of Sleep Disorders
ISI	Insomnia Severity Index
MA	meta-analysis
NRCT	non-randomized controlled trial
PICO	population, intervention, comparison, outcome
PSQI	Pittsburgh Sleep Quality Index
PSG	polysomnography
PTSD	post-traumatic stress disorder
QoL	quality of life
RCT	randomized controlled trial
RDC	Research Diagnostic Criteria
SE	sleep efficiency
SF-36	Short Form (36) Health Survey
SQ	sleep quality
SR	systematic review
SR+MA	systematic review plus meta-analysis
SS	sleep satisfaction
SOL/SL	sleep onset latency/sleep latency
TST	total sleep time
WASO	wake after sleep onset

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Protocol Amendments

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Executive Summary

Background

Insomnia is a common disorder in the general Canadian population. While precise estimates vary, approximately 40% of Canadian adults (18 years of age and older) report at least one symptom of insomnia three times per week and about 10% to 13% meet criteria for an insomnia disorder.[1,2] Persistent insomnia has a negative impact on the individual and society, as it is linked to reduced quality of life (QoL) due to problems with attention and memory, mood disturbances, lower ratings of enjoyment of interpersonal relationships, and more days unable to work or carry out normal daily activities than those without insomnia.[3] Furthermore, studies have indicated that insomnia may be an important risk factor for the onset of mental health disorders such as depression, anxiety, and substance abuse disorders.

Both pharmacological and non-pharmacological approaches are used in the management of insomnia, either alone, or in combination. Health Canada–approved pharmacological therapies for insomnia include benzodiazepine drugs (e.g., temazepam, lorazepam), non-benzodiazepine receptor agonists, also referred to as "z-drugs" (e.g., zopiclone, zolpidem), and doxepin, a sedating antidepressant drug. Several drugs belonging to various classes (anxiolytic benzodiazepine drugs, antipsychotic drugs, antidepressant drugs) are also prescribed for insomnia despite having no approved indication for insomnia.[4] The safety of pharmacological therapies for the treatment of insomnia — especially risks associated with long-term use — has been an increasing area of uncertainty. Moreover, benzodiazepine drugs and z-drugs alone have been associated with substantial costs for payers (public and private), regardless of the indication.[5]

Cognitive behavioural therapy (CBT) is the most common non-pharmacological intervention used in the management of insomnia; it is a multimodal intervention that combines behavioural and cognitive techniques and can be delivered in different formats including individual, group, or self-directed therapy. However, unlike medication, psychological therapy such as CBT is not widely available, is expensive for many individuals due to lack of insurance coverage, and may have long wait times for treatment.[5]

Objective and Research Questions

This report is a review of available evidence regarding the clinical effectiveness and safety of pharmacological and non-pharmacological interventions for the treatment of insomnia in adults. This report is part of a larger CADTH Health Technology Assessment (HTA) project that aims to inform policy and practice questions related to the treatment of insomnia in adults through an assessment of the clinical effectiveness and safety of available treatment (the current report); a summary of patients' and caregivers' perspectives and experiences; and an assessment of current practices and trends in drug and non-drug therapies for adult patients with insomnia disorder.

The research questions for this review were:

1. What are the effectiveness and comparative effectiveness of treatments for insomnia disorder in adults?
2. What is the long-term safety of interventions for insomnia disorder in adults?

Methods

A review of systematic reviews (SRs) that were conducted to assess the clinical effectiveness, comparative clinical effectiveness, and/or safety of interventions for the treatment of insomnia disorder in adults was carried out. The review of SRs approach was chosen as there are a number of SRs that exist on this topic (see Section 4 — Results of Clinical Evaluation). Leveraging this work through a review of existing SRs, rather than carrying out a de novo SR, was the most reasonable approach to reviewing this topic as this would avoid having to invest substantial resources and time with no obvious benefits.

Published literature was identified by searching bibliographic databases (MEDLINE, Embase, PsycINFO, the Cochrane Library, and PubMed) and 'grey literature' (non-commercially published sources) identified using the *Grey Matters* checklist. A filter was applied to limit database searches to SRs and meta-analyses (MAs); when possible animal studies were removed; and no restrictions on language or date of publication were applied. Searches were supplemented through searching the bibliographies of included reviews and other key papers.

Inclusion criteria for the review were established using the population, intervention, comparison, and outcome (PICO) framework.[6,7] Eligible populations were adults (18 years of age and older) with a diagnosis of acute (less than three months) or chronic (greater than three months) insomnia based on diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., (DSM-IV), the International Classification of Sleep Disorders (ICSD), or the Research Diagnostic Criteria (RDC) for insomnia.[8] Subgroups of interest (based on input from CADTH jurisdictional stakeholders) included older adults (64 years and older), patients in long-term care facilities, and patients in correctional facilities. Interventions of interest included pharmacological agents (i.e., benzodiazepine drugs, non-benzodiazepine receptor agonists, antidepressant drugs, melatonin, or other over-the-counter medications), non-pharmacological approaches (i.e., CBT and/or behavioural therapies [BT], sleep restriction, relaxation, or meditation/mindfulness-based therapies), or a combination of the two. Eligible interventions could be compared with an inactive control such as placebo, wait-list conditions, or sham interventions or with an active control (i.e., another eligible intervention). Nine effectiveness and seven harms outcomes of interest were identified as clinically important: sleep onset latency (SOL), total sleep time (TST), wake after sleep onset (WASO), sleep quality (SQ), sleep satisfaction (SS), sleep efficiency (SE), Insomnia Severity Index (ISI) scores, fatigue severity, health-related quality of life (HRQoL), hangover/morning sedation, accidental injuries, additional health care use related to harms of the intervention, delirium related to the intervention, sleep-disordered breathing related to the intervention, addiction, dependence, or diversion of medications, and all-cause mortality related to the intervention. SRs that included primary studies of any design were eligible for inclusion irrespective of whether an MA was conducted, and there were no restrictions on year of publication, publication status, or language of publication.

Non-systematic knowledge synthesis products (narrative, literature, or rapid reviews) and reviews of diagnostic test accuracy, causes or risk factors for insomnia, or prevention for insomnia were excluded. Additionally, reviews of complementary and alternative medicine (CAM) therapies for insomnia were not eligible for inclusion, due to concerns about the variability in formulations of herbal/natural remedies and the lack of standardized delivery for many alternative therapies. Based on feedback from clinical experts, an exception to this criterion was made for alternative therapies based on mindfulness and/or meditation.

The literature search results were screened using an online tool (synthesi.SR software)[9] for Level 1 and Level 2 screening (citations and full-text articles, respectively). A training exercise was conducted by the review team and when high per cent agreement (greater than 80%) was observed across the team, two team members then independently screened each title and abstract or full-text article for inclusion and conflicts were resolved by a third reviewer. Following screening, a charting exercise (high-level data abstraction of review characteristics) was completed. The review team completed a training exercise with the charting form to ensure reliability and then each article was charted by a single reviewer. The results of charting were applied to develop a draft data abstraction form in consultation with our methodologists and clinical experts. The form was tested by the review team, revised further as needed, and then all of the included reviews were abstracted by one reviewer and verified independently by a second. Quality appraisal was also completed during data abstraction using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) 2 tool, it was tested as part of the data abstraction form, and each article was appraised by one reviewer and verified independently by a second. Prior to commencing abstraction of the SRs, a list of primary studies included in the abstracted systematic reviews that also included meta-analyses (SR+MAs) was compiled and checked against the primary studies included in the SRs. Any SRs that had a complete overlap with the already abstracted SR+MAs were excluded from the review at this stage.

The results of the literature search and screening were summarized descriptively, as a large degree of heterogeneity was expected across the included interventions, so pooled analysis or indirect comparison was not considered an appropriate method for this review. The degree of overlap between the primary trials included in the body of literature was tabulated and examined for each outcome and treatment comparison and the results were tabulated and narratively described in the text.

Summary of Evidence

Sixty-four SRs were included in this review, 35 of which included an MA(SR+MA). The 35 SR+MAs were published between 1999 and 2017 and included 652 unique primary studies. The number of primary studies included in each meta-analysis ranged from three to 139, and included studies were a mix of randomized controlled trials (RCTs) and non-randomized or other quasi-experimental study designs. The 29 SRs were published between 1997 and 2017 and included 149 unique primary studies. The number of primary studies included in each review ranged from two to 22, and included studies were a mix of RCTs, non-randomized or quasi-experimental study designs, and observational study designs.

Sample sizes and patient characteristics varied considerably across the primary studies included in the SR+MAs and SRs. None of the SR+MAs or SRs focused on age-specific subgroups, patients in long-term care facilities, or individuals in a correctional facility. A total of 11 pharmacological treatments, eight non-pharmacological interventions, and one combination of pharmacological and non-pharmacological treatments were included in the

64 SRs. Very few of the SR+MAs or SRs examined the effects of dosing or route of administration for the pharmacological and non-pharmacological interventions.

The AMSTAR 2 assessment found that six SR+MAs (6/35; 17%) and two SRs (2/29; 7%) were high quality; 11 SR+MAs (11/35; 31%) and five SRs (5/29; 17%) were rated as moderate quality; eight SR+MAs (8/35; 23%) and five SRs (5/29; 17%) were rated as low quality; and 10 SR+MAs (10/35; 29%) and 17 SRs (17/29; 59%) were rated as critically low quality.

Consistent evidence of effectiveness from high or moderate quality SR+MAs was found for five types of pharmacologic interventions (benzodiazepine drugs, non-benzodiazepine receptor agonists, suvorexant, melatonin, and doxepin) and four types of non-pharmacologic interventions (CBT, multi-component CBT, CBT combined with relaxation therapy, and multi-component behavioural therapy [BT]). Among the pharmacological interventions, suvorexant was found to effectively improve the highest number of outcomes compared with placebo (SOL, TST, WASO, SQ, and ISI) followed in descending order by non-benzodiazepine receptor agonists such as zolpidem (SOL, TST, WASO, SQ) and zopiclone (SOL); benzodiazepine drugs including flurazepam (SOL), triazolam (SOL, WASO), and temazepam (WASO); melatonin (SOL); and the antidepressant doxepin (TST, ISI). Among the non-pharmacological interventions, the three CBT approaches were found to effectively improve almost all of the outcomes compared with control, with the exception of TST, SS, and HRQoL. CBT demonstrated effective improvement for six outcomes compared with inactive controls (SOL, WASO, SQ, SE, ISI, and fatigue severity), multi-component CBT demonstrated effective improvement across four outcomes compared with inactive controls (SOL, WASO, SQ, SE), and CBT combined with relaxation therapy demonstrated effective improvement for one outcome compared with inactive controls (SOL). BT with multiple components demonstrated effective improvement across two outcomes compared with inactive controls (SOL, WASO). None of the included SR+MA s or SRs included studies that directly compared pharmacological and non-pharmacological interventions for insomnia.

While suvorexant demonstrated effectiveness across the largest number of outcomes, it was also the only pharmacological agent with evidence of increased risk of harm compared with placebo from high or moderate quality SR+MAs. Reported harms included hangover or morning sedation, accidental injuries, and addiction to or dependence on the medication. It is notable that suvorexant is the most recently developed pharmacological agent for the management of insomnia and therefore may have been subject to contemporary regulatory safety requirements and evaluations as compared with older pharmacological agents. None of the included relevant SRs or SR+MAs reported on additional health care utilization related to the intervention, delirium related to the intervention, sleep-disordered breathing related to the intervention, or all-cause mortality related to the intervention.

Limitations

There are some limitations of the included SRs worth noting. More than 50% of the 64 included SRs were appraised as being low quality, suggesting that substantial improvements are required in the knowledge syntheses produced within the insomnia field and that current results should be interpreted with caution. There are also some limitations to the process followed for this review of reviews. Targeted literature searches for primary research on safety outcomes were not conducted due to time and resource constraints. As well, although there was an attempt to identify unpublished reviews and reviews written in languages other than English, only one unpublished review and two reviews written in

languages other than English were included. This suggests that the results are likely only generalizable to published SRs written in English. Only one person abstracted data and appraised risk of bias and another verified the responses; while this was necessary to increase the feasibility of the project, it may have led to inaccuracies in the data. Furthermore, variation across the interventions was apparent regarding their dose, duration, intensity, and frequency, which may have influenced our results. Finally, interpretations of the clinical or symptomatic significance of the results of the included reviews were not possible because of a lack of standards to interpret them (i.e., minimal clinically important difference) and because the impacts of symptomatic changes in insomnia disorder are currently poorly understood.

Conclusions

Short-duration treatment (less than and equal to 16 weeks on average) with zolpidem, triazolam, suvorexant, doxepin, and melatonin appears to improve sleep outcomes in adult patients with insomnia disorder. Clinical expert input indicates that use of these drugs is frequently for longer durations than the evidence supports. The comparative and long-term effectiveness of these and other pharmacological interventions for insomnia disorder is poorly understood and associated with a high degree of uncertainty. This fact needs to be balanced along with the lack of robust safety evidence — especially serious harms including mortality — for these interventions. Although there was insufficient evidence to evaluate harms, based on the mode of delivery, CBT is expected to be associated with infrequent and non-serious harms, if any at all. Therefore, overall, CBT appears to provide a favourable balance between effectiveness and harms for treating adult patients with insomnia disorder.

These results may be used to update clinical practice guidelines on insomnia. As well, funding agencies may use these results to fund high-quality research in the areas where data gaps were identified (e.g., comparative effects of interventions on HRQoL, long-term effectiveness, and safety). In particular, more primary studies and reviews are required to examine the harms associated with pharmacological treatment of insomnia. Future SRs should include important effectiveness outcomes, such as SS, fatigue severity, and HRQoL. As well, SRs on the effectiveness of interventions for patients in certain age groups (e.g., 65 years and older), those in long-term care facilities, or individuals in correctional facilities will help decision-makers tailor policy specifically for these settings.

1. Rationale and Policy Issues

1.1 Background and Rationale

Insomnia is a common disorder in the general Canadian population and in routine medical practice. Insomnia may be diagnosed as a primary disorder (insomnia disorder) or in association with another medical or psychiatric disorder (comorbid insomnia). While precise estimates vary as a function of definitions and methodology, approximately 40% of Canadian adults (18 years of age and older) report at least one symptom of insomnia three times per week, 20% are dissatisfied with their sleep, and about 10% to 13% meet criteria for an insomnia disorder.[1,2] Insomnia is characterized by dissatisfaction with sleep quantity or quality, difficulty falling asleep, maintaining sleep, or early-morning awakening.[10] The Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-V) is often used to diagnose insomnia in accordance with the criteria of dissatisfaction with sleep quantity or quality, with one or more of the following symptoms: (1) difficulty initiating sleep, difficulty maintaining sleep, early-morning awakening; (2) sleep disturbance causing significant distress or impairment in social, occupational, educational, academic, behavioural, or other important areas of functioning; (3) sleep difficulty occurs at least three nights per week, is present for at least three months, despite adequate opportunity for sleep; (4) insomnia does not co-occur with another sleep disorder; (5) insomnia is not explained by coexisting mental disorders or medical conditions.[11]

Persistent insomnia has a negative impact on the individual affected and on society from a psychosocial, occupational, economic, and public safety perspective.[3] Insomnia is linked to reduced QoL due to problems with attention and memory, mood disturbances, lower ratings of enjoyment of interpersonal relationships, and more days unable to work or carry out normal daily activities than those without insomnia.[3] Insomnia may contribute to significant functional impairments at work, at home, or while operating a motor vehicle. Furthermore, studies have indicated that insomnia may be an important risk factor for the onset of mental health disorders such as depression, anxiety, and substance abuse disorders.

Both pharmacological and non-pharmacological approaches are routinely used in the management of insomnia. Pharmacological interventions are most appropriate for patients presenting with insomnia lasting less than three months.[12] Health Canada–approved pharmacological therapies for insomnia include benzodiazepine drugs (e.g., temazepam, lorazepam), non-benzodiazepine-receptor agonists, also referred to as “z-drugs” (e.g., zopiclone, zolpidem), and doxepin, a sedating antidepressant drug. Several drugs belonging to various classes (anxiolytic benzodiazepine drugs, antipsychotic drugs, antidepressant drugs) are also prescribed for insomnia despite having no approved indication for insomnia.[4] However, despite the potential adverse effects of long-term use, these medications are often used for durations longer than three months.[13] Patients experiencing insomnia may also turn to non-prescription medications, such as melatonin, and first-generation antihistamine drugs, as well as a number of herbal sleep aids.[12] While medications such as melatonin or antihistamine drugs may be effective for short-term use, there is a lack of rigorous efficacy and safety data to recommend these treatments as long-term solutions for insomnia.[14]

According to *The Canadian Rx Atlas*,[5] $336 million was spent on benzodiazepine drugs and z-drugs in the country in 2013, regardless of the indication. Thirty-seven per cent of these costs were covered by public drug plans. All provinces provided restricted or unrestricted coverage for at least 11 of the 14 types of benzodiazepine drugs that had more than

$10,000 in sales in each province. Four provinces (Alberta, Manitoba, New Brunswick, and Prince Edward Island) provided unrestricted coverage for all drugs in this therapeutic category. Zopiclone was the leading drug for insomnia, accounting for 38% of spending. Many of the prescription drugs available for insomnia are reimbursed by Canadian public drug plans with few or no restrictions.

Cognitive behavioural therapy (CBT) is the most common non-pharmacological intervention used in the management of insomnia. CBT is a multimodal intervention that may combine behavioural and cognitive techniques, such as sleep hygiene, sleep restriction, stimulus control, sleep education, and relaxation therapies. CBT can be delivered in different formats, including individual therapy, group therapy, self-directed therapy or minimal intervention therapy (such as through phone counselling or online/ smartphone applications). CBT is generally considered safe and well-accepted by patients and as such, Canadian and American clinical practice guidelines recommend CBT as first-line treatment of adults with insomnia lasting longer than three months.[10,15] However, the availability of CBT and other psychotherapies is limited in Canada.

Psychotherapy can be used as an adjunct to pharmacotherapy for potentially enhanced effectiveness. Unlike medication, psychotherapy is not widely available, can be expensive to individuals who lack coverage, and may have long wait times associated with accessing it.

For insomnia that lasts longer than three months, treatment of the underlying causes and non-pharmacological therapies are recommended.[10]

1.2 Patient Group Input Summary

Patient group input was not sought by CADTH for this review. Instead, a CADTH rapid review of the scientific literature on patients' and caregivers' experiences and perspectives regarding treatments for insomnia was conducted. Information from the rapid review of the literature about outcomes and issues important to patients and caregivers who are affected by insomnia was used to inform the scope of this review and the interpretation of the data synthesized. The rapid review may be downloaded from the CADTH website at: https://www.cadth.ca/sites/default/files/pdf/htis/2017/RD0039-OP0527%20Insomnia%20PPE%20Final.pdf.[16]

1.3 Objectives

This report is a review of available evidence regarding the clinical effectiveness and safety of pharmacological and non-pharmacological interventions for the treatment of insomnia in adults. This report is part of a larger CADTH Health Technology Assessment (HTA) project that aims to inform policy and practice questions related to the treatment of insomnia in adults through an assessment of the clinical effectiveness and safety of available treatment (the current report); a summary of patients' and caregivers' perspectives and experiences; and an assessment of current practices and trends in drug and non-drug therapies for adult patients with insomnia disorder. Separate reports on current prescriber practice and patient perspectives and experiences are available.[4,16]

2. Research Questions

1. What are the effectiveness and comparative effectiveness of treatments for insomnia disorder in adults?
2. What is the long-term safety of interventions for insomnia disorder in adults?

3. Clinical Methods

A review of systematic reviews (SRs) was conducted on the clinical effectiveness, comparative clinical effectiveness, and safety of interventions for the treatment of insomnia disorder in adults. Using the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook) as a guide, a protocol for the review of systematic reviews (CRD42017072527)[17] was written a priori by the research team in consultation with the project owner and research officers from CADTH. The review of SRs design was chosen for this subject as it is well-suited to synthesizing evidence related to the effects of multiple different interventions on a single health problem or condition. In addition, there are a number of SRs that exist on this topic, allowing the opportunity to provide a review of the available evidence relevant to specific treatment decisions.[18] All changes to the protocol were documented in the Protocol Amendments table, along with a rationale (see Discussion section).

3.1 Clinical Evaluation

This section addressed Research Question 1: ("What are the effectiveness and comparative effectiveness of treatments for insomnia disorder in adults?") and Research Question 2: ("What is the long-term safety of interventions for insomnia disorder in adults?").

3.1.1 Literature Search Methods

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with epub ahead of print, in-process records, daily updates, and other non-indexed citations via Ovid, Embase Classic+Embase (1947–) via Ovid; PsycINFO (1806–) via Ovid; The Cochrane Library via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) (e.g., "Sleep Initiation and Maintenance Disorders"), and keywords (e.g., insomnia, hyposomnia, sleep initiation problems). The main indication/population search concept was insomnia and associated terminology; no vocabulary was incorporated for interventions. All searches were performed on June 14, 2017.

A methodological filter was applied to limit retrieval to SRs, HTAs, and meta-analyses (MAs). When possible, animal-only and opinion pieces were removed from the results. No date or language restrictions were applied. See Appendix 1 for the detailed search strategies.

Grey literature (literature that is not commercially published) was identified by searching the Grey Matters checklist (https://www.cadth.ca/grey-matters), and in particular the websites of HTA agencies listed therein. Google and other Internet search engines were used to search

for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. See Appendix 1 for more information on the grey literature search strategy.

3.2 Selection Criteria and Methods

3.2.1 Inclusion Criteria

The inclusion criteria for the review of reviews can be found in Table 1.

3.2.2 Exclusion Criteria

Non-systematic knowledge synthesis products were excluded, such as narrative reviews, literature reviews, and rapid reviews. Reviews of diagnostic test accuracy, causes and/or risk factors for insomnia and preventive interventions for insomnia were excluded. Additionally, reviews of complementary and alternative medicine (CAM) therapies for insomnia were not eligible for inclusion as per the request of project stakeholders (a detailed list of ineligible therapies is available in Appendix 2). Based on feedback from clinical experts, an exception to this criterion was made for alternative therapies based on mindfulness and/or meditation. The review was restricted to adult populations; however, reviews of mixed adult and pediatric populations were eligible only if the review reported results for these populations separately.

Table 1: Selection Criteria

Population(s)	• Adults aged 18 years and older with insomnia disorder (e.g., DSM diagnostic criteria, International Classification of Sleep Disorders [ICSD], Research Diagnostic Criteria [RDC] for insomnia) including patients with acute (< 3 months), as well as chronic (> 3 months) symptoms. • Subpopulations: o Age groups (18 years to 64 years; 65 years and above) o Patients in long-term care facilities o Patients in correctional facilities
Intervention(s)	Pharmacological interventions (prescription and non-prescription); non-pharmacological interventions (e.g., CBT techniques [e.g., group or individual therapy, phone counselling, or self-directed therapy], sleep restriction, sleep consolidation, stimulus control, meditation, mindfulness-based therapies, or relaxation therapies); combination pharmacological and non-pharmacological interventions
Comparator(s)	**Inactive controls:** Placebo, sham intervention, wait-list control **Active controls:** Other interventions in scope
Outcome(s)	**Efficacy outcomes:** 1. Sleep onset latency (SOL) 2. Total sleep time (TST) 3. Wake after sleep onset (WASO) 4. Sleep quality (SQ) 5. Sleep satisfaction (SS) 6. Sleep efficiency (SE) 7. Insomnia Severity Index (ISI) 8. Fatigue severity – using any measure 9. Health-related quality of life (HRQoL)

Outcome(s)	**Safety outcomes :** 1. Hangover/morning sedation 2. Accidental injuries (falls, fractures, traffic injuries) 3. Additional health care resource use related to harms of the intervention (hospitalizations, ER visits, doctor visits) 4. Delirium related to the intervention 5. Sleep-disordered breathing related to the intervention 6. Addiction, dependence, diversion 7. All-cause mortality related to the intervention
Study Design(s)	• SRs including primary studies of any design, with or without MA
Time Frame	• No time restrictions
Exclusion Criteria	• Narrative reviews, literature reviews, rapid reviews, and other non-systematic knowledge synthesis products • Reviews of diagnostic test accuracy, causes and/or risk factors for insomnia, preventive interventions for insomnia • Reviews of CAM therapies for insomnia • Reviews of insomnia in pediatric populations (mixed adult and pediatric populations were eligible for inclusion if the review reported results for these populations separately)

CAM = complementary and alternative medicine; CBT = cognitive behavioural therapy; DSM = Diagnostic and Statistical Manual of Mental Disorders; ER = emergency room; ISI = Insomnia Severity Index; MA = meta-analysis; SR = systematic review.

4.2.1 Population and Subgroups

The population of interest was adults aged 18 years and older with insomnia disorder (e.g., Diagnostic and Statistical Manual of Mental Disorders [DSM] diagnostic criteria, ICSD, RDC for insomnia). Patients with acute (less than three months), as well as chronic (greater than three months), symptoms were included. Subgroups of interest included classification by age (18 years to 64 years; and 65 years and above), patients in a long-term care facility, and patients in a correctional facility.

4.2.2 Intervention and Comparators

The final list of eligible interventions and relevant comparators was determined after consultation with clinical experts and project stakeholders from CADTH. Both pharmacological and non-pharmacological interventions were eligible, with the exception of CAM interventions (e.g., herbal remedies, acupuncture, aromatherapy). CAM interventions were excluded, based on expert suggestions, due to concerns about a lack of standard composition (for herbal remedies) and a lack of standard practices (for other therapies), that would severely limit interpretation. A detailed list of eligible interventions is available in Table 2.

Due to the wide variation in the composition and implementation of non-pharmacologic interventions, no restrictions were placed on the eligibility of these interventions based on the included components, method of delivery, number of sessions, or length of treatment. This was intended to capture as broad a sample of non-pharmacologic methods as possible and to ensure a comprehensive evidence base was collected.

Relevant comparators included other eligible interventions (active controls) and inactive control conditions such as wait-list, self-monitoring, treatment as usual, placebo, or sham interventions. On the advice of clinical experts, sleep hygiene/education and patient education interventions for insomnia that consist of teaching patients about appropriate sleep habits were not considered eligible interventions when delivered as a stand-alone treatment and were instead included as an inactive control (similar to 'treatment as usual'). However, therapeutic approaches that included sleep hygiene or patient education components alongside other cognitive/behavioural approaches were still eligible for this review.

Table 2: List of Eligible Interventions

Pharmacological Interventions: Prescription Drugs	
Trade Name	**Generic Name**
Antidepressant Drugs	
Silenor, generics	Doxepin
Generics	Trazodone
Elavil, Levate, generics	Amitriptyline
Remeron, generics	Mirtazapine
Generics	Imipramine
Antihistamine Drugs	
Advil Nighttime, Dreamol, Dormiphen, Insomnal, Nytol, Dormex, Sleep-Eze, Unisom, Zzzquil	Diphenhydramine

Pharmacological Interventions: Prescription Drugs	
Trade Name	**Generic Name**
Antipsychotic Drugs	
Seroquel, generics	Quetiapine
Zyprexa, generics	Olanzapine
Latuda	Lurasidone
Risperdal, generics	Risperidone
Benzodiazepine Drugs	
Som Pam, Dalmane, generics	Flurazepam
Mogadon, Nitrazadon, generics	Nitrazepam
Halcion, generics	Triazolam
Corax, Medilium, generics	Chlordiazepoxide
Xanax, generics	Alprazolam
Lectopam, generics	Bromazepam
Restoril, generics	Temazepam
Frisium, generics	Clobazam
Valium, generics	Diazepam
Rivotril, generics	Clonazepam
Ativan, generics	Lorazepam
Serax, generics	Oxazepam
Melatonin	
Many products	Melatonin
Non-Benzodiazepine Drugs	
Sublinox	Zolpidem
Imovane, generics	Zopiclone
Orexin Receptor Antagonists	
Belsomra	Suvorexant

Pharmacological Interventions: Prescription Drugs	
Trade Name	**Generic Name**
Non-Pharmacological Interventions	
Name	**Examples of Techniques**
Sleep Restriction	→ Restrict time awake in bed by setting sleep and wake schedules limited to the average number of hours of actual sleep → Keep a fixed wake-up time, regardless of sleep duration → If SE stays low or decreases, further restrict time in bed → Increase time in bed as SE increases
Relaxation Training	→ Progressive muscle relaxation → Guided imagery/imagery rehearsal → Paced breathing → Autogenic training
Stimulus Control Therapy	→ Limit time in bed to actual sleeping activities → Establish regular wake time regardless of sleep duration → Do not go to bed until sleepy → Do not stay in bed if awake
Cognitive Therapy	→ Change unhelpful fears/beliefs (e.g., overestimation of number of hours' sleep necessary to be rested) → Thought journaling → Behavioural 'experiments' to test ideas about sleep
CBT	→ Sleep education → Stimulus control → Sleep restriction → Cognitive therapy → Relaxation training
Mindfulness/ Meditation	→ Meditation → Daily monitoring and discussion of sleep and wakeful activities → Group discussion → Mindfulness skills → Sleep education, sleep restriction
Biofeedback	→ EMG biofeedback → Biofeedback training → EEG biofeedback

CBT = cognitive behavioural therapy; EEG = electroencephalography; EMG = electromyography; SE = sleep efficiency.

4.2.3 Outcomes Definition

After consultation with clinical experts and stakeholders, the efficacy and safety outcomes described below were included in the review. Outcomes definitions did not specify whether a standardized measure had to be used for the outcome to be eligible. Outcome data were abstracted as reported in the original reviews; this was in order to ensure the evidence base captured in the review was as comprehensive as possible.

a) Definitions of Effectiveness Outcomes

1. Sleep Onset Latency (SOL): The length of time that it takes to transition from full wakefulness to sleep; normally to the lightest of the non-rapid eye movement (REM) sleep stages.[19] SOL can be measured using polysomnography (PSG)/actigraphy or through patient self-report with sleep diaries/questionnaires.

2. Total Sleep Time (TST): The amount of actual sleep time in a sleep episode; equal to total sleep episode less awake time.[20] TST can be measured using PSG/actigraphy or through patient self-report with sleep diaries/questionnaires.
3. Wake After Sleep Onset (WASO): Periods of wakefulness occurring after defined sleep onset. This outcome measures wakefulness, excluding the wakefulness occurring before sleep onset.[21] WASO can be measured using PSG/actigraphy or through patient self-report with sleep diaries/questionnaires.
4. Sleep Quality (SQ): One's satisfaction of the sleep experience, integrating aspects of sleep initiation, sleep maintenance, sleep quantity, and refreshment upon awakening.[22] Typically measured using patient (or caregiver) self-report with standardized questionnaires, SQ can also be assessed through sleep diaries or rating (Likert) scales.
5. Sleep Satisfaction (SS): A subjective assessment of "good" or "poor" sleep.[23] Typically measured using patient (or caregiver) self-report with standardized questionnaires, SQ can also be assessed through sleep diaries or rating (Likert) scales.
6. Sleep Efficiency (SE): Refers to the percentage of total time in bed actually spent in sleep. SE gives an overall sense of how well the patient slept, but it does not distinguish frequent, brief episodes of wakefulness.[21] It can be measured using PSG/actigraphy or through patient self-report with sleep diaries/questionnaires.
7. ISI: A brief standardized instrument that was designed to assess the severity of both nighttime and daytime components of insomnia.[24]
8. Fatigue Severity: A subjective experience, includes symptoms such as rapid inanition, persisting lack of energy, exhaustion,[25] physical and mental tiredness, and apathy.
9. Health-Related Quality of Life (HRQoL): A multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning.[26]

b) Definitions of Safety Outcomes

1. Hangover/morning sedation: difficulty waking up in the morning.
2. Accidental injuries: falls, fractures, traffic injuries.
3. Additional health care resource use related to safety of the intervention: hospitalizations, emergency room visits, doctor's visits.
4. Delirium related to the intervention: an acutely disturbed state of mind.
5. Sleep-disordered breathing related to the intervention: related to increased upper airway resistance such as snoring, upper airway resistance syndrome, and obstructive sleep apnea.
6. Addiction, dependence, diversion: fact or condition of being addicted to a particular substance.
7. All-cause mortality related to the intervention: all of the deaths that occur in a population regardless of the cause.

4.2.4 Study Designs

The results were limited to SRs that included any type of study design. An SR was defined according to the Cochrane definition[27] as follows: "A systematic review attempts to identify, appraise, and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question. Researchers conducting SRs use explicit methods aimed at minimizing bias, in order to produce more reliable findings that can be used to inform decision-making." In the interest of capturing a comprehensive body of evidence, a conservative definition of SR was used for the study selection process. To be eligible for inclusion, publications were required to report that a literature search was conducted and to name at least one database where the search was conducted.

4.2.5 Study Selection Process

The literature search results were screened using the online synthesi.SR[9] software at Level 1 and Level 2 screening (citations and full-text articles, respectively). Synthesi.SR is a proprietary tool developed by the Knowledge Translation Program of St. Michael's Hospital in Toronto, Ontario, Canada, and is used to manage reviews and complete title/abstract and full-text screening. To ensure reliability, a training exercise was conducted by eight reviewers using the pre-defined eligibility criteria; one round of training for Level 1 screening was completed using 25 title and abstract citations. When high per cent agreement (greater than 80%) was observed, two team members (PR, RC, VN, DM, ZG, BF, SH) independently screened each title and abstract for inclusion. Pilot testing the full-text screening criteria involved two rounds of testing with eight reviewers using 15 and 25 full-text articles, after which two reviewers (PR, RC, VN, DM, ZG, BF, SH) independently reviewed the full text of potentially relevant articles to determine final eligibility. Conflicts were resolved by a third reviewer.

4.2.6 Quality Assessment

The methodological quality of the included reviews was appraised using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2).[28] Two pilot exercises were completed with nine reviewers using three articles each time. After pilot testing, one reviewer assessed the quality of included reviews (VN, ZG, DM, AN, BF, SH) and this assessment was then verified by a second independent reviewer (PR, RC). The AMSTAR 2 tool consists of 16 questions that are answered with "Yes" or "Partial Yes" to indicate the presence of an item and that has been completed to the AMSTAR 2 requirements, or "No" to indicate an item has not been reported or has not been completed to AMSTAR 2 requirements. When all 16 items have been answered, the review is then given an overall score of high, moderate, low, or critically low quality. Overall quality is determined based on two factors: the number of "No" responses that indicate a 'critical flaw' in the design or conduct of the review and the number of "No" responses that indicate a 'weakness' in the design or conduct of the review. No or few weaknesses result in a rating of 'high' quality; multiple weaknesses result in a rating of moderate quality (can be downgraded to low quality if there are too many); the presence of one critical flaw will automatically result in a low-quality rating with or without additional weaknesses; while multiple critical flaws or a critical flaw and a high number of additional weaknesses will result in a critically low rating of quality. The results of the quality assessment were applied to the interpretation of results and to provide context in the discussion of findings. As no formal quantitative or pooled analysis was carried out, quality assessment results were not used as a basis for exclusion or removal of data from the

report. The list of AMSTAR 2 items and additional guidance on the response categories can be found at amstar.ca.

c) Data Extraction

A charting exercise was completed to assess how outcomes were reported in the included reviews and to refine which measurement tools and scales were abstracted. A charting exercise is a type of high-level data abstraction used to collect information on the included articles in a review and is used to help refine inclusion criteria and focus the process of data abstraction. A pilot test with eight review team members was completed on three articles to ensure reliability of the charting process. Charting was completed by a single reviewer (PR, RC, VN, DM, ZG, BF, SH) and the results were later reviewed and compiled by the lead research coordinator (PR). The results of the charting exercise were discussed with project stakeholders (including CADTH team members) and clinical experts to help select the most relevant outcome measures for inclusion in the review. A total of 213 articles were charted and the exercise resulted in the exclusion of 108 articles prior to data abstraction; the excluded articles and the reason for exclusion are listed in Appendix 3.

After the charting exercise, data abstraction occurred. Data were abstracted on review characteristics (e.g., year of conduct/literature search, number of included studies, type of included study designs), patient characteristics (e.g., type and number of patients, age mean and standard deviation, comorbidities), interventions examined (e.g., type of intervention, dose/frequency), and outcomes examined (e.g., name of outcome, outcome measure/definition). A draft data abstraction form was established after consultation with our methodologists and clinical experts. Prior to data abstraction, the data abstraction form was tested by nine reviewers on a random sample of three articles. Subsequently, all of the included studies were abstracted by one reviewer (VN, ZG, DM, AN, BF, SH) and verified by a second (PR, RC). The data abstraction items and their descriptions are available in Appendix 4.

Additionally, data abstraction was conducted in two phases: in the first phase, the included SR+MAs were abstracted and verified; in the second phase the relevant SRs were abstracted and the data verified. Prior to commencing abstraction of the SRs, a “master list” of primary studies included in the abstracted SR+MAs was compiled and checked against the primary studies included in the SRs. Any SRs that had a complete overlap with the already abstracted SR+MAs (e.g., did not contribute any new primary studies to the overall body of evidence) were excluded from the review and data from these SRs were not abstracted.

3.3 Data Analysis and Synthesis

The results of the literature search and screening were summarized descriptively; as a large degree of heterogeneity was expected across the included interventions, a pooled analysis or indirect comparison was not considered an appropriate method of analysis for this review. The data were abstracted and reported as written in the original reviews with as little editing as possible and then compiled in tables to enable an in-depth comparison of the literature across outcomes and treatment comparisons. Descriptive syntheses of the characteristics and results of the included reviews were written to provide a review of the included body of evidence. Results of the reviews were interpreted with additional context provided by the results of quality assessment.

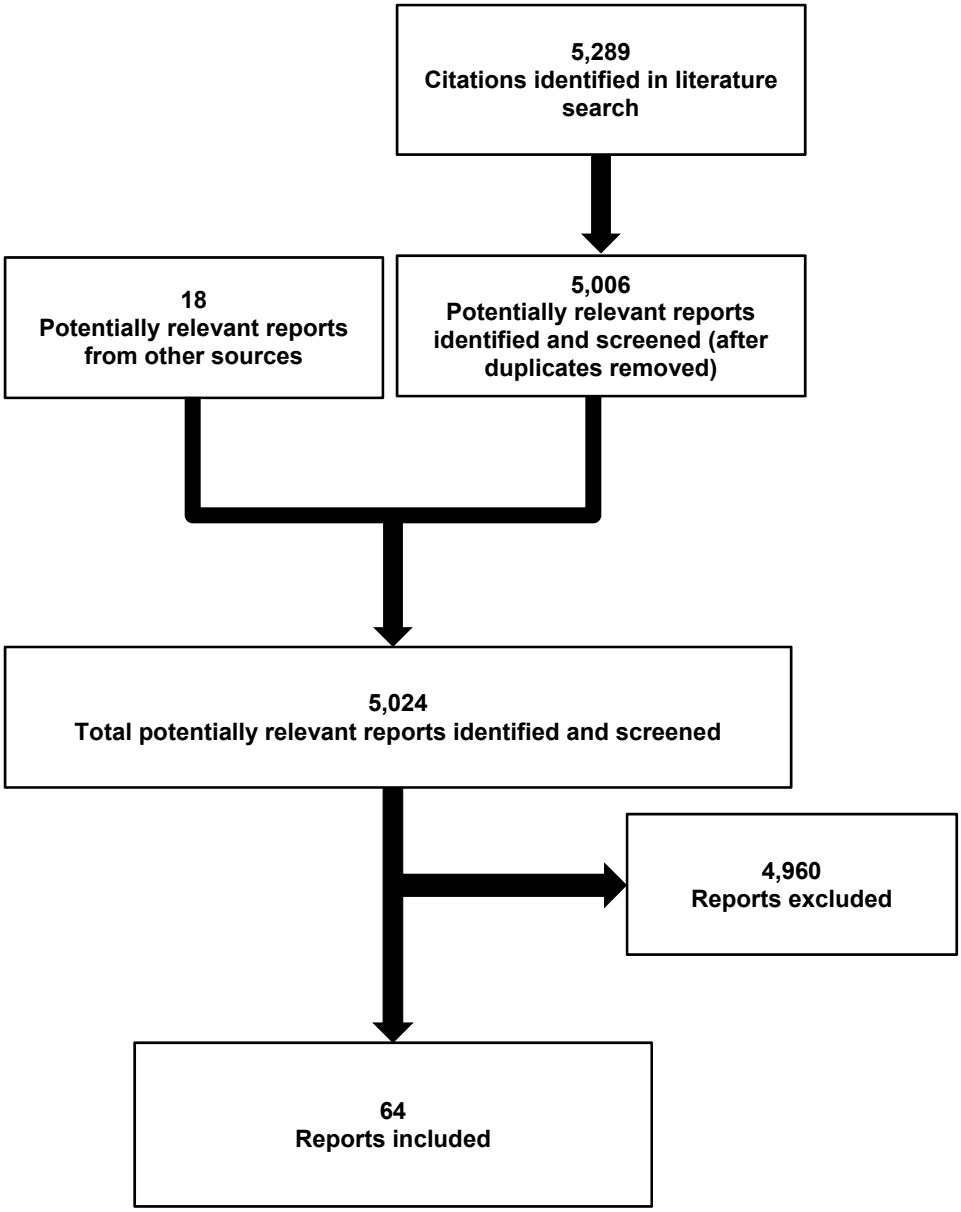
The degree of overlap between the primary trials included in the body of literature was tabulated and examined for each outcome and treatment comparison. Once the final set of included reviews was determined and results were tabulated, a detailed cross-referencing exercise was carried out to determine which primary studies were included in the SR+MAs and SRs that contributed data to each outcome for each treatment comparison. The results were tabulated according to treatment comparison and outcome and were also narratively described in the text.

4. Results of Clinical Evaluation

4.1 Selection of Primary Studies

The literature search resulted in 5,024 titles and abstracts, of which 4,499 were excluded for not fulfilling the eligibility criteria (Figure 1: PRISMA Flow Chart of Selected Reports). Of the 525 full-text articles retrieved and screened in duplicate, 312 articles were excluded. Sixty-four SRs were included in this review of SRs; 35 were SR+MAs[29-62] and 29 were SRs without an MA.[63-91] The lists of included and excluded studies are provided in Appendix 5 and Appendix 3, respectively.

Figure 1: PRISMA Flow Chart of Selected Reports



4.2 Study and Patient Characteristics

4.2.1 Review Characteristics

Systematic Reviews With Meta-Analysis

Thirty-five SRs with MA (SR+MAs), including 652 unique studies, were conducted between 1999 and 2017. The first authors of these studies were mostly from Asia (15/35), followed by North America (12/35), Europe (6/35), and Australia or New Zealand (3/35). The number of studies included in each MA ranged from three to 139. Thirty-two SR+MAs included only randomized clinical trials (RCTs), one SR+MA[61] included a mix of RCTs and quasi-experimental study designs (unspecified), and two SR+MAs[31,48] only reported on the total number of included studies without specifying the included designs. One non-English SR+MA[59] and one unpublished SR+MA[58] were included in the review. The remaining reviews were in English and were published in the grey or academic literature. Full details of the characteristics for each review are provided in Appendix 6.

Systematic Reviews Without Meta-Analysis

Twenty-nine SRs without an MA including 149 unique studies were conducted between 1997 and 2017. The first authors of the SRs were predominantly based in North America (19/29), Europe (6/29), Asia (2/29), and Australia or New Zealand (2/29). The number of studies included in each review ranged from two to 22. Sixteen SRs only included RCTs; four SRs[68,70,77,84] included a combination of RCTs and non-randomized controlled trials (NRCTs); two SRs[65,66] included both RCTs and quasi-experimental study designs; two SRs[81,89] included a combination of RCTs, NRCTs, and observational study designs; one SR[90] included a combination of RCTs, quasi-experimental study designs, and observational studies; one SR[88] included only observational studies; and three SRs[76,79,80] only reported on the total number of included studies without specifying the included designs. One non-English SR[88] was included in the review, and the remaining SRs were published in English. Full details of the characteristics for each review are provided in Appendix 6.

4.2.2 Population Characteristics

a) Systematic Reviews With Meta-Analysis

The overall sample size was reported in 24 SR+MAs (24/35) and ranged from 171 patients to 6,303 patients (overall sample size was not reported in the other 11 SR+MAs). Only seven SR+MAs provided information on the overall age of participants (means ranged from 45.3 years to 56.6 years). The percentage of females included in the sample was reported in seven SR+MAs and ranged from 35.6% to 74.2%. Twelve SR+MAs included studies of patients with insomnia only, nine SR+MAs included a mix of studies of patients with insomnia and studies of patients with insomnia and comorbid conditions, twelve SR+MAs only included studies of patients with insomnia and comorbid conditions, and thirteen SR+MAs did not provide information on the presence or absence of comorbid conditions in the patient sample. None of the SR+MAs focused on patients in long-term care facilities or individuals in a correctional facility. Full details of the participant characteristics are provided in Appendix 6.

b) Systematic Reviews Without Meta-Analysis

The sample size was reported in 15 (15/29) SRs (range from 34 patients to 1,794 patients). One review provided information on the overall age of participants (mean = 53.3 years, standard deviation [SD] = 10.2). None of the SRs provided information on the number of females included in the studies. Six SRs included studies of patients with insomnia only, nine SRs included a mix of studies of patients with insomnia and studies of patients with insomnia and a comorbid condition, nine SRs only included studies of patients with insomnia and a comorbid condition, and five SRs did not report on the presence or absence of comorbidities in the patient sample. None of the SRs focused on patients in long-term care facilities or individuals in a correctional facility. Full details of the participant characteristics are provided in Appendix 6.

4.2.3 Treatment Comparisons and Outcomes

A total of 11 pharmacological treatments, eight non-pharmacological interventions, and one combination of pharmacological and non-pharmacological treatments were included in the 64 SRs (Appendix 7). Very few of the SR+MAs or the SRs examined the effects of dosing or route of administration for the pharmacological (e.g., oral versus sublingual) and non-pharmacological (e.g., Internet versus in-person CBT) interventions. In cases where an analysis specifically compared different doses of a treatment, the relevant information and results are reported in tables and text. Specific results for all treatment comparisons can be found in Section 5.4. A summary of the treatment comparisons included in this review are provided in Table 3.

Table 3: Number of Reviews and Meta-Analyses for Each Treatment Comparison[a]

	Comparators												
Interventions	**Inactive Control**	**No Comparison** (Pre-Post)	**Benzodiazepine Drugs**	**Non-Benzodiazepine Drugs**	**Suvorexant**	**Antidepressant Drugs**	**Antipsychotic Drugs**	**Melatonin**	**Diphenhydramine**	**CBT** (CBT, CBT+Behavioural, Multi-CBT)	**Behavioural Intervention/BT**	**Mindfulness-Based Interventions**	**Combination Therapy**
Benzodiazepine Drugs (flurazepam, temazepam, triazolam)	3 MA 2 SR	1 SR											
Non-Benzodiazepine Drugs (zolpidem, zopiclone)	4 MA 4 SR	1 SR	2 SR	2 SR									
Suvorexant	3 MA 1 SR												
Antidepressant Drugs (doxepin, trazodone)	5 MA 5 SR	1 SR		3 SR									
Antipsychotic Drugs (quetiapine)	3 SR	4 SR											
Melatonin	8 MA 5 SR												
Diphenhydramine	1 MA 2 SR												
CBT (CBT, CBT+behavioural, multi-CBT)	20 MA 8 SR	4 SR								3 MA 1 SR	1 MA 1 SR		1 SR
Behavioural Intervention/BT (relaxation, sleep restriction, multi-BT)	3 MA 7 SR									1 MA			
Mindfulness-Based Interventions	1 MA												
Combination Therapy	1 MA	1 SR											

BT = behavioural therapy; CBT = cognitive behavioural therapy; MA = meta-analysis; multi = multi-component; SR = systematic review.

[a] One review can contribute to multiple treatment comparisons; table totals will exceed the number of included reviews.

a) Benzodiazepine Drugs Compared With Inactive Controls

Three SR+MAs[30,45,48] and two SRs[77,91] included studies that compared benzodiazepine drugs with inactive controls. Controls included placebo[30,45,48,91] and no comparison.[77] One SR+MA[30] included flurazepam, two SR+MAs[30,45] included temazepam, and two SR+MAs[30,48] and two SRs[77,91] included triazolam. Two SR+MAs[45,48] and one SR[91] only included studies of patients with insomnia alone, one SR[77] reported including patients with a comorbidity (recovering from alcohol addiction), and one SR+MA[30] did not report on the presence or absence of comorbidities in the patient sample. Outcomes reported in the three SR+MAs and two SRs included sleep latency (SL),[30,45,48] TST,[45,48,77,91] WASO[30] and SQ.[45] The study duration was reported in two SR+MAs[45,48] and lasted up to eight weeks. Length of follow-up was reported in two SRs[77,91] and lasted up to four weeks.

b) Benzodiazepine Drugs Compared With Active Controls

One SR[91] reported a comparison between zolpidem and triazolam. In order to avoid double reporting the information, all results and data related to this comparison will be reported under the "Non-Benzodiazepine Drugs Compared With Active Controls" treatment comparison category throughout the results.

c) Non-Benzodiazepine Drugs Compared With Inactive Controls

Four SR+MAs[29,30,45,48] and five SRs[68,76,78,80,91] included studies that compared non-benzodiazepine drugs with inactive controls. Four SR+MAs[29,30,45,48] and four SRs[76,78,80,91] compared the intervention with placebo and one SR[68] compared pre- and post-intervention effects. All four of the SR+MAs and three of the SRs[78,80,91] included zolpidem compared with an inactive control while two SR+MAs[30,48] and two SRs[68,76] included zopiclone compared with an inactive control. Two SR+MAs[45,48] and one SR[91] only included studies of patients with insomnia alone; two SRs[76,78] included a mix of studies of patients with insomnia alone and studies of patients with insomnia and a comorbidity; and one SR+MA[29] and one SR[80] only included studies of patients with insomnia and a comorbidity. No details were provided on patient diagnosis and/or comorbidities in one SR+MA[30] and one SR.[68] Patient comorbidities included depression,[78,80] cancer[76] and pain.[29] Outcomes reported in the four SR+MAs and five SRs were SL,[29,30,45,48,78,80,91] SE,[45,91] TST,[29,45,48,78,91] WASO,[30,45,78,80,91] SQ,[29,45,78,80] quality of life (QoL),[76] hangover/morning sedation,[68] as well as addiction, dependence, or diversion.[68] Follow-up duration was reported in two publications,[29,91] and ranged from two to 34.76 weeks.

d) Non-Benzodiazepine Drugs Compared With Active Controls

Three SRs[68,76,91] included studies that compared non-benzodiazepine drugs with active controls. One SR[68] compared zopiclone with triazolam, zolpidem, flurazepam, and temazepam; one SR[76] compared two different dose schedules for zolpidem (nightly vs. "as needed"); and one SR[91] compared zolpidem with triazolam. One SR[91] only included studies of patients with insomnia alone, one SR[76] included a mix of studies of patients with insomnia alone and studies of patients with insomnia and comorbid cancer diagnoses, and one SR[68] did not report on the presence or absence of comorbidities in the patient population. Outcomes reported in the three SRs included SL;[91] SE;[91] TST;[91] WASO;[91] QoL;[76] hangover/morning sedation;[68] and addiction, dependence, or diversion.[68] Follow-up duration was reported in two reviews[76,91] and ranged from two to seven weeks.

e) Suvorexant Compared With Inactive Controls

One SR[69] and one SR+MA[29,39,92] included studies that compared suvorexant with placebo. One SR[69] and two SR+MAs[39,41] only included studies of patients with insomnia alone, and one SR+MA[29] only included studies of patients with insomnia and comorbid conditions. Patients' comorbidities included pain, chronic low back pain, and hearing impairment.[29] Outcomes reported in the four publications included ISI,[39,41,69] SL,[29,39,41,69] TST,[29,39,41,69] WASO,[39,41,69] SQ,[39] hangover/morning sedation,[39,41] accidental injury[39,41] and addiction, dependence, or diversion.[39,41] Follow-up duration was reported in four reviews[29,39,41,69] and ranged from four weeks to 52 weeks.

f) Suvorexant Compared With Active Controls

No SRs or SR+MAs were identified for this comparison.

g) Antidepressant Drugs Compared With Inactive Controls

Five SR+MAs[29,30,42,45,59] and five SRs[77,78,80,83,87] compared an antidepressant drug with an inactive control. One SR+MA[30] and four SRs[77,78,80,83] compared trazodone with placebo, and five SR+MAs[29,30,42,45,59] and three SRs[78,83,87] compared doxepin with placebo. Two of the SRs[78,80] also included studies that compared the pre- and post-intervention effects of trazodone. Three SR+MAs[42,45,59] only included studies of patients with insomnia alone, two SRs[78,87] included a mix of studies of patients with insomnia alone and studies of patients with insomnia and comorbidities, one SR+MA[29] and three SRs[77,80,83] only included studies of patients with insomnia and comorbidities, and one SR+MA[30] did not report on the presence or absence of comorbidities in the patient population. One SR+MA[29] included patients with comorbid pain and/or hearing impairments, two SRs[77,83] included patients undergoing alcohol recovery/detoxification, three SRs[78,80,87] included patients with comorbid depression, one SR[87] included patients with comorbid anxiety, and one review included patients with comorbid dysthymia.[78] Outcomes reported in the 10 reviews included the ISI,[29] SL,[30,45,59,78,80,83,87] SE,[29,42,45,59,78,80,83,87] TST,[29,42,45,59,78,80,83,87] WASO,[30,45,59,77,78,80,83] and SQ.[45,59,77,78,80] Follow-up duration was reported in three reviews[29,77,87] and ranged from four weeks to 24 weeks.

h) Antidepressant Drugs Compared With Active Controls

Three SRs compared trazodone with doxepin.[78,80,83] One review only included studies of patients with insomnia alone,[78] and two reviews only included studies of patients with insomnia and a comorbidity.[80,83] Patients' comorbidities included depression,[78,80] dysthymia,[78] and alcohol use disorder recovery.[83] Outcomes reported in the three reviews included SL,[78,80,83] TST,[78,83] WASO,[78,83] and SQ.[78] Follow-up duration was not reported.

i) Antipsychotic Drugs Compared With Inactive Controls

Four SRs[63,70,77,86] included studies that compared quetiapine with inactive controls. Controls included placebo[63,70] and no therapy.[86] One review also included studies that had no comparison groups.[77] One SR[70] only included studies of patients with insomnia alone, one SR[86] included a mix of studies of patients with insomnia alone and studies of patients with insomnia and comorbidities, and two SRs[63,77] only included studies of patients with insomnia and comorbidities. Patient comorbidities included mental illness,[63,86] cancer,[63] Parkinson disease,[63,86] and poly-substance/alcohol recovery.[63,77] Outcomes reported in the four SRs included ISI,[63] SL,[63,70,86] SE,[63,70,86] TST,[63,70,86] SQ,[63,70,77,86] sleep satisfaction (SS),[63] and

hangover/morning sedation.[63] Follow-up duration was reported in three reviews[70,77,86] and ranged from two weeks to 16 weeks.

g) Antipsychotic Drugs Compared With Active Controls

No SRs or SR+MAs were identified for this comparison.

h) Melatonin Compared With Inactive Controls

Eight SR+MAs[30,31,33,43,45,52,58,60] and four SRs[64,67,71,72] compared melatonin with placebo and one systematic review did not report details of the type of inactive control used.[84] Two SR+MAs[45,58] and two SRs[71,72] included only studies of patients with insomnia alone, two SRs[64,67] included a mix of studies of patients with insomnia alone and studies of patients with insomnia and comorbidity, and four SR+MAs[33,43,52,60] only included studies of patients with insomnia and comorbidities. No details were provided on patient diagnosis and/or comorbidities in three reviews.[30,31,84] Patient comorbidities were schizophrenia,[64] dementia,[43,52,64] medical illness (unspecified),[64] Alzheimer disease,[60,64] and chronic disease (unspecified).[67] Outcomes in the thirteen reviews included SL,[30,31,33,58,64,72,84] SE,[31,43,52,58,60,64,67,72] TST,[31,33,43,52,58,60,64,67,71,72] WASO,[63,70,86] SQ,[31,33,43,58,64,67,71,72,84] SS,[84] and QoL.[84] Follow-up duration was reported in five reviews and ranged from one week to 29 weeks.[72,84]

i) Melatonin Compared With Active Controls

No SRs or SR+MAs were identified for this comparison.

j) Diphenhydramine Compared With Inactive Controls

Diphenhydramine was compared with placebo in two SRs[72,83] and one SR+MA.[45] Two reviews only included studies of patients with insomnia alone,[45,72] and one review only included studies of patients with insomnia and comorbidity (alcohol detoxification).[83] Outcomes reported in the three reviews included the ISI,[72] SL,[45,72,83] SE,[72,83] TST,[45,72,83] WASO,[72,83] and SQ.[72,83] Follow-up duration was reported in one SR and ranged from one day to four weeks.[72]

k) Diphenhydramine Compared With Active Controls

No SRs or SR+MAs were identified for this comparison.

l) Cognitive Behavioural Therapy Compared With Inactive Controls

CBT was compared with inactive controls in twenty SR+MAs[29,30,32,35-38,40,44,47,49-51,53-57,62,93] and eight SRs.[65,66,73,75,76,79,82,85] The most common controls were waiting list, placebo,[29,30,35,40,44,50,51,56,57,62,76,79] and sleep hygiene/education.[29,35,38,49,50,53,56,57,62,75,82,85] Five reviews only included studies of patients with insomnia alone,[36,37,50,57,62] twelve reviews included a mix of studies of patients with insomnia alone and studies of patients with insomnia and comorbidity,[32,40,44,47,51,54-56,66,76,79,82] ten reviews only included studies of patients with insomnia and comorbidity,[29,30,35,49,53,65,73,75,90] and one review did not report on the presence or absence of comorbidities.[85] The most common comorbidity was cancer[32,38,40,51,54-56,73,75,76,90] followed by depression,[35,47,54,56,82] pain,[29,40,49,51] alcohol use/dependence,[51,66,82,93] post-traumatic stress disorder (PTSD),[35,51,82] arthritis,[40,56] chronic disease,[40,93] medical illness (unspecified),[79] hypnotic dependence,[82] traumatic brain injury,[65] restless leg syndrome,[56] hearing impairment,[51] chronic obstructive pulmonary disease (COPD),[44] fibromyalgia,[40] end-stage kidney disease,[53] parasomnia,[44] and sleep apnea.[44]

Outcomes reported in the 26 reviews included the ISI,[29,32,35,38,47,51,54-56] SL,[29,30,32,35-38,40,44,47,50,51,53-57,93] SE,[32,35-38,40,44,47,50,51,53-57,75,79,82,85,93] TST,[29,32,35-37,40,44,47,50,51,54-57,85,93] WASO,[29,30,32,35-38,40,44,47,50,51,54-57,85,93] SQ,[29,30,32,35-37,40,49,51,53,55-57,65,75,79,90,93] SS,[85] fatigue severity,[49,53,62,73,75] and QoL.[66,73,75,76] Follow-up duration reported ranged from one week to 104 weeks.

m) Cognitive Behavioural Therapy Compared With Active Controls

CBT and CBT with a single additional component were compared with active controls in three SR+MAs[30,47,93] and three SRs.[76,79,85] Active controls included relaxation therapy,[85] combination therapy of CBT and temazepam,[79] combination of CBT and relaxation therapy,[30] and comparisons between different delivery methods of CBT including Internet-based CBT[47] and self-help CBT,[93] compared with in-person CBT and individual CBT, compared with group CBT.[76] One review included a mix of studies of patients with insomnia alone and studies of patients with insomnia and comorbidity,[47] three reviews only included studies of patients with insomnia and comorbidity,[76,79,93] and two reviews did not report the presence or absence of comorbidities.[30,85] Comorbid conditions included cancer,[76] depression,[47] chronic disease (unspecified),[93] medical illness (unspecified),[79] and alcohol use/dependence.[93] Outcomes reported in the six reviews included the ISI,[47] SL,[30,93] SE,[47,79,85,93] TST,[47,85,93] WASO,[30,79,85,93] SQ,[30,45,93] and QoL.[76] Follow-up duration was reported in four reviews and ranged from four weeks to 44 weeks.[47,76,85,93]

n) Behavioural Interventions Compared With Inactive Controls

Seven SRs[65,66,74,79,81,85,89] and four SR+MAs[29,30,61,62] compared behavioural interventions with inactive controls. Controls included placebo,[29,30,62,79] usual care,[74,89] patient education/information,[29] sleep hygiene,[29,65,81] waiting list,[29,79,81] stimulus control,[85] and solitary activity.[89] Two reviews did not give details on the inactive control.[29,61] Two reviews only included studies of patients with insomnia alone,[62,81] two reviews included a mix of studies of patients with insomnia alone and studies of patients with insomnia and comorbidity,[66,79] and three reviews only included studies of patients with insomnia and comorbidity.[29,65,89] Comorbid conditions included pain,[29] traumatic brain injury,[65] hearing impairment,[29] alcohol use/dependence,[66] medical illness (unspecified),[79] and individuals during post-surgery hospitalization.[89] One SR included studies that used no comparison group.[81] Outcomes reported in the 11 reviews included SL,[29,30,81,85] SE,[79,81] TST,[29,79,81] WASO,[29,30,81] SQ,[61,65,66,74,81,89] fatigue severity,[62] and SS.[79] Follow-up duration was reported in three reviews[29,30,81] and ranged from four weeks to 52 weeks.

o) Behavioural Interventions Compared With Active Controls

One MA[46] compared behavioural interventions with an active control, namely, multi-component CBT. The review only included studies of patients with insomnia and comorbidity (PTSD, nightmares) and follow-up duration was not reported. The review only reported on one outcome: SQ.

p) Mindfulness-Based Interventions Compared With Inactive Controls

One SR+MA[34] compared mindfulness-based interventions with wait-list, sleep hygiene education, and self-monitoring condition. Included patients had insomnia with comorbid cancer diagnoses. Outcomes reported include SL, SE, TST, and SQ. Duration of follow-up reported ranged from six weeks to eight weeks.

q) Mindfulness-Based Interventions Compared With Active Controls

No SRs or SR+MAs were identified for this comparison.

r) Combination Therapies Compared With Inactive Controls

One SR+MA[30] included studies that compared triazolam and/or temazepam combined with CBT compared with placebo, and one review[88] examined pharmacotherapy (unspecified) combined with mindfulness-based stress reduction. Neither review reported comorbidities or duration of follow-up. Outcomes reported in the two reviews included SL,[88] TST,[30,88] and SQ.[88]

s) Combination Therapies Compared With Active Controls

No SRs or SR+MAs were identified for this comparison.

4.3 Critical Appraisal of Included Studies

4.3.1 Systematic Reviews with Meta-Analysis

The AMSTAR 2 assessment for six SR+MAs (20%)[29-31,43,44,62] found that they were high quality: 11 SR+MAs (31%) were rated as moderate quality;[38,39,41,49,50,52,53,55,56,93,94] eight SR+MAs (23%) were rated as low quality;[32,34-36,46,47,51,58] and 10 SR+MAs (29%) were rated as critically low quality.[33,37,40,42,45,48,57,59-61] The two highest-rated items for the SR+MAs were the use of appropriate MA methods ("Yes" for 33/35 SR+MAs), and the inclusion of population, intervention, control, outcome (PICO) components in the eligibility criteria ("Yes" for 32/35 SR+MA). The two lowest-rated items for the SR+MAs were providing a rationale for the types of study designs included in the review ("No" 28/35 SR+MAs) and for the mention of an a priori design or registered protocol ("No" for 22/35 SR+MAs).

Details of the AMSTAR tool are available online at amstar.ca and the results of the AMSTAR assessment are available in Appendix 8, Table 75.

4.3.2 Systematic Reviews Without Meta-Analysis

Overall, the included SRs were rated as very low quality on the AMSTAR 2 tool: two SRs (7%) were rated high quality,[73,81] five SRs (17%) were rated moderate quality,[71,74,75,85,87] five SRs (17%) were rated low quality,[65,66,76,88,89] and 17 SRs (59%) were rated as critically low quality.[63,64,67-70,72,77-80,82-84,86,90,91] The two highest-rated items were adequate description of the included studies ("Yes" or "Partial Yes" for 28/29 SRs) and the presence of a comprehensive literature search ("Yes" or "Partial Yes" for 25/29 SRs). The two lowest-rated items were the reporting of funding sources in the primary studies in each review ("No" for 26/29 SRs) and reporting a list of excluded full-text articles with reasons for exclusion ("No" for 25/29 SRs).

Details of the AMSTAR tool are available online at amstar.ca and the results of the AMSTAR assessment are available in Appendix 8, Table 76.

4.4 Data Synthesis

4.4.1 Efficacy Outcomes

a) Sleep Onset Latency/Sleep Latency

Benzodiazepine Drugs Compared With Inactive Controls

Three SR+MAs compared flurazepam,[30] temazepam,[30,45] or triazolam[30,48] with placebo and reported on SOL in adult populations with insomnia. Two of the SR+MAs[45,48] included patients with insomnia and one SR+MA[30] did not report on comorbidities in the patient population. Across the MAs, SOL was measured using a combination of subjective self-report (sleep diary/log) and PSG.

The MA[30] that compared flurazepam with placebo included 10 RCTs representing 532 patients and reported a statistically significant decrease in SOL compared with placebo (mean difference –23.21 minutes, [95% confidence interval (CI), –34.26 to –12.16; I^2: 51.8%]). The analysis included only RCTs but did not report on study duration or length of follow-up in the included trials.

Two MAs[30,45] that compared temazepam with placebo included four and two RCTs representing 206 and 72 patients, respectively. Both MAs reported a decrease in SL compared with placebo (–11.61 minutes, [95% CI, –23.64 to 0.42; I^2: 84%] and –20.06 minutes, [95% CI, –39.05 to –1.07; I^2: 59%]) but only one analysis reached statistical significance. Both MAs only included RCTs and neither reported on study duration or length of follow-up of the included trials.

Two MAs[30,48] that compared triazolam with placebo included eight RCTs and 28 studies (design not specified) representing 539 and 222 patients, respectively. Both analyses found a statistically significant decrease in SL compared with placebo with mean differences of –19.69 minutes (95% CI, –28.36 to –11.01; I^2: 69%) and –15.5 minutes (95% CI, –19.5 to –11.4; I^2: not reported). One MA[30] only included RCTs and the other[48] did not report the type of included studies; neither reported study duration or length of follow-up.

Details of the interventions and results are available in Appendix 9, Table 77.

A total of 48 unique studies were included across the three SR+MAs that reported SOL outcomes. Two of the primary studies that examined flurazepam and triazolam appear to have been cited twice in two different SR+MAs (inadequate reporting in one SR+MA made it difficult to ascertain) and there was no other overlap of primary studies. The full list of primary studies and potential overlaps is available in Table 89, Appendix 10.1.

Benzodiazepine Drugs Compared With Active Controls

One SR without an MA compared zolpidem with triazolam and reported SOL;[91] results are detailed in the next section of the report (Non-Benzodiazepine Drugs Compared With Active Controls), Appendix 9, Table 77.

Table 4: Benzodiazepine Drugs — Summary of Evidence for Sleep Latency

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Flurazepam vs. placebo[30]	+	NA	NA	NA
Temazepam vs. placebo[30,45]	+/–	+	NA	NA
Triazolam vs. placebo[30,48]	+	+	NA	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Non-Benzodiazepine Drugs Compared With Inactive Controls

Four SR+MAs compared zolpidem[29,30,45] or zopiclone[30,48] with placebo and two SRs[78,80] compared zolpidem with placebo and reported SOL in adult populations with insomnia. Two of the SR+MAs[45,48] only included patients with insomnia, one SR+MA[29] included patients with comorbidities (chronic pain and hearing impairment), two SRs[78,80] included patients with comorbidities (depression and dysthymia), and one SR+MA[30] did not report on comorbidities in the patient population. In the four SR+MAs, SOL was measured using a combination of subjective self-report (e.g., sleep diary) and PSG, one SR[80] used subjective self-report to measure SOL, and one SR[78] did not report the methods used to collect SOL data.

Two MAs[45,48] that examined zolpidem and used objective measures of SOL (PSG) found a statistically significant decrease compared with placebo with mean differences of –11.65 minutes (95% CI, –19.15 to –4.15; I^2: 78%) and –17.6 minutes (95% CI, –23.2 to –12.0; I^2: not reported). The analyses included five RCTs and 29 studies (study designs not reported) representing 356 patients and 429 patients, respectively. Duration of the included studies ranged from one week to 32 weeks, and length of follow-up was not reported in either analysis. Three MAs[29,30,45] examining zolpidem and using subjective or combined objective and subjective measures of SOL also found statistically significant decreases compared with placebo with differences ranging from –12.75 minutes to –19.55 minutes, with heterogeneity ranging from 45% to 95% (I^2). The analyses included between four RCTs and 17 RCTs representing between 373 patients and 1,805 patients. The duration of the included studies and length of follow-up were not reported. An additional analysis[30] of zolpidem on an “as needed” basis that included two trials and 355 patients found similar results with a mean difference of –14.8 minutes (95% CI, –23.41 to –6.19; I^2: 0%). Two SRs[78,80] that compared zolpidem with placebo and that reported SOL outcomes, included the same RCT (306 patients) that also found a statistically significant decrease in SL (P = 0.037).

Two MAs[30,48] that examined zopiclone found a statistically significant decrease in SOL with mean differences of –30.91 minutes (95% CI, –49.37 to –12.44; I^2: 74%) and –19.1 minutes

(95% CI, –26.7 to –11.5; I^2: not reported). The two analyses included five RCTs (356 patients) and 14 studies (design not specified, 429 patients) respectively, and study duration or length of follow-up were not reported in either. No SRs were found that compared zopiclone with inactive controls and that reported on SOL.

Details of the interventions and results are available in Appendix 9, Table 77.

A total of 60 unique studies were reported across four SR+MAs and three SRs that reported on SOL outcomes. One primary study that examined zolpidem was cited four times across two SR+MAs and two SRs. Another primary study that also examined zolpidem was cited three times across three SR+MAs (and possibly included in a fourth, but the reporting was not clear enough to ascertain). Eight primary studies that examined zolpidem were cited at least twice across three SR+MAs. There were no other apparent overlaps in primary studies. The full list of primary studies and potential overlaps is available in Appendix 10.2, Table 91.

Non-Benzodiazepine Drugs Compared With Active Controls

No MAs that compared non-benzodiazepine drugs with active controls and that reported SOL were included in this review. One SR[91] that compared zolpidem with triazolam included one RCT (22 patients) that found a non-statistically significant difference in SOL (–23 minutes versus –15 minutes) after 14 days of treatment. Three SRs that compared trazodone with zolpidem reported on SOL. Results from these studies are detailed in Section 5.4.1.1.8.

Details of the interventions and results are available in Appendix 9, Table 77.

Table 5: Non-Benzodiazepine Drugs — Summary of Evidence for Sleep Latency

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Zolpidem vs. placebo[29,30,45,48,78,80,91]	+	+	NA	+
Zopiclone vs. placebo[30,48]	+	+	NA	NA
Zolpidem vs. triazolam[91]	NA	NA	NA	–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Suvorexant Compared With Inactive Controls

Three SR+MAs[29,39,41] and one SR[69] that compared suvorexant with placebo reported SOL outcomes. Two SR+MAs[39,41] and one SR[69] only included patients with insomnia, and one SR+MA[29] included patients with comorbidities (chronic pain and hearing impairment). Three of the SR+MAs[29,39,41] combined objective (PSG) and subjective (sleep diary) measures of SOL in the analysis, and two of the SR+MAs[39,41] also analyzed objective measures of SOL

alone (PSG). The SR included both subjective (sleep diary) and objective (PSG) measures and analyzed each separately.

Three primary studies reporting data from four RCTs (3,076 patients) were included across the three SR+MAs and one SR, resulting in complete overlap between the included reviews for this outcome. The three MAs found consistent results for SOL compared with placebo, based on objective and subjective measures, with statistically significant decreases ranging from –5.97 minutes (95% CI, –10.01 to –1.92; I^2: 0%) to –9.45 minutes (95% CI, –13.62, –5.65; I^2: 13%). The two analyses of only objective SOL data found similar results (–10.82 minutes [95% CI, –16.72 to –4.93; I^2: 35%] and –6.39 minutes [95% CI, –12.82 to 0.07, I^2: 67%]). However, only one analysis reached statistical significance compared with placebo. The SR compared two dosing schedules of suvorexant (15 mg to 20 mg versus 30 mg to 40 mg) to placebo and found that both statistically significantly decreased SOL on both subjective and objective measures with mean differences of –4.6 minutes (*P* = NS) and –5.9 minutes (*P* < 0.01) for 15 mg to 20 mg suvorexant and –6.4 minutes (*P* < 0.01) and –10.8 minutes (*P* < 0.001) for 30 mg to 40 mg suvorexant. Length of follow-up for the included trials ranged from four weeks to 52 weeks and study duration was not reported.

Details of the interventions and results are available in Appendix 9, Table 77.

The same three primary studies (reporting data from four RCTs) were cited by the three SR+MAs and one SR, resulting in complete overlap across all seven outcomes reported for this treatment comparison. The full list of primary studies and overlaps is available in Appendix 10.3, Tables 96 to 102.

Suvorexant Compared With Active Controls

No SR+MAs or SRs that compared suvorexant with active controls were included.

Table 6: Suvorexant — Changes in Sleep Latency

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Suvorexant vs. placebo[29,39,41,69]	+	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Antidepressant Drugs Compared With Inactive Controls

Three SR+MAs[30,45,59] and three SRs[78,83,87] that compared doxepin with placebo and one SR+MA[30] and three SRs[78,80,83] that compared trazodone with placebo reported SOL. Two SR+MAs[45,59] did not include any patients with comorbidities; one SR+MA[30] did not report on the presence of comorbidities; three SRs[78,80,87] included patients with depression, anxiety, or dysthymia; and one SR[83] included patients undergoing methadone-supported alcohol

withdrawal. Two SR+MAs[30,45] and three SRs[80,83,87] included a combination of objective (PSG) and subject (sleep diary, Likert scale) measures to collect SOL data, one SR+MA[78] did not report the method of data collection in the included studies.

Three MAs (in two publications)[45,59] that compared low doses of doxepin (1 mg to 3 mg) with placebo found a non-statistically significant decrease in SOL with the mean difference ranging from –9.35 minutes (95% CI, –21.89 to 3.19; I^2: 55%) to –0.85 minutes (95% CI, –5.82 to 4.13; I^2: not reported). One MA[59] that compared 3 mg doxepin with placebo found a non-statistically significant increase in SOL (0.37 minutes, [95% CI, –0.66 to 1.40; I^2: not reported]) based on objective and subjective measures. The analyses included between two and four RCTs representing between 279 patients and 558 patients. The duration of the included trials was up to 12 weeks and the length of follow-up was not reported.

Three MAs[30,45,59] that compared high doses of doxepin (6 mg to 25 mg) to placebo found statistically significant decreases in SOL with the mean difference ranging from –8.69 (95% CI, –13.72 to –3.67; I^2: 55%) to –5.29 minutes (95% CI, –9.25 to –1.34; I^2: 0%). One MA[59] that compared 6 mg doxepin with placebo found a non-statistically significant increase in SOL (0.37 minutes, [95% CI, –0.66 to 1.40; I^2: not reported]), based on objective and subjective measures. The analyses included between two and three RCTs representing between 60 and 415 patients. The duration of the included studies was up to 12 weeks and the length of follow-up was not reported.

The SRs that compared doxepin with placebo found similarly mixed results for low (3 mg) and high (6 mg) doxepin compared with placebo. One SR[87] reported that doxepin 3 mg had negative or mixed results based on both objective and subjective measures of SOL, but doxepin 6 mg had a positive impact on SOL in both adult and elderly (age greater than 65 years) populations with insomnia. Two other SRs[78,83] that compared doxepin with placebo that did not report dose information also reported mixed results from included studies, with some studies demonstrating that doxepin was superior to placebo for SOL and others finding no statistically significant difference on objective or subjective measures. The SRs included a range of one to six RCTs. The duration of the included trials ranged from two to 12 weeks. Sample sizes and length of follow-up were not reported.

The MA[30] that compared trazodone (50 mg to 250 mg) with placebo found a statistically significant decrease in SOL based on objective and subjective measures (–12.21 minutes; 95% CI, –22.26 to –2.15; I^2: 0%). The MA included two RCTs representing 208 patients. The duration of the included studies and length of follow-up was not reported. Three SRs[78,80,83] that compared trazodone (50 mg to 300 mg) with placebo, or that compared pre- and post-intervention effects, also found statistically significant decreases in SOL based on objective and subjective measures, however, while the direction of effect was generally consistent, not all the included studies reached statistical significance. The SRs included between one and five studies representing between 29 and 323 patients (two SRs[78,83] included only RCTs, one SR[80] did not specify). The duration of the included studies ranged from one to 12 weeks and length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 77.

A total of 21 unique studies were identified across three SR+MAs and four SRs that reported SOL outcomes. One primary study examining trazodone was cited four times across one SR+MA and three SRs, two primary studies examining doxepin were cited three times across one SR+MA and two SRs, five primary studies examining doxepin were cited twice across two SR+MAs (2 studies) and across one SR+MA and one SR (3 studies), one

primary study examining trazodone was cited twice across one SR+MA and one SR, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.4, Table 103.

Antidepressant Drugs Compared With Active Controls

Three SRs[78,80,83] compared trazodone with zolpidem and included the same RCT representing 306 patients and measuring SOL using subjective measures. The RCT found that SOL for zolpidem was statistically significantly shorter compared with placebo (P < 0.037) than for trazodone compared with placebo (P value not reported); but there was no statistically significant difference in SOL between zolpidem and trazodone.

Details of the interventions and results are available in Appendix 9, Table 77.

The same primary study that compared trazodone and zolpidem was cited across all three SRs in this treatment comparison resulting in complete overlap across all three outcomes. The full list of primary studies and overlaps is available in Appendix 10.5, Tables 108 to 110.

Table 7: Antidepressant Drugs — Summary of Evidence

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Doxepin vs. placebo[30,45,59,78,83,87]	+	+/–	+/–	+/–
Trazodone vs. inactive control[c] 30, 78,80,83	+	NA	NA	+/–
Trazodone vs zolpidem[78,80,83]	NA	NA	NA	+/–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes unspecified controls, placebos, and no comparator (pre- and post-measures).

Antipsychotic Drugs Compared With Inactive Controls

Three SRs[63,70,86] that compared quetiapine with placebo or compared pre- and post-intervention effects reported the SOL outcome; one of the SRs[86] included patients with PTSD and Parkinson disease, while the other two did not include patients with any comorbidities. One SR[63] included SOL data collected by PSG, actigraphy or the Spiegel Sleep Questionnaire, one SR[70] included data collected from sleep logs, and in one SR[86] the method of data collection was not reported.

The SRs included between one and two studies each, with samples sizes ranging from eight to 70 patients. One SR[63] included only RCTs, one SR[86] included only NRCTs, and one SR[70] included both RCTs and NRCTs, thus the included study designs were a mix of RCTs and NRCTs. All three SRs found a general decrease in SOL based on both subjectively and objectively recorded outcomes with changes ranging from –22 minutes (P = NS) to –96.16 minutes (P = 0.007), and two of the SRs[70,86] reported statistically significant reductions in

SOL either compared with placebo or baseline values (15.6 minutes [± 18.1] quetiapine versus 24.5 minutes [± 30.2] placebo, $P < 0.05$; 82 minutes [± 65] pre-intervention versus 29 minutes [± 23] post-intervention, [$P < 0.05$]). The duration of the included studies ranged from two to 12 weeks and the length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 77.

A total of five unique studies were included across three SRs that reported on SOL outcomes. Three primary studies examining quetiapine were cited at least twice across three different SRs and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.6, Table 111.

Antipsychotic Drugs Compared With Active Controls

No SR+MAs or SRs that compared antipsychotic drugs with active controls were identified.

Table 8: Antipsychotic Drugs — Summary of Evidence for Sleep Latency

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Quetiapine vs. inactive controls[c] [63,70,86]	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).
[c] Includes placebo and no comparator (pre- and post-measures).

Melatonin Compared With Inactive Controls

Four SR+MAs[30,31,33,58] and three SRs[64,72,84] that compared melatonin with placebo reported SOL outcomes. One SR+MA[58] and one SR[84] did not include any patients with comorbidities, one SR+MA[33] and two SRs[64,72] included patients with comorbidities (chronic pain, hearing impairment, schizophrenia, dementia/Alzheimer, medical illness, delayed sleep phase, or REM disorder), and two SR+MAs[30,31] and one SR[84] did not report on comorbidities. One SR+MA[33] only included objective measures of SOL (PSG, actigraphy), two SR+MAs[30,58] and two SRs[64,72] included both objective and subjective measures (sleep diary) of SOL, and one SR+MA[31] and one SR[84] did not report the method of data collection.

The four MAs of SOL data included between eight to 12 studies representing 206 to 345 patients (three SR+MAs[30,31,58] included only RCTs and one SR+MA[31] did not specify included study designs) and found a statistically significant decrease compared with placebo in both objective and subjective measures. The effect sizes (mean difference) ranged from –3.71 minutes (95% CI, –6.78 to –0.63; I^2: 39%) to –10.66 minutes (95% CI, –17.61 to –3.72; I^2: 81.5%). The duration of the included studies was not reported and length of follow-up ranged from one week to 28 weeks. The three SRs that compared melatonin with placebo also found a decrease in SL (point estimates not reported), however, many of the changes failed to reach significance. The SRs included between one and 13 studies representing 14

to 772 patients (two SRs[64,72] included only RCTs and one SR[84] included RCTs and NRCTs), the included studies lasted from one to six weeks and the length of follow-up ranged from one week to 29 weeks.

Details of the interventions and results are available in Appendix 9, Table 77.

A total of 24 unique studies were included across four SR+MAs and three SRs that reported SOL outcomes. One primary study was cited five times across four SR+MAs and one SR, three primary studies were cited four times across the four SR+MAs, four primary studies were cited three times across four different SR+MAs and two SRs, seven primary studies were cited twice across the four SR+MAs and two of the SRs, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.7, Table 115.

Melatonin Compared With Active Controls

No SR+MAs or SRs that compared melatonin with active controls were included in this review.

Table 9: Melatonin — Summary of Evidence for Sleep Latency

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Melatonin vs. inactive control[c] 30,31,33,58,64,72,84	+	+	NA	+/–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes inactive controls and placebo.

Diphenhydramine Compared With Inactive Controls

One SR+MA[45] and two SRs[72,83] that compared diphenhydramine with placebo reported SOL outcomes. The SR+MA and both SRs only included patients with insomnia. The SR+MA and both SRs used subjective measures to collect SOL data (sleep diary, questionnaire); one SR[83] also used data from PSG.

The MA of SOL data included two RCTs representing 163 patients and found a non-statistically significant decrease in SOL compared with placebo (mean difference [95% CI]: –2.47 [–8.17 to 3.23], I^2: 0%). The two SRs included three and four RCTs representing 226 and 332 patients, respectively. Both SRs similarly found mixed results in the included trials; all trials showed a decrease in SOL but few reached statistical significance (decrease ranged from 21.6 minutes [P = NS]) to 138.5 minutes [$P < 0.05$]). The duration of the included trials in the SR+MA and SRs ranged from five to 28 days, the length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 77.

A total of five unique studies were included across one SR+MA and two SRs that reported on SOL outcomes. Two primary studies examining diphenhydramine were cited at least three times across one SR+MA and two SRs and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.8, Table 120.

Diphenhydramine Compared With Active Controls

No SR+MAs or SRs that compared diphenhydramine with active controls were identified.

Table 10: Diphenhydramine — Summary of Evidence for Sleep Latency

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Diphenhydramine vs. placebo[45, 72,83]	NA	+/–	NA	+/–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Cognitive Behavioural Therapy Compared With Inactive Controls

Eighteen SR+MAs and seven SRs that compared CBT,[29,32,35,37,40,44,47,51,54,56,66,73,76,85,90,93] CBT with an additional behavioural intervention,[30] and multi-component CBT[30,36,38,50,55,57,75,79] (e.g., CBT combining three or more cognitive/behavioural interventions) to inactive control (e.g., treatment as usual, wait-list, sleep hygiene/sleep education) reported SOL outcomes. Thirteen SR+MAs[29,32,35,38,40,44,47,51,53-56,93] and six SRs[66,73,75,76,79,90] included patients with comorbidities (cancer, chronic pain, fibromyalgia, PTSD, depression, hearing impairment, fibromyalgia, arthritis, restless leg syndrome, chronic obstructive pulmonary disease, alcohol dependence/abuse, kidney disease, sleep apnea, parasomnia, and unspecified chronic or medical illness); one SR[85] and one SR+MA[30] did not report on comorbidities in the patient population; and four SR+MAS[36,37,50,57] did not include any patients with comorbid conditions. Two SR+MAs[56,57] and three SRs[66,85,90] included both objective and subjective measures of SOL. One SR[73] included only objective measures of SOL; 13 SR+MAs[29,30,32,35-38,40,44,47,50,51,93] and three SRs[75,76,79] included only subjective measures of SOL; and three SR+MAs[53-55] did not report the method for measuring SOL.

The fourteen MAs (in 12 publications) that compared CBT with inactive controls included between three and 108 RCTs representing between 122 and 2012 patients. Twelve of the nine MAs found a statistically significant improvement in SOL compared with control and reported effect sizes ranging from -0.83 to 0.29 (standardized mean difference), –9.98 minutes to –26.5 minutes (mean difference), and 0.47 to 0.57 (mean effect size/Hedges' g). Heterogeneity ranged from 0% to 78% with two of the MAs having an I^2 > 75%. The duration of the included studies ranged between two and 12 weeks and length of follow-up ranged from one to 104 weeks. The two MAs that failed to reach statistical significance[44,54] included

three RCTs (135 patients) and 15 RCTs (2,014 patients), respectively, and found similar improvements in SOL with mean differences of –3 minutes (95% CI, –8.92 to 2.92; I^2: 0%) and –18.41 minutes (95% CI, –23.21 to 13.60, I^2: 62%). Five SRs[66,73,76,85,90] that compared CBT with inactive controls included between one and eight studies representing between 60 and 660 patients. Two SRs included only RCTs;[73,85] two SRs included a combination of RCTs, quasi-experimental and/or observational studies;[66,90] and one SR did not report the included study designs.[76] The five SRs found that CBT improved SOL compared with control with three SRs,[73,76,85] reporting a statistically significant difference between groups with changes ranging from a 50% reduction in SOL ($P < 0.05$) to a mean change of –0.42 (95% CI, –0.80 to –0.01).The duration of included studies was not reported in any SR and length of follow-up ranged between four and 104 weeks.

Two SR+MAs,[30,53] that compared CBT combined with relaxation techniques to inactive controls included two and four RCTs representing 26 and 91 patients, respectively. Both found a statistically significant improvement in SOL for CBT and relaxation techniques compared with control with effect sizes of 1.33 (standardized mean difference, [95% CI, 0.46 to 2.19; I^2: 0%]) and –21.5 minutes (mean difference, [95% CI, –42.2 to -0.8; I^2: 74.4%]). The duration of the included studies was not reported in either SR+MA and the length of follow-up ranged from four to eight weeks.

Six MAs[30,36,50,55,57] (in 5 publications) that compared multi-component CBT with inactive controls included between two and 16 studies (sample sizes not reported). Four of the six MAs found a statistically significant improvement in SOL compared with control and reported effect sizes ranging from -0.4 to 0.59 (Cohen's *d*) and -0.70 to 0.41 (Hedges' *g*). Heterogeneity estimates ranged from 0% to 77% with only one SR+MA having estimated heterogeneity above 75%. The other two MAs also found improvements in SOL but failed to reach statistical significance with mean differences of –19.03 (95% CI, –23.93 to 14.12; I^2: 41.9%) and –4.57 (95% CI, –9.75 to 0.61; I^2: 12.5%).The duration of the included studies was not reported and length of follow-up ranged from four to 104 weeks. Two SRs[75,79] that compared multi-component CBT with inactive controls included one and three studies, respectively, representing 235 and 92 patients. Both SRs reported that CBT significantly decreased SL compared with placebo in the included studies (values not reported), duration of the studies was not reported and length of follow-up ranged from eight to 74 weeks.

Details of the interventions and results are available in Appendix 9, Table 77.

A total of 89 unique primary studies were included across the eighteen SR+MAs and seven SRs that reported on SOL outcomes. Five primary studies were cited at least five times across ten different SR+MAs and one SR, six primary studies were cited at least four times across eight different SR+MAs and three different SRs, six primary studies were cited at least three times across eight different SR+MAs and two SRs, thirteen primary studies were cited at least twice across seven different SR+MAs and two SRs, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.9, Table 122.

Cognitive Behavioural Therapy Compared With Active Controls

One SR+MA that compared CBT and relaxation techniques with relaxation techniques only and CBT and relaxation techniques to CBT only,[30] and one SR+MA[93] that compared self-help CBT with in-person CBT reported on SOL outcomes. One SR+MA[93] included patients with comorbidities (alcohol dependence, chronic disease) and one SR+MA[30] did not report

on comorbidities in the patient population. Both SR+MAs only included subjective measures of SOL (sleep diary).

The MA that compared CBT and relaxation techniques with relaxation alone included two studies representing 34 patients and found a non-statistically significant decrease in SOL with a mean difference of –9.2 minutes (95% CI, –37.9 to 19.5; I^2: 37.1%). The duration and length of follow-up of the included studies was not reported.

The MA that compared CBT and relaxation techniques with CBT alone included two studies representing 47 patients and found a non-statistically significant decrease in SOL with a mean difference of –4.6 minutes (95% CI, –20.7 to 11.5; I^2: 0%). The duration and length of follow-up of the included studies was not reported.

The MA that compared self-help CBT with in-person CBT included three studies (sample size not reported) and found SOL was statistically significant worse in the self-help CBT group compared with in-person CBT with a standardized mean difference of –0.37 (95% CI, –0.73 to –0.02; I^2: 0%). The duration of the included studies was not reported and length of follow-up ranged from 17 to 43 weeks.

Details of the interventions and results are available in Appendix 9, Table 77.

Table 11: Cognitive Behavioural Interventions — Summary of Evidence for Sleep Latency

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
CBT vs. inactive control [29,32,35,37,38,40,44,47,51,54,56,66,73,76,85,90,93]	+	+	+	+
CBT + relaxation techniques vs. inactive control[30,53]	+	NA	NA	NA
Multi-component CBT vs. inactive controls[30,36,50,55,57,75,79]	+/–	+	+	+
CBT + relaxation vs. progressive muscle relaxation[30]	–			
CBT + relaxation vs. CBT[30]	–	NA	NA	NA
self-help CBT vs. in-person CBT[93]	–	NA	NA	NA

CBT = cognitive behavioural therapy; MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Behavioural Interventions Compared With Inactive Controls

Two SR+MAs and two SRs that compared sleep restriction,[29,81] relaxation techniques,[30] and multi-component behavioural interventions[29,85] with inactive controls (e.g., placebo, wait-list, sleep hygiene education) reported on SOL outcomes. One SR+MA[29] included patients with comorbidities (chronic pain, hearing impairment), one SR[81] did not include any patients with

comorbid conditions, and one SR+MA[30] and one SR[85] did not report on comorbidities. One SR[81] included a combination of objective and subjective measures to collect SOL data, while the two SR+MAs[29,30] and one SR[85] included only subjective measures of SOL.

The MA[29] that compared sleep restriction to inactive controls included two RCTs (141 patients) and found a non-statistically significant decrease in SOL compared with control, with a mean difference of –11.38 minutes (95% CI, –27.74 to 4.99; I^2: 87%). The length of follow-up for the included studies ranged from four to 26 weeks. The duration of the studies was not reported. The SR[81] examining sleep restriction included four studies representing 192 patients (the SR included a combination of RCTs, NRCTs, and observational designs) and found a decrease in SL compared with control (–19.34 minutes vs. –3.64 minutes; medium weighted effect size 0.64). The length of follow-up of the included studies ranged from 13 to 52 weeks. The duration of the studies was not reported.

The MA[30] that compared relaxation techniques with inactive controls included 13 RCTs (384 patients) and found a non-statistically significant decrease in SOL compared with control with a mean difference –14.56 minutes (95% CI, –29.33 to 0.20; I^2: 96.1%). The duration and length of follow-up of the included studies was not reported.

The MA[30] that compared a multi-component behavioural intervention (e.g., combined multiple behavioural approaches such as sleep restriction, relaxation, sleep hygiene, and/or stimulus control) with inactive controls included three RCTs (146 patients) and found a statistically significant decrease in SOL compared with control with a mean difference of –10.43 minutes (95% CI, –16.31 to –4.55; I^2: 0%). The length of follow-up for the included studies ranged from four to 26 weeks, the duration of the studies was not reported. The SR[85] that compared a multi-component behavioural intervention with stimulus control included one RCT (18 patients) found that both groups had a statistically significant decrease in SOL with decreases from 77.3 minutes to 17.5 minutes ($P < 0.001$) for the multi-component group and 74.9 minutes to 28 minutes ($P < 0.001$) in the stimulus control group. However a statistically significantly larger proportion of patients in the multi-component group (six out of nine) achieved an SOL of less than and equal to 20 minutes compared with the stimulus control group (two out of nine). The length of follow-up of the included study was four weeks and duration of the study was not reported.

Details of the interventions and results are available in Appendix 9, Table 77.

A total of 22 unique studies were included across two SR+MAs and two SRs that reported on SOL outcomes. Two primary studies were cited twice — one in an SR+MA and an SR and the other in two SR+MAs — and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.11, Table 132.

Behavioural Interventions Compared With Active Controls

No included SR+MAs or SRs that compared behavioural interventions with active controls were identified that reported this outcome.

Table 12: Behavioural Interventions — Summary of Evidence for Sleep Latency

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Sleep restriction vs. inactive controls[29,81]	–	NA	NA	+
Relaxation training vs. inactive controls[30]	–	NA	NA	NA
Multi-component behavioural intervention vs. inactive controls[29,85]	+	NA	+	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Mindfulness-Based Interventions Compared With Inactive Controls

One SR+MA[34] that compared mindfulness-based stress reduction and meditation with wait-list, sleep hygiene education, and self-monitoring controls reported SOL outcomes. The SR+MA included patients with comorbidities (depression and cancer) and SOL data were collected using a sleep diary.

The MA included two RCTs representing 83 patients and found a statistically significant decrease in SOL with a standardized mean difference of –0.53 (95% CI, –0.97 to –0.09; I^2: 0%). The length of follow-up of the included trials ranged from six to eight weeks. Study duration was not reported.

Details of the interventions and results are available in Appendix 9, Table 77.

Mindfulness-Based Interventions Compared With Active Controls

No SR+MAs or SRs that compared mindfulness-based interventions with active controls were included in this review.

Table 13: Mindfulness-Based Interventions — Summary of Evidence for Sleep Latency

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Mindfulness-Based stress reduction vs. sleep hygiene education[34]	NA	+	NA	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Combination Therapies Compared With Inactive Controls

One SR[88] examined the pre- and post-intervention effects of a combination of mindfulness-based cognitive therapy/stress reduction and pharmacotherapy on SOL. The SR did not report any comorbidities in the study population and did not report the method of collecting SOL data.

The SR included a single trial representing 14 patients and found the median SOL time was reduced from 30 minutes to 26 minutes. The study duration and length of follow-up were not reported.

Details of the interventions and results are available in Appendix 9, Table 77.

Combination Therapies Compared With Active Controls

No SR+MAs or SRs that compared combination therapies with active controls were included in this review.

Table 14: Combination Therapies — Summary of Evidence for Sleep Latency

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Pharmacotherapy and mindfulness-based cognitive therapy (pre- and post-measures)[88]	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

a) Total Sleep Time

Benzodiazepine Drugs Compared With Inactive Controls

Two SRs with MA (SR+MA) that compared temazepam[45] and triazolam[48] with placebo reported on TST. Two SRs reported on this outcome as well: one that compared triazolam with placebo,[91] and the other that compared pre- and post-intervention effects of triazolam.[77] The two SR+MAs and one SR[91] included patients with insomnia only, and one SR[77] included patients in recovery from alcohol abuse. TST data were collected through subjective measures,[45] sleep diary,[77] from a sleep laboratory,[48] and one SR[91] did not report the method of data collection.

The MA[45] of TST that compared temazepam with placebo included two RCTs representing 72 patients and found a statistically significant increase in TST compared with placebo, with a mean difference of 64.41 minutes (95% CI, 8.07 to 120.76; I^2: 59%). The duration of the included studies was up to eight weeks and length of follow-up was not reported.

The MA[48] of TST that compared triazolam with placebo included 12 studies; the included study designs, sample size, study duration, and length of follow-up were not reported. The analysis found a statistically significant increase in TST compared with placebo with a mean difference of 49.2 minutes (95% CI, 36.0 to 62.5; I^2: not reported). The SRs examining triazolam each included one RCT representing 12 patients and 16 patients, respectively. Both found a statistically significant increase in TST compared with placebo or baseline. The duration of the included studies and the length of follow-up were not reported.

Details of the interventions and results are available in Appendix 9, Table 78.

A total of 33 unique studies were included across the two SR+MAs and two SRs that reported on TST outcomes. Only one primary study that examined triazolam appears to have been cited twice across two different SR+MAs (inadequate reporting in one SR+MA made it difficult to ascertain) and there were no other apparent overlaps between primary studies. The full list of primary studies and potential overlaps is available in Appendix 10.1, Table 90.

Benzodiazepine Drugs Compared With Active Controls

One SR compared zolpidem with triazolam and reported TST; results are detailed in the next section of the report and Appendix 9, Table 78.

Table 15: Benzodiazepine Drugs — Summary of Evidence for Total Sleep Time

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Temazepam vs. placebo[45]	NA	+	NA	NA
Triazolam vs. inactive control[c] [48,77,91]	NA	+	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.

Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.

– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.

+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes placebo and no comparator (pre- and post-measures).

Non-Benzodiazepine Drugs Compared With Inactive Controls

Three SR+MAs that compared zolpidem[29,45,48] or zopiclone[48] with placebo and two SRs that compared zolpidem with placebo,[78,91] reported TST in adult populations with insomnia. Two of the MAs[45,48] and one SR[91] only included patients with insomnia; one MA[29] included patients with comorbidities (chronic pain and hearing impairment), and one SR[78] included patients with comorbidities (depression and dysthymia). In the three MAs, TST was measured using a combination of subjective self-report (e.g., sleep diary) and PSG. The two SRs[78,91] did not report the methods used to collect SOL data.

Two MAs[45,48] examining zolpidem and using objective measures of TST found a statistically significant increase compared with placebo with mean differences of 28.91 minutes (95% CI, 10.85 to 46.97; I^2: 49%) and 32 minutes (95% CI, 21.7 to 42.3; I^2 not reported). The analyses included two RCTs (112 patients) and 23 studies (study designs and sample size not reported); duration of the included studies ranged from one week to 32 weeks, and length of follow-up was not reported in either analysis. Two MAs[29,45] examining zolpidem and using subjective measures of TST also found statistically significant increases compared with placebo with mean differences of 22.95 minutes (95% CI, 2.01 to 43.88; I^2: 0%) and 30.04 minutes (95% CI, 15.12 to 44.96; I^2: 71%), respectively. The analyses included three RCTs (167 patients) and eight RCTs (sample size not reported); neither duration of the included studies nor length of follow-up was reported. Two SRs[78,91] that compared zolpidem with placebo and that reported TST, each included one RCT (306 and 16 patients, respectively) that also found a statistically significant increase compared with placebo ($P < 0.05$).

One MA[48] examining zopiclone found a statistically significant increase in TST with a mean difference of 56.3 minutes (95% CI, 37.3 to 75.4; I^2: not reported), the analysis included 13 studies (sample size and study designs not reported) and the study duration or length of

follow-up was not reported. No SRs that compared zopiclone with inactive controls that reported on TST were found.

Details of the interventions and results are available in Appendix 9, Table 78.

A total of 41 unique studies were reported across three SR+MAs and two SRs that reported on TST outcomes. One primary study that examined zolpidem was possibly cited across three SR+MAs (two are known for certain; in the third SR+MA reporting was not clear enough to ascertain), three primary studies that examined zolpidem were cited at least twice across three SR+MAs and one SR, and there were no other apparent overlaps in primary studies. The full list of primary studies and potential overlaps is available in Table 2, Appendix 10.2.

Non-Benzodiazepine Drugs Compared With Active Controls

No MAs that compared non-benzodiazepine drugs with active controls that reported TST were included in this review. One SRs[91] that compared zolpidem with triazolam included one RCT representing 16 patients that found a statistically significant difference ($P < 0.05$) in TST (+35 minutes versus –112 minutes). Study duration was not reported and length of follow-up was up to seven weeks.

Details of the interventions and results are available in Appendix 9, Table 78.

Table 16: Non-Benzodiazepine Drugs — Summary of Evidence for Total Sleep Time

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Zolpidem vs. placebo[29,45,48,78,91]	+	+	NA	+
Zopiclone vs. placebo[48]	NA	+	NA	NA
Zolpidem vs. triazolam[91]	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Suvorexant Compared With Inactive Controls

Three SR+MAs[29,39,41] and one SR[69] that compared suvorexant with placebo reported TST outcomes. Two SR+MAs[39,41] and one SR[69] only included patients with insomnia and one SR+MA[29] included patients with comorbidities (chronic pain and hearing impairment). Two of the SR+MAs[29,39] and the SR included only subjective (sleep diary) measures, one SR+MA[41] combined objective (PSG) and subjective (sleep diary) measures of TST.

Three primary studies reporting data from four RCTs (3,076 patients) were included across the three SR+MAs and one SR resulting in complete overlap between the included reviews for this outcome. The three MAs found consistent results for TST compared with placebo based on objective and subjective measures with statistically significant increases ranging from 15.97 minutes (95% CI, 4.73 to 27.22; I^2: 63%) to 20.16 minutes (95% CI, 15.30 to 25.01; I^2: 0%). The SR compared two dosing schedules of suvorexant (15-20 mg v 30-40mg) with placebo and found that both statistically significantly increased TST with mean differences of 16 minutes ($P < 0.001$) and 22.1 minutes ($P < 0.0001$). Length of follow-up for the included trials ranged from four to 52 weeks. Study duration was not reported.

Details of the interventions and results are available in Appendix 9, Table 78.

The same three primary studies (reporting data from four RCTs) were cited by the three SR+MAs and one SR across for this treatment comparison, resulting in complete overlap across all seven outcomes reported for this treatment comparison. The full list of primary studies and overlaps is available in Appendix 10.3, Tables 96 to 102.

Suvorexant Compared With Active Controls

No SR+MAs or SRs that compared suvorexant with active controls were included in this review.

Table 17: Suvorexant — Summary of Evidence for Total Sleep Time

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Suvorexant vs. placebo[29,39,41,69]	+	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Antidepressant Drugs Compared With Inactive Controls

Four SR+MAs[29,42,45,59] and three SRs[78,83,87] that compared doxepin with placebo and three SRs[78,80,83] that compared trazodone with placebo reported TST (four SRs total reported TST). Two SR+MAs[45,59] did not include any patients with comorbidities, one SR+MA[29] did not report on the presence of comorbidities, two SRs[78,87] included patients with depression, anxiety, or dysthymia, and one SR[83] included patients undergoing methadone-supported alcohol withdrawal. One SR+MA[45] and two SRs[83,87] included a combination of objective (PSG) and subjective (sleep diary, Likert scale) measures to collect TST data; one SR+MA[29] and one SR[78] only included subjective measures of TST; one SR+MA[42] and one SR[80] included only objective measures of TST; and, one SR+MA[78] did not report the method of data collection in the included studies.

Nine of the ten MAs (in four publications)[29,42,45,59] that compared varying doses of doxepin with placebo (1 mg to 25 mg; two SR+MAs dose not reported), found a statistically significant increase in TST across both objective and subjective measures. The effect sizes (mean difference) ranged from 17.24 minutes (95% CI, 7.43 to 27.05; I^2: not reported) to 70.74 minutes (95% CI, 42.61 to 98.88; I^2: not reported), and the analyses included between two and seven RCTs representing between 60 and 1,476 patients. The included studies lasted for up to 12 weeks and length of follow-up ranged from four to 12 weeks. The three SRs[78,83,87] that compared doxepin with placebo found results consistent with the MAs, specifically, a large majority of the included trials (n = 1/1 trials in one SR,[78] n = 6/7 trials in one SR;[83] number of trials with significant results not reported in one SR[87]) reported that doxepin statistically significantly increased TST compared with placebo. The SRs included between one and seven RCTs (sample sizes not reported), the duration of the included studies ranged from two to 12 weeks and the length of follow-up ranged from four to 12 weeks.

Three SRs[78,80,83] that compared trazodone with placebo or that compared pre- and post-intervention effects of trazodone also found statistically significant increases in TST based on objective and subjective measures (estimates not reported), however, while the direction of effect was generally consistent, not all of the included studies reached statistical significance: two out of three trials in one SR;[78] four of eight trials in one SR;[80] and zero of two trials in one SR,[83] reached statistical significance ($P < 0.05$). The SRs included between one and five studies, representing between 39 and 323 patients. Two SRs[78,83] included only RCTs and one SR[80] did not specify the included study designs. The duration of the included studies ranged from one to 12 weeks and length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 78.

A total of 24 unique studies were identified across four SR+MAs and four SRs that reported TST outcomes. The primary studies in one SR were not clearly reported thus the results here are based on the four SR+MAs and three SRs where primary studies could be identified. Three primary studies examining doxepin were cited four times across three SR+MAs and one SR, two primary studies examining doxepin were cited three times across two SR+MAs and one SR, two primary studies examining doxepin were cited across one SR+MA and one SR, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.4, Table 104.

Antidepressant Drugs Compared With Active Controls

Two SRs[78,83] that compared trazodone with zolpidem included the same RCT representing 306 patients that reported TST and found no statistically significant differences between the two treatment groups (estimates not reported).

Details of the interventions and results are available in Appendix 9, Table 78.

The same primary study that compared trazodone and zolpidem was cited across both SRs in this treatment comparison resulting in complete overlap across all three outcomes. The full list of primary studies and overlaps is available in Appendix 10.5, Tables 108 to 110.

Table 18: Antidepressant Drugs — Summary of Evidence for Total Sleep Time

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Doxepin vs. placebo[29,42,45,59,78,83,87]	+	+	+	+
Trazodone vs. inactive control[c] [78,80,83]	NA	NA	NA	+/-
Trazodone vs. zolpidem[78,83]	NA	NA	NA	-

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.

Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.

– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.

+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes unspecified controls, placebos, and no comparator (pre- and post- measures).

Antipsychotic Drugs Compared With Inactive Controls

Three SRs[63,70,86] that compared quetiapine with placebo or that compared pre- and post-intervention effects reported TST outcomes. One of the SRs[86] included patients with PTSD and Parkinson disease, while the other two did not include patients with any comorbidity. One SR[63] included TST data collected by PSG or actigraphy, one SR[70] included data collected from sleep logs and through objective measures, and in one SR[86] the method of data collection was not reported.

The SRs included between one and two studies each, with samples sizes ranging from eight to 52 patients. Included study designs were a mix of RCTs and NRCTs. All three SRs found a general increase in TST compared with placebo or from baseline, based on both subjectively and objectively recorded outcomes; however, none of the results were consistently statistically significant. Pre-intervention TST values for the quetiapine treatment groups ranged from 240 (± 60) minutes to 347.5 (± 100.9) minutes and post-interventions TST values ranged from 360 (± 120) minutes to 395.6 (± 62.3) minutes. One SR included a trial (18 patients) that reported a significant decrease in TST compared with baseline values (396 ± 62 minutes to 358 ± 51 minutes, $P < 0.05$).The duration of the included studies ranged from two to 12 weeks and the length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 78.

A total of four unique studies were included across three SRs that reported on TST outcomes. One primary study examining quetiapine was cited three times across the three SRs, one primary study examining quetiapine was cited twice across two SRs, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.6, Table 112.

Antipsychotic Drugs Compared With Active Controls

No SR+MAs or SRs that compared antipsychotic drugs with active controls were included in this review.

Table 19: Antipsychotic drugs — Summary of Evidence for Total Sleep Time

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Quetiapine vs. inactive controls[c] [63,70,86]	NA	NA	NA	+/–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).
[c] Includes placebo and no comparator (pre- and post- measures).

Melatonin Compared With Inactive Controls

Six SR+MAs[31,33,43,52,58,60] and four SRs[64,67,71,72] that compared melatonin with placebo reported TST outcomes. Two SR+MAs[45,58] and two SRs[71,72] did not include any patients with comorbidities; three SR+MAs[52,60,72] and one SR[64] included patients with comorbid dementia, Alzheimer or Parkinson disease; one SR[67] included patients with a comorbid chronic illness; one SR+MA[33] and one SR[60] included patients with comorbid sleep disorders (delayed sleep phase or REM sleep disorder); and two SR+MAs[30,31] and one SR[84] did not report on comorbidities. Four SR+MA[33,52,60,72] only included objective measures of TST (PSG, actigraphy); one SR+MA and three SRs included both objective and subjective measures (sleep diary) of TST; and one SR+MA did not report the method of data collection.

Two of the six MAs of TST data collected through objective and subjective measures found a statistically significant increase with effect sizes ranging from 3.2 minutes (95% CI, 7.04 to 13.65; I^2: 12%) to 24.36 minutes (95% CI, 3.26 to 45.46; I^2: 59%). The other four MAs found a similar direction of effect that failed to reach statistical significance with mean differences in three SR+MAs[31,43,60] ranging from 4 (95% CI, –10.5 to 18.5; I^2: 67.6%) to 12.68 (95% CI, –10.38 to 35.15; I^2: 34%), and a mean change in one SR+MA[33] of 0.34 (95% CI, –11.19 to 11.87; I^2: not reported). The analyses included between two to 11 studies representing 197 to 497 patients, five SR+MAs[33,43,52,58,60] included only RCTs and one SR+MA[31] did not report the included study designs. The duration of the included studies and the length of follow-up were not reported. The four SRs included between one and 15 RCTs representing between 25 and 791 patients and also found an increase in TST; however, for many of the primary studies included in the reviews, the change failed to reach significance (estimates not consistently reported). The duration of the included studies and the length of follow-up were not reported.

Details of the interventions and results are available in Appendix 9, Table 78.

A total of 31 unique studies were included across six SR+MAs and four SRs that reported TST outcomes. Inadequate reporting in one SR prevented identification of the primary studies included in the review. The results below represent only the numbers of primary studies and overlaps that could be ascertained with some certainty. Four primary studies

were cited three times across five different SR+MAs and three SRs, twelve primary studies were cited at least twice across four SR+MAs and two SRs, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.7, Table 116.

Melatonin Compared With Active Controls

No SR+MAs or SRs that compared melatonin with active controls were included in this review.

Table 20: Melatonin — Summary of Evidence for Total Sleep Time

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Melatonin vs. inactive controls[c] 31,33,43,52,58,60,64,67,71,72	+/–	+/–	+	+/–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes inactive controls and placebo.

Diphenhydramine Compared With Inactive Controls

One SR+MA[45] and two SRs[72,83] that compared diphenhydramine with placebo reported TST outcomes. The SR+MA and both SRs only included patients with insomnia. The SR+MA and both SRs used subjective measures to collect TST data (sleep diary, questionnaire); one SR[83] also used data from PSG.

The MA of TST data included 2 RCTs representing 164 patients and found a non-statistically significant increase in TST compared with placebo (17.86 minutes; 95% CI, -3.79 to 39.51; I^2: 0%). The two SRs included two and four RCTs representing 204 and 332 patients, respectively. Both SRs found mixed results in the included trials with some showing no change or non-statistically significant increases in TST; In one SR,[83] only one trial found a statistically significant increase in TST compared with placebo, while the other found no difference. The duration of the included trials in the SR+MA and SRs ranged from five days to 28 days. The length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 78.

A total of four unique studies were included across one SR+MA and two SRs that reported on TST outcomes. Two primary studies examining diphenhydramine were cited at least three times across one SR+MA and two SRs and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Table 2, Appendix 10.8.

Diphenhydramine Compared With Active Controls

No SR+MAs or SRs that compared diphenhydramine with active controls were included in this review.

Table 21: Diphenhydramine — Summary of Evidence for Total Sleep Time

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Diphenhydramine vs. placebo[45,72,83]	NA	-	NA	+/-

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Cognitive Behavioural Therapy Compared With Inactive Controls

Fifteen SR+MAs and three SRs compared CBT,[29,32,35,37,40,44,47,51,54,56,73,90,93] or multi-component CBT,[36,50,55,57,75] with inactive control and assessed TST outcomes. Eleven SR+MAs[29,32,35,40,44,47,51,54-56,93] and three SRs[73,75,90] included patients with comorbidities (chronic pain, cancer, hearing impairment, PTSD, depression, restless leg syndrome, arthritis, alcohol dependence, COPD, parasomnia, sleep apnea, and unspecified chronic disease) and four SR+MAS[36,37,50,57] did not include any patients with comorbid conditions. Three SR+MAs[44,56,57] and two SRs[73,90] included both objective and subjective measures of TST; 11 SR+MAs[29,32,35-37,40,47,50,51,54,93] included only subjective measures of TST; one SR[75] included only objective measures of TST; and one SR+MA[55] did not report the method of measuring TST.

The twelve MAs (in 11 publications)[29,32,35,37,40,44,47,51,54,56,93] that compared CBT with inactive controls included between two and 91 RCTs representing between 202 and 2,012 patients. Four of the seven MAs found a statistically significant improvement in TST compared with control and reported effect sizes ranging from 14.24 minutes to 22.3 minutes (mean difference) and a standardized mean difference of 0.16. Heterogeneity ranged from 0% to 56% with none of the MAs having an I^2 greater than 75%. The other eight MAs also found improvements in TST with effect sizes ranging from –0.01 to 0.39 (standardized mean difference) and –14.56 to 18.93 (mean difference). Heterogeneity ranged from 0% to 38% and no MAs had an estimated heterogeneity of greater than 75%. . The duration of the included RCTs ranged between two and 12 weeks and length of follow-up ranged from one to 104 weeks. Two SRs[73,90] compared CBT with inactive controls and included one and eight studies representing between 12 and 660 patients respectively. One SR[73] included only RCTs and one SR[90] included a combination of RCTs, quasi-experimental, and observational designs. Both SRs found that CBT improved TST compared with control, with no SR reporting a statistically significant difference between groups. The duration of included studies was not reported in any SR and length of follow-up ranged between four and eight weeks.

Five MAs (in four publications)[36,50,55,57] that compared multi-component CBT with inactive controls included between two and 16 RCTs (sample sizes not reported). Four of the five MAs found a statistically significant improvement in TST compared with control and reported effect sizes ranging from 0.21 to 0.71 (standardized mean difference). Heterogeneity ranged from 0% to 78% with only one SR+MA having heterogeneity estimated above 75%. The other meta-analysis also found an improvement in TST that failed to reach statistical significance with a mean difference of 7.61 minutes (95% CI, –0.51 to 15.74; I^2: 3.1%). The duration of the included studies was not reported and length of follow-up ranged from four to 104 weeks. One SR[75] that compared multi-component CBT with inactive controls included two studies representing 369 patients and found a non-statistically significant change in TST compared with control (estimates not reported). The duration of the included studies was not reported and the length of follow-up ranged from eight to 74 weeks.

Details of the interventions and results are available in Appendix 9, Table 78.

A possible total of 72 unique primary studies were included across the 15 SR+MAs and three SRs that reported on TST outcomes. Due to inadequate reporting in two SR+MAs and two SRs, the specific primary studies associated with this outcome could not be determined and they are not included in the following counts. Three primary studies were cited at least five times across five SR+MAs: six primary studies were cited at least four times across nine different SR+MAs; five primary studies were cited at least three times across six different SR+MAs and two SRs; eleven primary studies were cited at least twice across eight different SR+MAs and two SRs; and there were no other apparent overlaps in primary studies. The full list of primary studies and overlapping primary studies is available in Appendix 10.9, Table 123.

Cognitive Behavioural Therapy Compared With Active Controls

Two SR+MAs[47,93] that compared different delivery methods of CBT and one SR[85] that compared CBT with relaxation techniques reported on TST outcomes. Both SR+MAs[47,93] included patients with comorbidities (alcohol dependence, chronic disease, major depression) and one SR[85] did not report on comorbidities in the patient population. The two SR+MAs included only subjective measures of TST (sleep diary). The SR included both objective and subjective measures of TST.

The two MAs that compared different delivery methods of CBT included three and two RCTs respectively (sample sizes not reported) and found discordant results. One SR+MA[93] compared self-help CBT with in-person CBT and found a non-statistically significant decrease in TST (Cohen's *d* 0.50 [95% CI, –0.40 to 0.31]; I^2: 50.9%) for the self-help CBT group. The other SR+MA[47] compared Internet-based CBT with in-person CBT and found a non-statistically significant increase in TST (mean difference 0.73 [95% CI, –311.8 to 313.3]; I^2: 75%) for the Internet-based CBT group. The duration of the included studies was not reported and the length of follow-up ranged from four to 48 weeks.

The SR that compared CBT with relaxation therapy included one RCT representing 46 patients and found that CBT increased TST (351.24 minutes pre-intervention to 372.4 minutes post-intervention) while relaxation decreased overall TST (352.1 minutes pre-intervention to 337.9 minutes post-intervention). The statistical significance of this change was not reported. The duration of the included studies was not reported and the length of follow-up ranged from 12 weeks to 104 weeks.

Details of the interventions and results are available in Appendix 9, Table 78.

Inadequate reporting in one of the SR+MAs[93] that compared multi-component CBT with CBT alone prevented ascertainment of the specific primary studies that contributed data to this outcome and thus prevented any determination of overlap between the two SR+MAs that compared multi-component CBT with CBT alone and reported TST. The primary studies that could be ascertained from one of the SR+MAs[47] are reported in Appendix 10.10, Table 130.

Table 22: Cognitive Behavioural Interventions — Summary of Evidence for Total Sleep Time

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
CBT vs. inactive controls[29,32,35,37,40,44,47,51,54,56,73,90,93]	+/–	+/–	+/–	+/–
Multi-component CBT vs. inactive controls[36,50,55,57,75]	+/–	+	–	NA
Multi-component CBT vs. CBT[47,93]	–	–	NA	NA
CBT vs. relaxation techniques[85]	NA	NA	NA	+/–

CBT = cognitive behavioural therapy; MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Behavioural Interventions Compared With Inactive Controls

One SR+MA[29] and two SRs[79,81] that compared sleep restriction[29,79,81] and relaxation techniques[29] with inactive controls (e.g., placebo, wait-list, sleep hygiene education) reported on TST outcomes. One SR+MA[29] and one SR[79] included patients with comorbidities (chronic pain, hearing impairment; medical illness) and one SR[81] did not include any patients with comorbid conditions. One SR[81] included a combination of objective and subjective measures to collect TST data; one SR[79] included only objective measures of TST; and, the SR+MAs[29] included only subjective measures of TST.

The MA[29] that compared sleep restriction with inactive controls included two RCTs (141 patients) and found a non-statistically significant decrease (worsening) in TST compared with control with a mean difference of –17.57 minutes (95% CI, –102.36 to 67.21; I^2: 93%). The length of follow-up for the included studies ranged from four to 26 weeks, the duration of the studies was not reported. The two SRs[79,81] examining sleep restriction included one and four studies (55 and 192 patients, respectively; a combination of RCTs, NRCTs, and observational study designs) and, in contrast to the MA, found non-statistically significant increases in TST compared with control conditions, with one SR[81] reporting a change of 17.06 minutes from pre- to post-intervention for patients receiving sleep restriction therapy (overall effect size of 0.3, *P* value not reported); estimates of treatment effects were not reported in the other SR[79] but it reported that sleep restriction was more effective than control. The length of follow-up of the included studies ranged from 13 to 52 weeks; the duration of the studies was not reported.

The MA[29] that compared relaxation therapy with passive control included two RCTs (77 patients) and found a non-statistically significant increase in TST compared with control with a mean difference of 10.23 minutes (95% CI, –19.64 to 40.11; I^2: 29%). The length of follow-up for the included studies ranged from four to 26 weeks, the duration of the studies was not reported.

Details of the interventions and results are available in Appendix 9, Table 78.

A total of seven unique studies were included across one SR+MA and two SRs that reported on TST outcomes. Two primary studies were cited twice - one in an SR+MA and an SR and the other in two SR+MAs - and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.11, Table 133.

Behavioural Interventions Compared With Active Controls

No included SR+MAs or SRs that compared behavioural interventions with active controls were identified that reported this outcome.

Table 23: Behavioural interventions — Summary of Evidence for Total Sleep Time

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Sleep restriction vs. inactive controls[29,79,81]	-	NA	-	-
Relaxation training vs. inactive controls[29]	-	NA	NA	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Mindfulness-Based Interventions Compared With Inactive Controls

One SR+MA[34] that compared mindfulness-based stress reduction and meditation with wait-list, sleep hygiene education, and self-monitoring controls reported TST. The SR+MA included patients with comorbidities (depression and cancer) and TST data were collected using a sleep diary.

The MA included two RCTs representing 58 patients and found a small, non-statistically significant increase in TST with a standardized mean difference of 0.28 (95% CI, –0.24 to 0.80; I^2: 0%). The length of follow-up of the included trials ranged from six to eight weeks; study duration was not reported.

Details of the interventions and results are available in Appendix 9, Table 78.

Mindfulness-Based Interventions Compared With Active Controls

No SR+MAs or SRs that compared mindfulness-based interventions with active controls were included in this review.

Table 24: Mindfulness-Based Interventions — Summary of Evidence for Total Sleep Time

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Mindfulness-based stress reduction vs. sleep hygiene education[34]	NA	–	NA	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Combination Therapies Compared With Inactive Controls

One SR+MA[30] and one SR[88] examined the effect of combination therapies on TST. The SR+MA examined a combination of triazolam or temazepam with CBT compared with placebo. The SR examined pre- and post-treatment effects of mindfulness-based cognitive therapy/stress reduction with pharmacotherapy (unspecified). The SR+MA and the SR did not report on comorbidities in the patient population and only the SR+MA reported the method of collecting TST data (sleep diary).

The MA for TST included two RCTs representing 52 patients and found a non-statistically significant increase in TST compared with placebo (mean difference 23.2 minutes, [95%CI –2.3 to 48.8; I^2: 0%]). The analysis did not report on study duration or the length of follow-up. The SR included two observational studies representing 30 patients and found that TST increased post-treatment and that effects persisted for at least 12 months (significance / *P* values not reported).

Details of the interventions and results are available in Appendix 9, Table 78.

A total of four unique studies were included across one SR+MA and one SR that reported on TST outcomes. There were no apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.13, Table 139.

Combination Therapies Compared With Active Controls

No SR+MAs or SRs that compared combination therapies with active controls were included in this review.

Table 25: Combination Therapies — Summary of Evidence for Total Sleep Time

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Triazolam, temazepam, and CBT[30]	–	NA	NA	NA
Pharmacotherapy and mindfulness-based cognitive therapy and stress reduction[88]	NA	NA	NA	+

CBT = cognitive behavioural therapy; MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

a) Wake After Sleep Onset

Benzodiazepine Drugs Compared With Inactive Controls

One[30] SR+MA that compared temazepam and triazolam with placebo reported on WASO. The SR+MA did not report on comorbidities in the patient population and, in the included studies, data were collected through both subjective self-report (sleep diary) and PSG.

The MA that compared temazepam with placebo included two RCTs representing 72 patients. The MA found a statistically significant decrease in WASO compared with placebo with a mean difference of –23.66 minutes (95% CI, –36.57 to –10.76; I^2: 0%). Neither the study duration nor length of follow-up of the included trials was reported.

The MA that compared triazolam with placebo included two RCTs representing 57 patients and found a statistically significant decrease in WASO compared with placebo with a mean difference of–39.96 minutes (95% CI, –64.47 to –15.45; I^2: 0%). Neither the study duration nor length of follow-up of the included trial was reported.

Details of the interventions and results are available in Appendix 9, Table 79.

Benzodiazepine Drugs Compared With Active Controls

One SR compared zolpidem with triazolam and reported WASO. Results are detailed in the next section of the report and in Appendix 9, Table 79.

Table 26: Benzodiazepine Drugs — Summary of Evidence for Wake After Sleep Onset

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Temazepam vs. placebo[30]	+	NA	NA	NA
Triazolam vs. placebo[30]	+	NA	NA	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Non-Benzodiazepine Drugs Compared With Inactive Controls

Two SR+MAs that compared zolpidem[30,45] with placebo and three SRs that compared zolpidem with placebo[78,80,91] reported WASO in adult populations with insomnia. One of the MAs[45] and one SR[91] only included patients with insomnia, two SRs[78,80] included patients with comorbidities (depression and dysthymia), and one meta-analysis[30] did not report on comorbidities in the patient population. In the two MAs, WASO was measured using a combination of subjective self-report (e.g., sleep diary) and PSG; one SR[80] used subjective self-report to measure WASO and two systematic reviews[78,91] did not report the methods used to collect WASO data.

One MA[45] examining zolpidem and using objective measures of WASO (PSG) found a statistically significant decrease compared with placebo with mean differences of –25.46 minutes (95% CI, –32.99 to –17.94; I^2: 0%). The analysis included two RCTs representing 112 patients. Duration of the included studies ranged from two to 32 weeks and length of follow-up was not reported in either analysis. Two MAs[30,45] examining zolpidem and using subjective or combined objective and subjective measures of WASO also found decreases compared with placebo with one meta-analysis with a non-statistically significant difference of –8.46 minutes (95% CI, –20.17 to 3.26; I^2: 64.1%) and the other with a statistically significant difference of –13.57 minutes (95% CI, –19.84 to –7.30; I^2: 92%). The analyses included seven and six RCTs representing 690 and 784 patients, respectively. Duration of the included studies ranged from two to 32 weeks for one MA,[45] and was not reported for the other;[30] and, length of follow-up was not reported by either. Two of the SRs[78,80] comparing zolpidem to placebo and reporting WASO outcomes included the same RCT (306 patients) that also found a statistically significant decrease compared with placebo (P = 0.04) and one SR[91] included two RCTs (83 patients) with discordant results; one trial found a statistically significant decrease in WASO (pre- / post-intervention –35 to +116 minutes; P < 0.05) while the other found a non-statistically significant increase compared with placebo (pre- / post-intervention +6 to –8 minutes; P = NS).

Details of the interventions and results are available in Appendix 9, Table 79.

A total of 15 unique studies were reported across two SR+MAs and three SRs that reported WASO outcomes. One primary study that examined zolpidem was cited four times across two SR+MAs and two SRs and there were no other apparent overlaps in primary studies. The full list of primary studies and potential overlaps is available in Appendix 10.2, Table 93.

Non-Benzodiazepine Drugs Compared With Active Controls

No MAs that compared non-benzodiazepine drugs with active controls that reported WASO were included in this review. One SR[91] that compared zolpidem with triazolam included three RCTs (102 patients) that found a statistically significant decrease in WASO in two trials ($P < 0.05$ and $P < 0.01$) and a non-statistically significant increase in one trial. Length of follow-up of the included trials ranged from two to seven weeks. Duration of the studies was not reported.

Details of the interventions and results are available in Appendix 9, Table 79.

Table 27: Non-Benzodiazepine Drugs — Summary of Evidence for Wake After Sleep Onset

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Zolpidem vs. placebo [30,45,78,80,91]	+	+	NA	+
Zolpidem vs. triazolam[91]	NA	NA	NA	+/–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.

Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.

– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.

+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Suvorexant Compared With Inactive Controls

Two SR+MAs[39,41] and one SR[69] that compared suvorexant with placebo reported WASO outcomes. The two SR+MAs[39,41] and one SR[69] only included patients with insomnia. The two SR+MAs and the SR analyzed objective (PSG) and subjective (sleep diary) measures of WASO separately.

Three primary studies reporting data from four RCTs (3,076 patients) were included across the two SR+MAs and one SR resulting in complete overlap between the included reviews for this outcome. The two MAs found consistent improvements for WASO compared with placebo on both objective and subjective measures, however the magnitude of the change was substantially different between the two. On objective measures the change in WASO was –25.32 and –24.19 minutes while on the subjective measures the change was –7.75 and –7.51 minutes. The SR found results consistent with two MAs, the change in WASO for both dosing schedules (15 mg to 20 mg versus 30 mg to 40 mg) compared with placebo was statistically significant for both objective and subjective measures but with a difference in magnitude (15 mg to 20 mg: –23.1 versus –4.7 minutes; 30 mg to 40mg: –25.9 versus

–7.8 minutes). Length of follow-up for the included trials ranged from four to 52 weeks and study duration was not reported.

Details of the interventions and results are available in Appendix 9, Table 79.

The same three primary studies (reporting data from four RCTs) were cited by the three SR+MAs and one SR across for this treatment comparison, resulting in complete overlap across all seven outcomes reported for this treatment comparison. The full list of primary studies and overlaps is available in Appendix 10.3, Tables 96 to 102.

Suvorexant Compared With Active Controls

No SR+MAs or SRs that compared suvorexant with active controls were included in this review.

Table 28: Suvorexant — Summary of Evidence for Wake After Sleep Onset

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Suvorexant vs. placebo[39,41,69]	+	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Antidepressant Drugs Compared With Inactive Controls

Two SR+MAs[45,59] and two SRs[83,87] that compared doxepin with placebo and four SRs[77,78,80,83] that compared trazodone with placebo reported WASO. Two SR+MAs[45,59] did not include any patients with comorbidities, two SRs[78,80] included patients with depression or dysthymia, one SR[83] included patients undergoing methadone-supported alcohol withdrawal, and one SR[77] included patients in recovery from alcohol abuse. One SR+MA[45] and three SRs[80,83,87] included a combination of objective (PSG) and subjective (sleep diary, Likert scale) measures to collect WASO data, one SR[77] only included objective measures of WASO, and one SR+MA[59] and one SR[78] did not report the method of data collection in the included studies.

Six of the seven MAs (in two publications)[45,59] that compared varying doses of doxepin (1 mg to 25 mg) with placebo found a statistically significant decrease in WASO across both objective and subjective measures, the seventh meta-analysis also found a decrease in WASO but failed to reach statistical significance (mean difference –3.57 minutes; 95% CI, –7.46 to 0.32; I^2: not reported). The effect sizes for the statistically significant analyses (mean difference) ranged from –5.71 minutes (95% CI, –9.39 to –2.02; I^2: not reported) to –23.4 minutes (95% CI, –30.34 to –16.46; I^2: 0%). The seven MAs included between two and four RCTs representing between 60 and 558 patients. The included studies lasted for up to 12 weeks, and the length of follow-up was not reported. The two SRs[83,87] that compared doxepin with placebo found results consistent with the MAs. A large majority of the included

trials (six out of seven trials) reported that doxepin statistically significantly decreased WASO compared with placebo. One SR included seven studies (samples sizes not reported) and the other SR did not report the number of included studies or sample sizes. The duration of the included studies ranged from two to 12 weeks, and the length of follow-up ranged from four to 12 weeks.

Four SRs[77,78,80,83] that compared trazodone with placebo or that compared pre- and post-intervention effects of trazodone also found statistically significant decreases in WASO based on objective and subjective measures, however while the direction of effect was generally consistent not all the included studies reached statistical significance (values not reported). The SRs included between one and two studies representing between 15 and 306 patients, the duration of the included studies ranged from one to 12 weeks and length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 79.

A total of 13 unique studies were identified across two SR+MAs and five SRs that reported WASO outcomes. The primary studies in one SR were not clearly reported, thus the results here are based on the two SR+MAs and four SRs where primary studies could be identified. Two primary studies examining doxepin were cited twice across two SR+MAs and one SR, four primary studies examining doxepin and one study examining trazodone were cited twice across one SR+MA and one SR, one primary study examining trazodone was cited twice across two SRs, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.4, Table 105.

Antidepressant Drugs Compared With Active Controls

Two SRs[78,83] that compared trazodone with zolpidem included the same RCT representing 306 patients that reported WASO and found no statistically significant differences between the two treatment groups (values not reported).

Details of the interventions and results are available in Appendix 9, Table 79.

The same primary study that compared trazodone with zolpidem was cited across both SRs in this treatment comparison, resulting in complete overlap for this outcome The full list of primary studies and overlaps is available in Appendix 10.5, Tables 108 to 110.

Table 29: Antidepressant Drugs — Summary of Evidence for Wake After Sleep Onset

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Doxepin vs. placebo[45,59,83,87]	NA	+	+	+
Trazodone vs. inactive control[c 77,78,80,83]	NA	NA	NA	+/–
Trazodone vs. zolpidem[78,83]	NA	NA	NA	–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).
[c] Includes unspecified controls, placebos, and no comparator (pre- and post-measures).

Antipsychotic Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared antipsychotic drugs with active controls reported this outcome.

Antipsychotic Drugs Compared With Active Controls

No SR+MAs or SRs that compared antipsychotic drugs with active controls were included in this review.

Melatonin Compared With Inactive Controls

Three SR+MAs [30,31,60] and two SRs [67,84] that compared melatonin with placebo reported WASO outcomes. One SR included patients with comorbid dementia, Alzheimer or Parkinson disease; one SR included patients with a comorbid chronic illness; and two SR+MAs and one SR did not report on comorbidities. One SR+MA and one SR only included objective measures of WASO (PSG, actigraphy); one SR+MA included both objective and subjective measures (sleep diary) of WASO; and one SR+MA and one SR did not report on the included outcome.

None of the four MAs (three publications) of WASO data collected through objective and subjective measures found a statistically significant change in WASO with mean differences ranging from –6.3 minutes (95% CI, –16.6 to 3.9; I^2: 35.3%) to 10.93 minutes (95% CI, –6.07 to 27.92; I^2: 0%), The analyses included between two to five studies representing 144 patients to 497 patients; the duration of the included studies and the length of follow-up were not reported. The two SRs each included one study representing 12 patients and found a statistically significant decrease in WASO. The duration of the included studies and the length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 79.

A total of 13 unique studies were included across three SR+MAs and two SRs that reported WASO outcomes. Three primary studies were cited at least twice across two SR+MAs and one SR, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Table 3, Appendix 10.7.

Melatonin Compared With Active Controls

No SR+MAs or SRs that compared melatonin with active controls were included in this review.

Table 30: Melatonin — Summary of Evidence for Wake After Sleep Onset

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Melatonin vs. inactive controls[c] [30,31,60,67,84]	–	–	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes inactive controls and placebo.

Diphenhydramine Compared With Inactive Controls

One SR[83] that compared diphenhydramine with placebo reported WASO outcomes: it did not include any patients with comorbidities and used a subjective measure (questionnaire) to collect data.

The SR included one RCT representing 17 patients that reported WASO data and found there was no statistically significant difference between groups. The trial lasted for three weeks and length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 79.

Diphenhydramine Compared With Active Controls

No SR+MAs or SRs that compared diphenhydramine with active controls were included in this review.

Table 31: Diphenhydramine — Summary of Evidence for Wake After Sleep Onset

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Diphenhydramine vs. placebo[83]	NA	NA	NA	–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Cognitive Behavioural Therapy Compared With Inactive Controls

Seventeen SR+MAs and six SRs that compared CBT,[29,32,35,37,38,40,44,47,51,54,56,66,73,85,90,93] CBT with an additional behavioural intervention,[30] and multi-component CBT[36,50,55,57,75,79] to inactive control reported WASO outcomes. Twelve SR+MAs[29,32,35,38,40,44,47,51,54-56,93] and five SRs[66,73,75,79,90] included patients with comorbidities (cancer, chronic pain, PTSD, depression, hearing impairment, fibromyalgia, arthritis, restless leg syndrome, COPD, alcohol dependence/abuse, sleep apnea, parasomnia, and unspecified chronic or medical illness), one SR[85] and one SR+MA[30] did not report on comorbidities in the patient population, and four SR+MAs[36,37,50,57] did not include any patients with comorbid conditions. Two SR+MAs[44,56] and six SRs[66,73,75,79,85,90] included both objective and subjective measures of WASO; 13 SR+MAs[29,30,32,35,36,38,40,47,50,51,54,57,93] included only subjective measures of WASO, and one SR+MA[55] did not report the method of measuring WASO.

The fifteen MAs (in 12 publications)[29,32,35,37,38,40,44,47,51,54,56,93] that compared CBT with inactive controls included between three and 71 studies representing between 122 and 1,655 patients. Fourteen of the fifteen MAs found a statistically significant reduction in WASO compared with control and reported effect sizes ranging from –1.02 to 0.3 (standardized mean difference), –20.44 minutes to –38.18 minutes (mean difference), and 0.63 to 0.65 (mean effect size/Hedges' g). Heterogeneity ranged from 0% to 76% with one of the MAs having an I^2 > 75%. The 15th MA found similar results with a non-statistically significant decrease in WASO compared with control (standardized mean difference –0.18, [95% CI, –0.43 to 0.06; I^2:55%]). The duration of the included studies ranged between two and 12 weeks and length of follow-up ranged from one to 104 weeks. Four SRs[66,73,85,90] that compared CBT with inactive controls included between one and eight studies representing between 12 and 660 patients. The four SRs all found that CBT improved WASO compared with control with at least one SR[85] reporting a statistically and clinically significant improvement. The duration of included studies was not reported in any SR and length of follow-up ranged between four and 104 weeks.

One SR+MA[30] that compared CBT combined with relaxation techniques with inactive controls included two studies representing 49 patients and found a non-statistically significant decrease in WASO compared with control with a mean difference of –7.6 minutes (95% CI, –26.3 to 11.1; I^2:0%). The duration and length of follow-up of the included studies was not reported.

Four MAs[36,50,55,57] that compared multi-component CBT with inactive controls included between six and 14 studies (sample sizes not reported). Three of the four MAs found a statistically significant improvement in WASO compared with control and reported effect sizes ranging from -0.74 to 0.45 (standardized mean difference). Heterogeneity ranged from 0% to 93% with only one SR+MA having heterogeneity above 75%. The fourth MA found a non-statistically significant decrease in WASO compared with control with a mean difference of –26 minutes (95% CI, –36.52 to 15.48; I^2: 47.2%). The duration of the included studies was not reported and length of follow-up ranged from four to 104 weeks. Two SRs[75,79] that compared multi-component CBT with inactive controls included two and four studies, respectively, representing 207 and 158 patients. Both SRs reported that CBT statistically significantly decreased WASO compared with control in the included studies. The duration of the studies was not reported and length of follow-up ranged from eight to 74 weeks.

Details of the interventions and results are available in Appendix 9, Table 79.

A total of 70 unique primary studies were included across the seventeen SR+MAs and six SRs that reported on WASO outcomes. Two primary studies were cited at least six times across seven different SR+MAs and one SR, three primary studies were cited at least five times across five SR+MAs, seven primary studies were cited at least four times across eleven different SR+MAs and four different SRs, six primary studies were cited at least three times across nine different SR+MAs and one SR, eight primary studies were cited at least twice across eight different SR+MAs and one SR, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.9, Table 124.

Cognitive Behavioural Therapy Compared With Active Controls

One SR+MA that compared CBT and relaxation techniques with CBT alone,[30] one SR+MA that compared self-help CBT with in-person CBT,[93] one SR that compared CBT with relaxation techniques,[85] and one SR that compared CBT combined with temazepam to CBT alone, reported on WASO outcomes. One SR+MA[93] and one SR[79] included patients with comorbidities (alcohol dependence and unspecified chronic/medical illness), and one SR+MA[30] and one SR[85] did not report on comorbidities in the patient population. One SR+MA[93] and one SR[79] included only subjective measures to collect WASO data, one SR[85] included both objective and subjective measures of WASO, and one SR+MA[30] did not report on the measures used to collect WASO data.

The MA[30] that compared CBT and relaxation techniques with CBT alone included three studies (sample size not reported) and found a non-statistically significant increase in WASO with a mean difference of 5.1 minutes (95% CI, -12.0 to 22.2; I^2: 0%). The duration and length of follow-up of the included studies was not reported.

The MA[93] that compared self-help CBT with in-person CBT alone included three studies (sample size not reported) and found a non-statistically significant decrease in WASO with a standardized mean difference of –0.03 (95% CI, –0.32 to 0.38; I^2: 44.5%). The duration of the included studies was not reported and length of follow-up ranged from 17 to 43 weeks.

The SR[85] that compared CBT with relaxation techniques included one study representing 46 patients and found that CBT decreased WASO by 54% compared with a 16% decrease in the relaxation only group ($P < 0.01$). The duration of the included study was not reported and length of follow-up was up to 104 weeks.

The SR[79] that compared CBT with CBT plus temazepam included one study representing 78 patients and found that both groups showed statistically significant improvement in WASO compared with placebo. Statistical comparisons between the groups were not reported. The duration and length of follow-up of the included study was not reported.

Details of the interventions and results are available in Appendix 9, Table 79.

Table 32: Cognitive Behavioural Interventions — Summary of Evidence for Wake After Sleep Onset

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
CBT vs. inactive controls[c] 29,32,35,37,38,40,44,47,51,54,56,66,73,85,90,93	+	+	+	+
CBT + relaxation techniques vs. inactive controls[30]	–	NA	NA	NA
Multi-component CBT vs. inactive controls[c] 36,50,55,57,75,79	+/–	+	+	+
CBT + relaxation vs. CBT[30]	–	NA	NA	NA
CBT vs. relaxation[85]	NA	NA	+	NA
Self-help CBT vs. In-person CBT[93]	–	NA	NA	NA
CBT + Temazepam vs. CBT[79]	NA	NA	NA	+

CBT = cognitive behavioural therapy; MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes placebo and no comparator (pre- and post- measures).

Behavioural Interventions Compared With Inactive Controls

Two SR+MAs[29,30] and one SR[81] that compared sleep restriction,[81] relaxation techniques,[30] and multi-component behavioural interventions[29] with inactive controls (e.g., placebo, wait-list, sleep hygiene education) reported on WASO outcomes. One SR+MA[29] included patients with comorbidities (chronic pain, hearing impairment), one SR[81] did not include any patients with comorbid conditions, and one SR+MA[30] did not report on comorbidities. One SR[81] included a combination of objective and subjective measures to collect WASO data, while the two SR+MAs[29,30] included only subjective measures of WASO.

The SR[81] that compared sleep restriction with inactive controls included three studies (160 patients) and found a decrease in WASO compared with control conditions (–42.17 minutes vs. –11.30 minutes). The length of follow-up of the included studies ranged from 13 to 52 weeks, the duration of the studies was not reported.

The MA[30] that compared relaxation techniques with inactive controls included three studies (117 patients) and found a non-statistically significant decrease in WASO compared with control with a mean difference of –1.61 minutes (95% CI, –14.05 to 10.82; I^2: 0.2%). The duration and length of follow-up of the included studies was not reported.

The MA[30] that compared a multi-component behavioural intervention with inactive controls included three studies (146 patients) and found a statistically significant decrease WASO compared with control with a mean difference of –14.9 minutes (95% CI, –22.66 to –7.14; I^2: 0%). The length of follow-up for the included studies was up to four weeks; the duration of the studies was not reported.

Details of the interventions and results are available in Appendix 9, Table 79.

A total of nine unique studies were included across two SR+MAs and one SR that reported on WASO outcomes. There were no apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Table 3, Appendix 10.11.

Behavioural Interventions Compared with Active Controls

No included SR+MAs or SRs that compared behavioural interventions with active controls were identified that reported this outcome.

Table 33: Behavioural Interventions — Summary of Evidence for Wake After Sleep Onset

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Sleep restriction vs. inactive controls[81]	NA	NA	+	NA
Relaxation training vs. inactive controls[30]	–	NA	NA	NA
Multi-component behavioural intervention vs. inactive controls[29]	+	NA	NA	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Mindfulness-Based Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared mindfulness-based interventions with inactive controls reported this outcome.

Mindfulness-Based Interventions Compared With Active Controls

No SR+MAs or SRs that compared mindfulness-based interventions with active controls were identified.

Combination Therapies Compared with Inactive Controls

No included SR+MAs or SRs that compared combination therapies (non-pharmacologic plus pharmacologic) with inactive controls were identified that reported this outcome.

Combination Therapies Compared with Active Controls

No SR+MAs or SRs that compared combination therapies with active controls were identified.

a) Sleep Quality

Benzodiazepine Drugs Compared with Inactive Controls

One SR+MA[45] that compared temazepam with placebo reported on SQ. The SR+MA did not include any patients with comorbidities and, in the included studies, data were collected through subjective measures.

The MA of SQ that compared temazepam to placebo included two RCTs representing 78 patients and found a non-statistically significant increase in SQ compared with placebo with a mean difference of 0.25 points (95% CI, –0.20 to 0.70; I^2: 0%). The duration of the included trials was up to eight weeks and length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 80.

Benzodiazepine Drugs Compared with Active Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with active controls reported this outcome.

Table 34: Benzodiazepine Drugs — Summary of Evidence for Sleep Quality

Treatment Comparison	SR With MA		SR Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Temazepam vs. placebo[45]	NA	–	NA	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Non-Benzodiazepine Drugs Compared With Inactive Controls

Two SR+MAs[29,45] and two SRs that compared zolpidem with placebo[78,80] reported SQ in adult populations with insomnia. One SR+MA[45] only included patients with insomnia, one SR+MA[29] included patients with comorbidities (chronic pain and hearing impairment), and the two SRs[78,80] included patients with comorbidities (depression and dysthymia). In the two SR+MAs and one SR,[80] SQ was measured using a subjective self-report. One SR[78] did not report the methods used to collect SQ data.

Two MAs[45,48] examining zolpidem found a statistically significant increase in SQ compared with placebo, with mean differences of 1.4 points (95% CI, 1.20 to 1.65; I^2: 14%) and 0.64 (95% CI, 0.03 to 1.26; I^2: 92%). The analyses included three and six RCTs representing 557 and 638 patients, respectively. Duration of the included studies ranged from one week to 32 weeks and length of follow-up ranged from four to 34 weeks. Two SRs[78,80] that compared zolpidem with placebo and that reported SQ outcomes included the same RCT (306 patients) that also found a statistically significant increase in SQ compared with placebo.

Details of the interventions and results are available in Appendix 9, Table 80.

A total of nine unique studies were reported across two SR+MAs and two SRs that reported SQ outcomes. One primary study that examined zolpidem was cited three times across one SR+MA and two SRs, and there were no other apparent overlaps in primary studies. The full list of primary studies and potential overlaps is available in Table 4, Appendix 10.2.

Non-Benzodiazepine Drugs Compared With Active Controls

No included SR+MAs or SRs that compared non-benzodiazepine drugs with active controls reported this outcome.

Table 35: Non-Benzodiazepine Drugs — Summary of Evidence for Sleep Quality

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Zolpidem vs. placebo[29,45,78,80]	+	+	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Suvorexant Compared With Inactive Controls

One SR+MA[39] that compared suvorexant with placebo reported SQ. The study only included patients with insomnia and included a subjective measure (4-point scale in a sleep diary) to collect SQ data.

The MA of SQ included two RCTs representing 1,915 patients and found a statistically significant improvement in SQ compared with placebo (mean difference, [95% CI]), –0.17, [–0.25 to –0.09]; I^2: 0%). Length of follow-up for the included trials ranged from four to 52 weeks and study duration was not reported.

Details of the interventions and results are available in Appendix 9, Table 80.

Suvorexant Compared With Active Controls

No SR+MAs or SRs that compared suvorexant with active controls were included in this review.

Table 36: Suvorexant — Summary of Evidence for Sleep Quality

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Suvorexant vs. placebo[39]	+	NA	NA	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Antidepressant Drugs Compared With Inactive Controls

One SR+MA[45] and one SR[78] that compared doxepin with placebo, and three SRs[77,78,80] that compared trazodone with placebo reported SQ. One SR+MA[45] did not include any patients with comorbidities, two SRs[78,80] included patients with depression or dysthymia, and one SR[77] included patients in recovery from alcohol abuse. The SR+MA and three SRs included SQ measures such as the Pittsburgh Sleep Quality Index (PSQI),[77,78,80] Leeds Sleep Evaluation Questionnaire,[80] and subjective measures for self-report (visual analogue scale [VAS]).[45,80]

The MA that compared doxepin 3 mg or 6 mg with placebo found statistically significant increase in SQ compared with placebo, with standardized mean differences of 0.57 (95% CI, 0.26 to 0.88; I^2: 43%) and 0.28 (95% CI, 0.06 to 0.49; I^2: 15%) respectively. The MAs each included two RCTs (191 and 404 patients, respectively); the duration of the included trials ranged from five to 12 weeks, and length of follow-up was not reported. The SR[78] that compared doxepin with placebo included two studies and also found a statistically significant increase in SQ compared with placebo ($P < 0.001$).

Three SRs[77,78,80] that compared trazodone with placebo or that compared pre- and post-intervention effects of trazodone also found statistically significant increases in SQ. However, while the direction of effect was generally consistent, not all the effects observed in the included studies reached statistical significance. The SRs included between one and five studies representing between nine and 767 patients. The duration of the included studies was up to two weeks, and length of follow-up ranged from four to 24 weeks.

Details of the interventions and results are available in Appendix 9, Table 80.

A total of 13 unique studies were included across one SR+MA and three SRs that reported SQ outcomes. One primary study examining trazodone was cited twice across two SRs, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.4, Table 106.

Antidepressant Drugs Compared With Active Controls

One SR that compared trazodone with zolpidem included one RCT representing 306 patients that reported SQ and found no statistically significant differences between the two treatment groups.

Details of the interventions and results are available in Appendix 9, Table 80.

Table 37: Antidepressant Drugs — Summary of Evidence for Sleep Quality

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Doxepin vs. placebo[45,78]	NA	+	NA	+
Trazodone vs. inactive control[c 77,78,80]	NA	NA	NA	+/–
Trazodone vs. zolpidem[78]	NA	NA	NA	-

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).
[c] Includes unspecified controls, placebos, and no comparator (pre- and post- measures).

Antipsychotic Drugs Compared With Inactive Controls

Four SRs[63,70,77,86] that compared quetiapine with placebo or that compared pre- and post-intervention effects reported SQ outcomes, one of the SRs[86] included patients with PTSD and Parkinson disease, one SR[77] included patients in recovery from alcohol abuse, and the other two SRs did not include patients with any comorbidities. One SR[63] included SQ data collected by actigraphy, one SR[70] included data collected from a sleep diary, three SRs[63,70,86] included data from the PSQI, one from the Spiegel Sleep Questionnaire,[63] and one from the Hamilton Depression Scale (HAM-D) Sleep Question subset.[77]

The SRs included between one and three studies each with samples sizes ranging from 18 to 74 patients; included study designs were a mix of RCTs and NRCTs. All four SRs found statistically significant improvements in SQ compared with placebo or compared from baseline regardless of data collection method. The duration of the included studies ranged from two to 12 weeks and the length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 80.

A total of six unique studies were included across four SRs that reported on SQ outcomes. One primary study examining quetiapine was cited at least twice across two SRs and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.6, Table 113.

Antipsychotic Drugs Compared with Active Controls

No SR+MAs or SRs that compared antipsychotic drugs with active controls were identified.

Table 38: Antipsychotic Drugs — Summary of Evidence for Sleep Quality

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Quetiapine vs. inactive controls[c] 63,70,77,86	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes placebo and no comparator (pre- and post-measures).

Melatonin Compared With Inactive Controls

Five SR+MAs[31,33,43,45,58] and five SRs[64,67,71,72,84] that compared melatonin with placebo reported SQ outcomes. Two SR+MAs and two SRs did not include patients with comorbidities, one SR+MA and one SR included patients with comorbid dementia, Alzheimer or Parkinson disease, one SR included patients with a comorbid chronic illness, one SR+MA included patients with a comorbid sleep disorder, and one SR+MA and one SR did not report on comorbidities. Across the SR+MAs and SRs, SQ data were collected with objective (PSG) and subjective measures including sleep diaries and questionnaires (e.g., PSQI).

One of the five MAs of SQ data collected through objective and subjective measures found a statistically significant change in SQ scores compared with placebo with a mean difference of 0.22 (95% CI, 0.13 to 0.32; $I^{2:}$ 0%). The other four MAs had the same direction of effect but failed to reach statistical significance with standardized mean differences ranging from 0.04 (95% CI, –0.29 to 0.38) to 0.5 (95% CI, –0.1 to 1.1), heterogeneity (I^2) ranged from 0% to 58%. The analyses included between two to 14 studies representing 164 to 1,347 patients, the duration of the included studies and the length of follow-up were not reported. The five SRs included between one and 11 studies each on SQ representing between 10 and 344 patients and also found an improvement in SQ compared with placebo however, a number of the changes failed to reach statistical significance (values not reported). The duration of the included studies and the length of follow-up were not reported.

Details of the interventions and results are available in Appendix 9, Table 80.

A total of 25 unique studies were included across four SR+MAs and five SRs that reported SQ outcomes. One primary study was cited six times across three SR+MAs and three SRs, one primary study was cited five times across four SR+MAs and one SR, one primary study was cited four times across three SR+MAs and one SR, three primary studies were cited at least three times across three different SR+MAs and one SR, four primary studies were cited twice across the three SR+MAs and one SR, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.7, Table 118.

Melatonin Compared with Active Controls

No SR+MAs or SRs that compared melatonin with active controls were identified.

Table 39: Melatonin — Summary of Evidence for Sleep Quality

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Melatonin vs. inactive controls[c] [72]	NA	NA	NA	-

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).[c] Includes inactive controls and placebo.

Diphenhydramine Compared with Inactive Controls

One SR[72] that compared diphenhydramine with placebo reported SQ outcomes; it did not include any patients with comorbidities and used a subjective measure (sleep diary) to collect data.

The SR included one study representing 20 patients that reported SQ data and found there was no statistically significant difference between groups. The duration of the trial was not reported and length of follow-up was between four and 29 weeks.

Details of the interventions and results are available in Appendix 9, Table 80.

Diphenhydramine Compared with Active Controls

No SR+MAs or SRs that compared diphenhydramine with active controls were included in this review.

Table 40: Diphenhydramine — Summary of Evidence for Sleep Quality

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Diphenhydramine vs. placebo[72]	NA	NA	NA	–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Cognitive Behavioural Therapy Compared with Inactive Controls

Fourteen SR+MAs and four SRs that compared CBT,[29,32,35,37,40,49,51,56,65,90,93] CBT with an additional behavioural intervention,[30,53] or multi-component CBT,[36,55,57,75,79] to inactive control reported SQ outcomes. Ten SR+MAs[29,32,35,40,49,51,53,55,56,93] and four SRs[65,75,79,90] included patients with comorbidities (cancer, chronic pain, fibromyalgia, PTSD, depression, hearing impairment, fibromyalgia, arthritis, restless leg syndrome, chronic obstructive pulmonary disease, alcohol dependence/abuse, kidney disease, sleep apnea, parasomnia, traumatic brain injury, and unspecified chronic or medical illness), one SR+MA[30] did not report on comorbidities in the patient population, and three SR+MAS[36,37,57] did not include any patients with comorbid conditions. One SR[75] included both objective and subjective measures of SQ, twelve SR+MAs[29,32,35-37,40,51,53,56,57,80,93] and three SRs[65,79,90] included only subjective measures of SQ (e.g., PSQI), and two SR+MAs[30,55] did not report the method of measuring SQ.

The ten MAs (in nine publications)[29,32,35,37,40,49,51,56,93] that compared CBT with inactive controls included between four and 40 studies and only two SR+MAs[29,49] reported the sample size (580 and 965 patients, respectively). Nine of the 10 MAs found a statistically significant improvement in SQ compared with control and reported effect sizes ranging from –0.87 to 0.78 (standardized mean difference) and one SR+MA reported a mean difference of –2.1 points on the PSQI (95% CI, –2.87 to –1.34; I^2:0.37%) Heterogeneity ranged from 0% to 74% and none of the MAs had an I^2 greater than 75%. The 10th MA also found an improvement in SQ with a mean effect size of 0.4 (95% CI, –0.14 to 0.93; I^2: not reported). The duration of the included studies ranged between two and 12 weeks and length of follow-up ranged from one to 104 weeks. Two SRs[65,90] that compared CBT with inactive controls included one and two studies respectively, representing three and 215 patients. The two SRs found opposing results with one[65] reporting no meaningful change in SQ in either group and the other[90] reporting a reduction in PSQI scores (reduced score indicates improved SQ), compared with baseline. The duration and length of follow-up of the included studies was not reported.

Two SR+MAs[30,53] that compared CBT combined with relaxation techniques to inactive controls included two and three studies representing 49 and 184 patients respectively. One MA[53] of global PSQI scores found a statistically significant improvement in SQ compared with placebo with a standardized mean difference of 0.85 points (95% CI, 0.37 to 1.34; I^2: 56%), the other analysis in this publication found a non-statistically significant improvement in subjective SQ scores a standardized mean difference of 0.44 (95% CI, –0.28 to 1.17; I^2: 64%). The other SR+MA[30] also found a non-statistically significant improvement in SQ compared with control with a mean difference of 0.69 points (95% CI, –0.34 to 1.73; I^2: 65.4%). The duration of the included studies was not reported in either SR+MA; the length of follow-up ranged from four to eight weeks.

Three MAs[36,55,57] that compared multi-component CBT with inactive controls included between two and eight studies (sample sizes not reported). All three of the MAs found a statistically significant improvement in SQ scores (measured by self-report in sleep diaries in one analysis, PSQI in one analysis, and not reported in one analysis) compared with control and reported standardized mean differences ranging from 0.43 to 0.77. Heterogeneity ranged from 0% to 34.5% and no MA had heterogeneity estimated above 75%. The duration of the included studies was up to 60 days and length of follow-up ranged from four to 104 weeks. Two SRs[75,79] that compared multi-component CBT with inactive controls included two and four studies respectively, representing 233 and 210 patients. Both SRs reported that CBT statistically significantly improved SQ scores compared with control in the included

studies (values not reported); duration of the studies was not reported and length of follow-up ranged from eight to 74 weeks.

Details of the interventions and results are available in Appendix 9, Table 80.

A total of 47 unique primary studies were included across the fourteen SR+MAs and four SRs that reported on SQ outcomes. Five primary studies were cited at least three times across six different SR+MAs and two SRs, seven primary studies were cited at least twice across six different SR+MAs and one SR, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.9, Table 125.

Cognitive Behavioural Therapy Compared With Active Controls

Two SR+MAs that compared CBT and relaxation techniques with relaxation techniques only[30,93] and self-help CBT to in-person CBT reported on SQ outcomes. One SR+MA[93] included patients with comorbidities (alcohol dependence, chronic disease) and one SR+MA[29] did not report on comorbidities in the patient population. One SR+MA[93] included subjective measures of SQ (sleep diary) and the other SR+MA did not report the included measures of SQ.[30]

The MA that compared CBT and relaxation techniques with relaxation alone included two studies representing 47 patients and found a non-statistically significant increase in SQ scores with a mean difference of 0.2 (95% CI, –0.38 to 0.77; I^2: 0%). The duration and length of follow-up of the included studies were not reported.

The MA that compared self-help CBT with in-person CBT included two studies (sample size not reported) and found a non-statistically significant decrease in SQ scores with a standardized mean difference of –0.5 (95% CI, –0.90 to 0.02; I^2: 0%). The duration of the included studies was not reported and length of follow-up ranged from 17 to 43 weeks.

Details of the interventions and results are available in Appendix 9, Table 80.

Table 41: Cognitive Behavioural Interventions — Summary of Evidence for Sleep Quality

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
CBT vs. inactive controls[c] 29,32,35,37,40,49,51,56,65,90,93	+	+	NA	+/–
CBT + relaxation vs. inactive controls[30,53]	–	NA	NA	NA
Multi-component CBT vs. inactive controls[36,55,57,75, 79]	+	+	+	+
CBT + relaxation vs. CBT[30]	–	NA	NA	NA
Self-help CBT vs. in-person CBT[93]	–	NA	NA	NA

CBT = cognitive behavioural therapy; MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).
[c] Includes placebo and no comparator (pre- and post- measures).

Behavioural Interventions Compared With Inactive Controls

One SR+MA[61] and five SRs[65,66,74,81,89] that compared BT,[61,65] sleep restriction,[81] and relaxation techniques,[66,74,89] with inactive controls reported on SQ outcomes. Three SRs[65,66,89] included patients with comorbidities (traumatic brain injury; alcohol use; hospitalized patients), one SR[81] did not include any patients with comorbid conditions, and one SR+MA[61] and one SR[74] did not report on comorbidities. All of the SR+MAs and SRs used subjective measures to collect SQ data including sleep diaries[66,81] and questionnaires/scales[61,65,74,89] (e.g., PSQI, Richards Campbell Sleep Questionnaire).

The MA[61] that compared BT with inactive control included five studies (sample size not reported) and found a statistically significant improvement in PSQI scores compared with control with a standardized mean difference of 1.90 points (95% CI, 0.04 to 2.94; I^2: 96.27%). The duration of the included studies and the length of follow-up were not reported. The SR[65] that compared BT with a sleep education control included one study (356 patients) and found a statistically significant increase in PSQI scores at six-month follow-up (P = 0.003) but the effect did not persist at 12-month follow-up (P = 0.88). The duration of the included study was not reported.

The SR[81] examining sleep restriction included one study (94 patients) and found an increase in SQ scores compared with baseline values in the sleep restriction group (2.77 to 2.90 points). The length of follow-up in the included study was up to 52 weeks; the duration of the study was not reported.

The three SRs[66,74,89] that compared relaxation techniques with inactive controls included between one and three studies representing between 36 and 211 patients. Overall, the SRs found mixed results with one review[66] (one study, 37 patients) that found a statistically significant increase in post-treatment SQ scores compared with the control group and two

SRs[74,89] that found small non-statistically significant effects of relaxation techniques on SQ (one study with 36 patients and three studies with 211 patients, respectively).

Details of the interventions and results are available in Appendix 9, Table 80.

A total of 13 unique studies were included across one SR+MA and five SRs that reported on SQ outcomes. There were no apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.11, Table 135.

Behavioural Interventions Compared With Active Controls

One SR+MA[46] that compared relaxation techniques with CBT combined with relaxation reported SQ outcomes. The SR+MA included patients with comorbidities (PTSD, nightmares) and used the PSQI to measure SQ.

The MA included eight studies (sample size not reported) and found that the addition of CBT to a relaxation technique had a statistically significant effect resulting in improved SQ scores on the PSQI with a change (Cohen's *d)* of 1.32 points in the CBT plus relaxation group (95% CI, 0.68 to 1.96) and 0.50 points in the CBT alone group (95% CI, 0.16 to 0.84), the heterogeneity for the analysis was measured by the Q-statistic (4.75, *P* = 0.03). The duration of the studies and length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 80.

Table 42: Behavioural Interventions — Summary of Evidence for Sleep Quality

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Behavioural therapy vs. inactive controls[61,65]	NA	+	NA	+/–
Sleep restriction therapy vs. inactive controls[81]	NA	NA	+	NA
Relaxation techniques vs. inactive controls[66,74,89]	NA	NA	–	+/–
Imagery rehearsal therapy vs. CBT[46]	NA	+	NA	NA

CBT = cognitive behavioural therapy; MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Mindfulness-Based Interventions Compared With Inactive Controls

One SR+MA[34] that compared mindfulness-based stress reduction and meditation with wait-list, sleep hygiene education, and self-monitoring controls reported sleep quality outcomes. One SR[90] that compared pre- and post- intervention effects of mindfulness-based stress reduction, mind-body bridging, and mindfulness meditation reported sleep quality outcomes. The SR+MA included patients with comorbid depression and cancer and the SR included

adult cancer patients undergoing curative treatment. Sleep quality data were collected using a sleep diary (SR+MA) and the Pittsburgh Sleep Quality Index (PSQI; SR+MA and SR).

The meta-analysis of sleep diary data included 2 RCTs representing 83 patients and found a statistically significant increase in sleep quality with a standardized mean difference of 0.68 (95% CI 0.24 to 1.13, I^2: 0%). The meta-analysis of PSQI data (2 RCTs, 109 patients) found similar results with a non-statistically significant decrease in overall PSQI scores (–1.09, 95% CI, –1.50 to 0.69; I^2: 0%). The SR included one quasi-experimental study representing 63 patients and found the proportion of patients with high scores on the PSQI was reduced by almost half (PSQI >10: 51% vs. 27%). The length of follow-up of the trials included in the meta-analysis ranged from 6 to 8 weeks, study duration was not reported; the length of follow-up and study duration of the study included in the SR were not reported.

Details of the interventions and results are available in Appendix 9 and Appendix Table 9.4.

A total of four unique studies were included across one SR+MA and one SR that reported on sleep quality outcomes. There were no apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Table 1, Appendix 10.12.

Mindfulness-Based Interventions Compared With Active Controls

No SR+MAs or SRs that compared mindfulness-based interventions with active controls were included in this review.

Table 43: Mindfulness-Based Interventions — Summary of Evidence for Sleep Quality

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Mindfulness-based stress reduction vs. sleep hygiene education[34]	NA	+	NA	NA
Mindfulness-based stress reduction (pre- and post- measures)[90]	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Combination Therapies Compared With Inactive Controls

One SR[88] examining pre- and post- treatment effects of mindfulness-based cognitive therapy/stress reduction and pharmacotherapy reported on SQ. The presence of comorbidities in the patient population was not reported, neither was the method used to collect SQ data.

The SR included one observational study representing 30 patients and found statistically significant improvements in SQ (*P* value not reported) that were maintained at 12-month follow-up and that levels of 'mindfulness' of the participants were directly correlated with the quality of sleep.

Details of the interventions and results are available in Appendix 9, Table 80.

Combination Therapies Compared With Active Controls

No SR+MAs or SRs that compared combination therapies with active controls were included in this review.

Table 44: Combination Therapies — Summary of Evidence for Sleep Quality

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Pharmacotherapy and mindfulness-based cognitive therapy and stress reduction[88]	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

b) Sleep Satisfaction

Benzodiazepine Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with inactive controls were identified that reported this outcome.

Benzodiazepine Drugs Compared With Active Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with active controls were identified that reported this outcome.

Non-Benzodiazepine Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared non-benzodiazepine drugs with inactive controls were identified that reported this outcome.

Non-Benzodiazepine Drugs Compared With Active Controls

No included SR+MAs or SRs that compared non-benzodiazepine drugs with active controls were identified that reported this outcome.

Suvorexant Compared With Inactive Controls

No included SR+MAs or SRs that compared suvorexant with inactive controls were identified that reported this outcome.

Suvorexant Compared With Active Controls

No SR+MAs or SRs that compared suvorexant with active controls were identified.

Antidepressant Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared antidepressant drugs with inactive controls were identified that reported this outcome.

Antidepressant Drugs Compared With Active Controls

No included SR+MAs or SRs that compared antidepressant drugs with active controls were identified that reported this outcome.

Antipsychotic Drugs Compared With Inactive Controls

One SR[63] that compared quetiapine with placebo reported SS outcomes; the SR did not include any patients with comorbidities and the data were collected through use of a visual analogue scale.

The SRs included one trial representing 25 patients and found no statistically significant improvement in sleep satisfaction compared with placebo. The duration of the included study was 12 weeks and the length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 81.

Antipsychotic Drugs Compared With Active Controls

No SR+MAs or SRs that compared antipsychotic drugs with active controls were identified.

Table 45: Antipsychotic Drugs — Summary of Evidence for Sleep Satisfaction

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Quetiapine vs. inactive controls[c 63]	NA	NA	NA	–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).
[c] Includes placebo and no comparator (pre- and post-measures).

Melatonin Compared With Inactive Controls

One SR[84] that compared melatonin with placebo reported on SS. The SR included one study representing 112 patients that found a statistically significant increase in SS on a self-reported measure. The duration of the study and length of follow-up were not reported.

Details of the interventions and results are available in Appendix 9, Table 81.

Melatonin Compared With Active Controls

No SR+MAs or SRs that compared melatonin with active controls were identified.

Table 46: Melatonin — Summary of Evidence for Sleep Satisfaction

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Melatonin vs. inactive controls[c 84]	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes inactive controls and placebo.

Diphenhydramine Compared With Inactive Controls

No included SR+MAs or SRs that compared diphenhydramine with inactive controls were identified that reported this outcome

Diphenhydramine Compared With Active Controls

No SR+MAs or SRs that compared diphenhydramine with active controls were identified.

Cognitive Behavioural Therapy Compared With Inactive Controls

One SR[85] that compared CBT with inactive control reported on SS. The SR did not report on comorbidities in the patient population and included subjective questionnaires to measure SS.

The SR included two studies representing 81 patients and found that CBT improved scores on the Dysfunctional Attitudes and Beliefs about Sleep scale (DBAS) and the Beliefs and Attitudes about Sleep scale (BAS) compared with control (values not reported). The duration of the included studies was not reported and length of follow-up ranged from 12 to 104 weeks.

Details of the interventions and results are available in Appendix 9, Table 81.

Cognitive Behavioural Therapy Compared With Active Controls

No included SR+MAs or SRs that compared CBT with active controls were identified that reported this outcome.

Table 47: Cognitive behavioural interventions — Summary of Evidence for sleep satisfaction

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
CBT vs. inactive controls[85]	NA	NA	+	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Behavioural Interventions Compared With Inactive Controls

One SR that compared sleep restriction[79] with inactive controls reported on SS outcomes. The SR included patients with comorbidities (medical illness) and did not report the method used for measuring SS.

The SR included one study representing 125 patients and found that sleep restriction and sleep hygiene guidance delivered using a video resulted in improved SS scores compared with control (values not reported). The duration and length of follow-up of the included studies was not reported.

Details of the interventions and results are available in Appendix 9, Table 81.

Behavioural Interventions Compared With Active Controls

No included SR+MAs or SRs that compared behavioural interventions with active controls were identified that reported this outcome.

Table 48: Behavioural Interventions — Summary of Evidence for Sleep Satisfaction

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Behavioural therapy vs. inactive controls[79]	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Mindfulness-Based Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared mindfulness-based interventions with inactive controls were identified that reported this outcome.

Mindfulness-Based Interventions Compared With Active Controls

No SR+MAs or SRs that compared mindfulness-based interventions with active controls were identified.

Combination Therapies Compared With Inactive Controls

No included SR+MAs or SRs that compared combination therapies (non-pharmacologic plus pharmacologic) with inactive controls were identified that reported this outcome.

Combination Therapies Compared With Active Controls

No SR+MAs or SRs that compared combination therapies with active controls were identified.

c) Sleep Efficiency

Benzodiazepine Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with inactive controls were identified that reported this outcome.

Benzodiazepine Drugs Compared With Active Controls

One SR compared zolpidem to triazolam and reported SE. Results are detailed in the next section of the report and in Appendix 9, Table 82.

Non-Benzodiazepine Drugs Compared With Inactive Controls

One SR+MA[45] and one SR[91] that compared zolpidem with placebo reported SE in adult populations with insomnia; both the SR+MA and SR included only patients with insomnia. In the SR+MA, SE was measured using PSG. The SR did not report the method used to collect data.

The MA[45] examining zolpidem found a statistically significant increase compared with placebo with a mean difference of 6.12% (95% CI, 4.39 to 7.85; I^2: 35%). The analysis included four RCTs representing 226 patients. The duration of the included studies was up to eight weeks and the length of follow-up was not reported. The SR that compared zolpidem with placebo and that reported SE included one study representing 69 patients and found a non-statistically significant change in SE.

Details of the interventions and results are available in Appendix 9, Table 82.

A total of four unique studies were reported across one SR+MA and one SR that reported on SE outcomes. One primary study that examined zolpidem was cited across both the SR+MA and the SR and there were no other apparent overlaps in primary studies. The full list of primary studies and potential overlaps is available in Appendix 10.2, Table 95.

Non-Benzodiazepine Drugs Compared With Active Controls

No MAs that compared non-benzodiazepine drugs with active controls that reported SE were included in this review. One SR[91] that compared zolpidem with triazolam included two RCTs (86 patients) that found discordant results, with one trial reporting a statistically

significant increase in SE (pre- / post-intervention +10 minutes to –6 minutes, $P < 0.01$) and the other reporting a non-statistically significant change (pre- / post-intervention –3 minutes to –15 minutes, P = NS). The SR did not include any patients with comorbidities and did not report the method of measuring SE.

Details of the interventions and results are available in Appendix 9, Table 82.

Table 49: Non-Benzodiazepine Drugs — Summary of Evidence for Sleep Satisfaction

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Zolpidem vs. placebo[45,91]	NA	+	NA	–
Zolpidem vs. triazolam[91]	NA	NA	NA	+/–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Suvorexant Compared With Inactive Controls

No included SR+MAs or SRs that compared suvorexant with inactive controls reported this outcome.

Suvorexant Compared With Active Controls

No SR+MAs or SRs that compared suvorexant with active controls were included in this review.

Antidepressant Drugs Compared With Inactive Controls

Two SR+MAs[45,59] and three SRs[78,83,87] that compared doxepin with placebo and two SRs[80,83] that compared trazodone with placebo reported SE. Two SR+MAs[45,59] did not include any patients with comorbidities, two SRs[78,87] included patients with depression, anxiety, or dysthymia, and one SR included patients undergoing methadone-supported alcohol detoxification. One SR+MA[45] and two SRs[80,87] included only objective measures of SE (PSG), one SR[83] included objective and subjective (sleep diary, questionnaire) measures, and one SR+MA[59] and one SR[78] did not report the included measures of SE.

Six MAs (in two publications)[45,59] that compared varying doses of doxepin (1 mg to 25 mg) with placebo found a statistically significant increase in SE, with mean differences ranging from 3.59% (1 mg) (95% CI, 1.55 to 5.63; I^2: not reported) to 12.58% (25 mg) (95% CI, 7.60 to 17.56; I^2: not reported). The MAs each included between two to three RCTs representing 60 to 423 patients. The duration of the included trials ranged from five to 12 weeks, and length of follow-up was not reported. The three SRs[78,83,87] that compared doxepin with placebo included between one and six studies and also found a statistically significant improvement in SE compared with placebo.

Two SRs[80,83] that compared trazodone with placebo, or that compared pre- and post-intervention effects of trazodone, also found statistically significant improvements in SE. However, while the direction of effect was generally consistent, not all of the effects observed in the included studies reached statistical significance. The SRs included between two and three studies representing 20 to 56 patients. The duration of the included studies was up to two weeks and the length of follow-up ranged from four to 24 weeks.

Details of the interventions and results are available in Appendix 9, Table 82.

A total of 15 unique studies were included across two SR+MAs and four SRs that reported SE outcomes. One primary study examining doxepin was cited four times across one SR+MA and three SRs, two primary studies examining doxepin were cited three times across two SR+MAs and one SR, one primary study examining doxepin was cited twice across one SR+MA and one SR, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.4, Table 107.

Antidepressant Drugs Compared With Active Controls

No included SR+MA or SRs that compared antidepressant drugs with active controls reported this outcome.

Table 50: Antidepressant Drugs — Summary of Evidence for Sleep Efficiency

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Doxepin vs. placebo[45,59,78,83,87]	NA	+	+	+
Trazodone vs. inactive control[c] [80,83]	NA	NA	NA	+/–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).
[c] Includes unspecified controls, placebos, and no comparator (pre- and post-measures).

Antipsychotic Drugs Compared With Inactive Controls

Three SRs[63,70,86] that compared quetiapine with placebo, or that compared pre- and post-intervention effects, reported SE outcomes. One of the SRs[86] included patients with PTSD and Parkinson disease while the other two did not include patients with any comorbidities. One SR[63] included SE data collected by PSG or actigraphy, one SR[70] included data collected through objective measures (PSG or actigraphy), and in one SR[86] the method of data collection was not reported.

The SRs included between one and two studies each with sample sizes ranging from 18 to 27 patients. Included study designs were a mix of RCTs and NRCTs. All three SRs found statistically significant improvements in SE compared with placebo or compared with

baseline. The duration of the included studies ranged from two to 12 weeks and the length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 82.

A total of two unique studies were included across three SRs that reported on SE outcomes. One primary study examining quetiapine was cited three times across three SRs. There were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.6, Table 114.

Antipsychotic Drugs Compared With Active Controls

No SR+MAs or SRs that compared antipsychotic drugs with active controls were included in this review.

Table 51: Antipsychotic Drugs — Summary of Evidence for Sleep Efficiency

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Quetiapine vs. inactive controls[c] [63,70,86]	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes placebo and no comparator (pre- and post- measures).

Melatonin Compared With Inactive Controls

Five SR+MAs[31,52,58,60,72] and three SRs[64,67,72] that compared melatonin with placebo reported SE outcomes. One SR+MA[58] and one SR[72] did not include any patients with comorbidities, three SR+MA[52,60,72] and two SRs[64,67] included patients with comorbidities (chronic pain, hearing impairment, schizophrenia, dementia/Alzheimer, medical/chronic illness, delayed sleep phase, or REM disorder), and one SR+MA[31] did not report on comorbidities. Three SR+MAs and two SRs only included objective measures of SE (PSG, actigraphy), one SR+MA and one SR included both objective and subjective measures (sleep diary) of SE, and one SR+MA did not report the method of data collection.

One of the five MAs of SE data collected through objective and subjective measures found a statistically significant improvement compared with placebo with an effect size of 2.74% (95% CI, 0.41 to 5.88; $I^{2:}$ 54%). The other four MAs had similar direction of effect (improvement) but failed to reach significance with mean differences ranging from –0.01 to 1.78 and heterogeneity ranged from 0% to 62.8%. The analyses included between one to nine studies representing 144 to 446 patients. The duration of the included studies and the length of follow-up were not reported. The three SRs included between one and 12 studies each representing 40 or more patients and also found an improvement in SE compared with placebo, however, a number of the changes failed to reach statistical significance. The duration of the included studies and the length of follow-up were not reported.

Details of the interventions and results are available in Appendix 9, Table 82.

A total of 20 unique studies were included across five SR+MAs and three SRs that reported SE outcomes. Three primary studies were cited at least three times across two SR+MAs and one SR, five primary studies were cited at least twice across the five SR+MAs, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.7, Table 119.

Melatonin Compared With Active Controls

No SR+MAs or SRs that compared melatonin with active controls were included in this review.

Table 52: Melatonin — Summary of Evidence for Sleep Efficiency

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Melatonin vs. inactive controls[c] 31,43,52,58,60,64,67,72	+	+/–	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes inactive controls and placebo.

Diphenhydramine Compared With Inactive Controls

One SR[83] that compared diphenhydramine with placebo reported SE. It did not include any patients with comorbidities and used subjective and objective measures (questionnaire and PSG) to collect data.

The SR included one RCT representing 204 patients and found that while subjective data from sleep diaries demonstrated statistically significant improvement in SE compared with placebo, the data from the PSG showed no difference compared with placebo. The trial lasted for four weeks and length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 82.

Diphenhydramine Compared With Active Controls

No SR+MAs or SRs that compared diphenhydramine with active controls were included in this review.

Table 53: Diphenhydramine — Summary of Evidence for Sleep Efficiency

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Diphenhydramine vs. placebo[83]	NA	NA	NA	+/–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Cognitive Behavioural Therapy Compared With Inactive Controls

Sixteen SR+MAs and nine SRs that compared CBT,[32,35,37,38,40,44,47,51,54,56,65,66,73,76,82,85,90,93] CBT with an additional behavioural intervention,[53] and multi-component CBT[36,50,55,57,75,79] to inactive control, reported SE outcomes. Twelve SR+MAs[32,35,38,40,44,47,51,53,54,56,93] and seven SRs[65,66,73,75,76,82,90] included patients with comorbidities (cancer, chronic pain, fibromyalgia, PTSD, depression, hearing impairment, fibromyalgia, arthritis, restless leg syndrome, chronic obstructive pulmonary disease, alcohol dependence/abuse, kidney disease, sleep apnea, parasomnia, traumatic brain injury, and unspecified chronic or medical illness), one SR[85] did not report on comorbidities in the patient population, and four SR+MAs[36,37,50,57] did not include any patients with comorbid conditions. Three SR+MAs[44,56,57] and three SRs[66,85,90] included both objective and subjective measures of SE, one SR[73] included only objective measures of SE, twelve SR+MAs[32,35-38,40,47,50,51,53,54,93] and five SRs[65,73,75,76,82] included only subjective measures of SE, and one SR+MA[55] did not report the method of measuring SE.

The twelve MAs (in 11 publications)[32,35,37,38,40,44,47,51,54,56,93] that compared CBT with inactive controls included between two and 79 studies representing between 143 and 2012 patients. Eleven of the twelve MAs found a statistically significant improvement in SE compared with control and reported effect sizes ranging from 0.14 to 1.15 (standardized mean difference) and mean differences ranging from 7.22% to 9.58%.Heterogeneity ranged from 0% to 76% with one MA having an I^2 > 75%. The 11th MA also found an improvement in SE but failed to reach statistical significance with a mean difference of –7.49 (95% CI, –15.45 to 0.47; I^2: 77%). The duration of the included studies ranged between two and 12 weeks, and length of follow-up ranged from one to 52 weeks. Seven SRs[65,66,73,76,82,85,90] that compared CBT with inactive controls included between one and 13 studies representing between 11 and 660 patients. The six SRs all found that CBT improved SE compared with control, with at least four SRs[65,76] reporting a statistically significant difference between groups (values not reported). The duration of included studies was not reported in any SR and length of follow-up ranged between two and 104 weeks.

One SR+MA[53] that compared CBT combined with relaxation techniques to inactive controls included two studies representing 162 patients. The MA found a non-statistically significant decrease in SE for CBT and relaxation techniques compared with control with a standardized mean difference of –0.43 (95% CI, –1.68 to 0.83; I^2: 0.86%) The duration of

the included studies was not reported in either SR+MA, the length of follow-up ranged from four to eight weeks.

Five MAs (in four publications)[36,50,55,57] that compared multi-component CBT with inactive controls included between two and 17 studies (sample sizes not reported). All four of the MAs found a statistically significant improvement in SE compared with control and reported effect sizes ranging from 0.43 to 0.79 (standardized mean difference) and one mean difference of 9.91% (95% CI, 8.09 to 11.73; I^2: not reported). Heterogeneity ranged from 0% to 92% with only one SR+MA having heterogeneity estimated above 75%. The duration of the included studies was not reported and length of follow-up ranged from four to 104 weeks. Two SRs[75,79] that compared multi-component CBT with inactive controls included between one and three studies representing 154 and 209 patients, respectively. Both SRs reported that CBT statistically significantly improved SE compared with placebo (values not reported). The duration of the included studies was not reported and length of follow-up ranged from four to 104 weeks.

Details of the interventions and results are available in Appendix 9, Table 82.

A total of 83 unique primary studies were included across the sixteen SR+MAs and nine SRs that reported on SE outcomes. One primary study was cited at least five times across four SR+MAs and one SR, seven primary studies were cited at least four times across ten SR+MAs and three SRs, seven primary studies were cited at least three times across eight different SR+MAs and four SRs, eleven primary studies were cited at least twice across nine different SR+MAs and three SRs, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.9, Table 126.

Cognitive Behavioural Therapy Compared With Active Controls

Two SR+MAs[47,93] that compared different delivery methods for CBT, one SR[85] that compared CBT plus relaxation techniques to CBT alone, and one SR[79] that compared CBT with CBT plus temazepam reported on SE outcomes. Two SR+MAs[47,93] and one SR[79] included patients with comorbidities (alcohol dependence, chronic disease/medical illness, depression), and one SR[85] did not report on comorbidities in the patient population. Both SR+MAs included only subjective measures of SE (sleep diary) and both SRs included both objective and subjective measures of SE.

The two MAs that compared delivery methods for CBT included three and two studies, respectively (sample sizes not reported). The MA that compared self-help CBT with in-person CBT[93] found a non-statistically significant improvement in SE for the in-person CBT group (Cohen's *d* –0.29; [95% CI, –0.65 to 0.06; I^2: 22.4%]). The MA that compared Internet-based CBT with in-person CBT found similar results, with a non-significant improvement in SE for the in-person CBT group (mean difference –1.21%; [95% CI, –49.0 to 46.6; I^2: 59.7%]). The duration of the included studies was not reported and length of follow-up ranged from four to 48 weeks.

One SR[85] compared CBT alone with CBT combined with relaxation therapy (one RCT representing 46 patients) and found an increase in SE for the CBT group (pre- / post-intervention 77.8% to 85.5%) compared with the CBT combined with relaxation group (pre- / post-intervention 77.8% to 78.1%), but did not report on the clinical or statistical significance of the change. The duration of the included studies was not reported and the length of follow-up ranged from 12 to 104 weeks.

One SR[79] that compared CBT alone with CBT combined with temazepam (one study representing 76 patients) found that CBT combined with temazepam was statistically significantly more effective than CBT alone (values not reported). The duration of the included studies and the length of follow-up were not reported.

Details of the interventions and results are available in Appendix 9, Table 82.

Inadequate reporting in one of the SR+MAs[93] that compared multi-component CBT with CBT alone prevented ascertainment of the specific primary studies that contributed data to this outcome and thus prevented any determination of overlap between the two SR+MAs that compared multi-component CBT with CBT alone, and reported SE. The primary studies that could be ascertained from one of the SR+MAs[47] are reported in Appendix 10.10, Table 131.

Table 54: Cognitive Behavioural Therapy — Summary of Evidence for Sleep Efficiency

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
CBT vs. inactive controls[32,35,37,38,40,44,47,51,54,56,65,66,73,76,82,85,90,93]	+	+	+	+
CBT + relaxation vs. inactive controls[53]	–	NA	NA	NA
Multi-component CBT vs. inactive controls[36,50,55,57,75,82]	+	+	+	+
Self-help CBT vs. in-person CBT[93]	–	NA	NA	NA
Internet-based CBT vs. in-person CBT[47]	NA	–	NA	NA
CBT vs. CBT + relaxation[85]	NA	NA	+	NA
CBT + temazepam vs. CBT[79]	NA	NA	NA	+

CBT = cognitive behavioural therapy; MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Behavioural Interventions Compared With Inactive Controls

Two SRs that compared sleep restriction[79,81] with inactive controls reported on SE outcomes. One SR[79] included patients with comorbidities (medical illness) and one SR[81] did not include any patients with comorbid conditions. One SR[81] included a combination of objective and subjective measures to collect SE data, and one SR[79] included only subjective measures of SE.

The SRs included two and three studies representing 129 and 78 patients respectively, and both found an increase in SE compared with control conditions. One SR reported the change was statistically significant.[79] One SR[81] reported the length of follow-up of the included studies (13 to 52 weeks) but not the duration of the studies. The other SR[79] reported neither the duration nor the length of follow-up of the included studies.

Details of the interventions and results are available in Appendix 9, Table 82.

A total of four unique studies were included across two SRs that reported on SE outcomes. One primary study was cited twice across the two SRs and there were no apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.11, Table 136.

Behavioural Therapy Compared With Active Controls

No included SR+MAs or SRs that compared BT with active controls were identified that reported this outcome.

No included SR+MAs or SRs that compared multi-component BT with active controls were identified that reported this outcome.

Table 55: Behavioural Therapy — Summary of Evidence for Sleep Efficiency

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Sleep restriction therapy vs. inactive controls[79,81]	NA	NA	+	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Mindfulness-Based Interventions Compared With Inactive Controls

One SR+MA[34] that compared mindfulness-based stress reduction and meditation with wait-list, sleep hygiene education, and self-monitoring controls reported SE outcomes. One SR[90] that compared pre- and post-intervention effects of mindfulness-based stress reduction, mind-body bridging, and mindfulness meditation, reported SE outcomes. The SR+MA included patients with comorbid depression and cancer and the SR included adult cancer patients undergoing curative treatment. SE data were collected using a sleep diary in the SR+MA. The data collection method was not reported in the SR.

The MA of SE data included two RCTs representing 58 patients and found a non-statistically significant increase in SE (standardized mean difference: 0.85; [95% CI, –0.31 to 1.40; I^2: 0%]). The SR included three RCTs representing 205 patients, two of the trials reported statistically significant increases in SE while one RCT showed no statistically significant improvement. The length of follow-up of the trials included in the MA ranged from six to eight weeks, and study duration was not reported. The length of follow-up and study duration of the study included in the SR were not reported.

Details of the interventions and results are available in Appendix 9, Table 82.

A total of five unique studies were included across one SR+MA and one SR that reported on SE outcomes. There were no apparent overlaps in primary studies. The full list of primary studies and overlaps is available in Appendix 10.12, Table 138.

Mindfulness-Based Interventions Compared With Active Controls

No SR+MAs or SRs that compared mindfulness-based interventions with active controls were included in this review.

Table 56: Mindfulness-Based Interventions — Summary of Evidence for Sleep Efficiency

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Mindfulness-based stress reduction vs. sleep hygiene education[34]	NA	–	NA	NA
Mindfulness-based stress reduction (pre- and post-measures)[90]	NA	NA	NA	+/–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Combination Therapies Compared With Inactive Controls

No included SR+MAs or SRs that compared combination therapies (non-pharmacologic plus pharmacologic) with inactive controls reported this outcome.

Combination Therapies Compared With Active Controls

No SR+MAs or SRs that compared combination therapies with active controls were included in this review.

d) Insomnia Severity Index

Benzodiazepine Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with inactive controls were identified that reported this outcome.

Benzodiazepine Drugs Compared With Active Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with active controls were identified that reported this outcome.

Non-Benzodiazepine Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared non-benzodiazepine drugs with inactive controls were identified that reported this outcome.

Non-Benzodiazepine Drugs Compared With Active Controls

No included SR+MAs or SRs that compared non-benzodiazepine drugs with active controls were identified that reported this outcome.

Suvorexant Compared With Inactive Controls

Two SR+MAs[39,41] and one SR[69] that compared suvorexant with placebo reported ISI scores. The two SR+MAs[39,41] and one SR[69] only included patients with insomnia.

Three primary studies reporting data from four RCTs (3,076 patients) were included across the two SR+MAs and one SR, resulting in complete overlap between the included reviews for this outcome. The two MAs both found a small but statistically significant decrease in ISI scores with mean differences of -1.35 points (95% CI, –1.78 to –0.93; I^2: 0%) and –1.42 points (95% CI, –1.85 to –0.98; I^2: 0%) compared with placebo. The SR found results consistent with the MA, with a statistically significant proportion of respondents achieving greater than 6-point improvement on the ISI for patients receiving both 15 mg to 20 mg and 30 mg to 40mg doses compared with placebo (55.5% versus 42.2% and 54.9% versus 42.2%, respectively). Length of follow-up for the included trials ranged from four to 52 weeks, and study duration was not reported.

Details of the interventions and results are available in Appendix 9, Table 83.

The same three primary studies (reporting data from four RCTs) were cited by the three SR+MAs and one SR, resulting in complete overlap across all seven outcomes reported for this treatment comparison. The full list of primary studies and overlaps is available in Appendix 10.3, Tables 96 to 102.

Suvorexant Compared With Active Controls

No SR+MAs or SRs that compared suvorexant with active controls were identified.

Table 57: Suvorexant — Summary Table for Insomnia Severity Index

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Suvorexant vs. placebo[39,41,69]	+	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Antidepressant Drugs Compared With Inactive Controls

One SR+MA[29] that compared doxepin with placebo reported ISI scores. It included patients with comorbidities (chronic pain and hearing impairment). The MA included two RCTs representing 494 patients and found a statistically significant decrease in ISI scores with a mean difference of –1.74 points (95% CI, –2.59 to –0.88; I^2: 0%). The length of follow-up of the included studies was four to 12 weeks, and the duration of the studies was not reported.

Details of the interventions and results are available in Appendix 9, Table 83.

Antidepressant Drugs Compared With Active Controls

No included SR+MA or SRs that compared antidepressant drugs with active controls reported this outcome.

Table 58: Antidepressant Drugs — Summary of Evidence for Insomnia Severity Index

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Doxepin vs. placebo[29]	+	NA	NA	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Antipsychotic Drugs Compared With Inactive Controls

One SR[63] that compared pre- and post-intervention effects of quetiapine reported ISI scores. The SR did not include any patients with comorbidities.

The SRs included one trial representing six patients and found that, in five out of six patients; ISI scores were reduced from “moderate” insomnia to “absence of insomnia” after one week of treatment. The duration of the included study and the length of follow-up were not reported.

Details of the interventions and results are available in Appendix 9, Table 83.

Antipsychotic Drugs Compared With Active Controls

No SR+MAs or SRs that compared antipsychotic drugs with active controls were included in this review.

Table 59: Antipsychotic Drugs — Summary of Evidence for Insomnia Severity Index

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Quetiapine vs. inactive controls[c 63]	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).
[c] Includes placebo and no comparator (pre- and post- measures).

Melatonin Compared With Inactive Controls

No included SR+MAs or SRs that compared melatonin with inactive controls reported this outcome.

Melatonin Compared With Active Controls

No SR+MAs or SRs that compared melatonin with active controls were identified.

Diphenhydramine Compared With Inactive Controls

One SR[72] that compared diphenhydramine with placebo reported ISI scores. It did not include any patients with comorbidities.

The SR included one RCT representing 184 patients and found there was a statistically significant decrease in ISI scores compared with placebo, indicating improvement in overall insomnia symptoms (9.39 versus 11.63; $P < 0.01$). The trial lasted for two weeks and length of follow-up was not reported.

Details of the interventions and results are available in Appendix 9, Table 83.

Diphenhydramine Compared With Active Controls

No SR+MAs or SRs that compared diphenhydramine with active controls were identified.

Table 60: Diphenhydramine — Summary of Evidence for Insomnia Severity Index

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Diphenhydramine vs. placebo[72]	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Cognitive Behavioural Therapy Compared With Inactive Controls

Nine SR+MAs and five SRs that compared CBT[29,32,35,38,47,51,54,56,65,73,76,90] or multi-component CBT[55,75] with inactive control reported ISI scores.

All of the SR+MAs[29,32,35,38,47,51,54-56] and SRs[65,73,75,76,90] included patients with comorbidities (cancer, chronic pain, fibromyalgia, PTSD, depression, hearing impairment, fibromyalgia, arthritis, restless leg syndrome, chronic obstructive pulmonary disease, alcohol dependence/abuse, traumatic brain injury, sleep apnea, parasomnia, and unspecified chronic or medical illness).

The nine MAs (in eight publications)[29,32,35,38,47,51,54,56] that compared CBT with inactive controls included between two and 38 studies representing between 131 and 1,655 patients. The nine MAs found a statistically significant improvement in ISI score compared with control and reported effect sizes ranging from –1.15 to 0.98 (standardized mean difference), –5.15 points to –7.1 points (mean difference). Heterogeneity ranged from 0% to 90% with two of the MAs having an I^2 greater than 75%. The duration of the included studies ranged between two and 12 weeks and length of follow-up ranged from one to 104 weeks. Four SRs[65,73,76,90] that compared CBT with inactive controls included between one and eight studies representing between 10 and 660 patients. The four SRs all found that CBT improved ISI scores compared with control, and all SRs reported a statistically significant difference between groups in at least 50% of the included studies. One SR[73] included two studies and reported a change in ISI score of 0.37 (95% CI, 0.10 to 0.84) compared with placebo in one study (72 patients) and a pre- to post-intervention change of 2.67 points (95% CI, 1.37 to 3.73) in the other study (10 patients). Another SR[90] that compared different delivery methods for CBT reported that three of eight trials (660 patients) examining group CBT found statistically significant changes in post-intervention ISI scores with average decreases ranging from 39.9% to 63.9% ($P < 0.05$); five of five trials (132 patients) examining professionally administered CBT found a reduction in post-intervention ISI scores with average decreases ranging from 27.4% to 63.9% (*P* value not reported); and four of four trials (328 patients) examining self-help CBT found non-statistically significant changes in post-intervention ISI scores, with average decreases ranging from 44.5% to 56.2% (*P* values not reported). The other two SRs[65,76] did not report specific values, but stated that ISI scores improved significantly for CBT compared with placebo ($P < 0.01$). The duration of

included studies was not reported in any SR and length of follow-up ranged between four and 52 weeks.

Three MAs[38,47,55] that compared multi-component CBT with inactive controls included between four and eight studies (sample sizes not reported), and all three MAs found a statistically significant improvement in ISI scores compared with control, with reported effect sizes ranging from 0.547 (standardized mean difference) to –3.74 points (mean difference). Heterogeneity ranged from 0% to 90% with only two MAs having heterogeneity greater than 75%. The duration of the included studies was not reported and length of follow-up ranged from four to 52 weeks. One SR[75] that compared multi-component CBT with inactive controls included four studies representing 180 patients. The SR reported that multi-component CBT statistically significantly improved ISI scores compared with control in the included studies (values not reported). The duration of the included studies was not reported and length of follow-up ranged from eight to 74 weeks.

Details of the interventions and results are available in Appendix 9, Table 83.

A total of 46 unique primary studies were included across the nine SR+MAs and five SRs that reported ISI scores. One primary study was cited at least five times across five SR+MAs, two primary studies were cited at least four times across six different SR+MAs and two SRs, two primary studies were cited at least three times across three SR+MAs and one SR, nine primary studies were cited at least twice across three different SR+MAs and three SRs, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlapping primary studies is available in Appendix 10.9, Table 127.

Cognitive Behavioural Therapy Compared With Active Controls

One SR+MA[47] that compared self-help CBT with in-person CBT reported ISI scores. The SR+MA included patients with comorbid depression.

The MA included two studies (sample size not reported) and found a non-statistically significant increase in ISI scores for the Internet-based CBT group (mean difference: 1.07; [95% CI, –6.23 to 8.38; I^2: 0%]). The duration of the included studies was not reported and the length of follow-up ranged from four to 52 weeks.

Details of the interventions and results are available in Appendix 9, Table 83.

Table 61: Cognitive Behavioural Therapy — Summary of Evidence for Insomnia Severity Index

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
CBT vs. inactive controls[c] 29,32,35,38,47,51,54,56,65,73,76,90	+	+	+	+
Multi-component CBT vs. inactive controls[55,75]	+	NA	+	NA
Self-help CBT vs. in-person CBT[47]	NA	–	NA	NA

CBT = cognitive behavioural therapy; MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes placebo and no comparator (pre- and post- measures).

Behavioural Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared behavioural interventions with inactive controls were identified that reported this outcome.

Behavioural Interventions Compared With Active Controls

No included SR+MAs or SRs that compared behavioural interventions with active controls were identified that reported this outcome.

Mindfulness-Based Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared mindfulness-based interventions with inactive controls were identified that reported this outcome.

Mindfulness-Based Interventions Compared With Active Controls

No SR+MAs or SRs that compared mindfulness-based interventions with active controls were identified.

Combination Therapies Compared With Inactive Controls

No included SR+MAs or SRs that compared combination therapies (non-pharmacologic plus pharmacologic) with inactive controls were identified that reported this outcome.

Combination Therapies Compared With Active Controls

No SR+MAs or SRs that compared combination therapies with active controls were identified.

e) Fatigue Severity

Benzodiazepine Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with inactive controls were identified that reported this outcome.

Benzodiazepine Drugs Compared With Active Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with active controls were identified that reported this outcome.

Non-Benzodiazepine Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared non-benzodiazepine drugs with inactive controls were identified that reported this outcome.

Non-Benzodiazepine Drugs Compared With Active Controls

No included SR+MAs or SRs that compared non-benzodiazepine drugs with active controls were identified that reported this outcome.

Suvorexant Compared With Inactive Controls

No included SR+MAs or SRs that compared suvorexant with inactive controls were identified that reported this outcome.

Suvorexant Compared With Active Controls

No SR+MAs or SRs that compared suvorexant with active controls were identified.

Antidepressant Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared antidepressant drugs with inactive controls were identified that reported this outcome.

Antidepressant Drugs Compared With Active Controls

No included SR+MAs or SRs that compared antidepressant drugs with active controls were identified that reported this outcome.

Antipsychotic Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared antipsychotic drugs with active controls were identified that reported this outcome.

Antipsychotic Drugs Compared With Active Controls

No SR+MAs or SRs that compared antipsychotic drugs with active controls were identified.

Melatonin Compared With Inactive Controls

No included SR+MAs or SRs that compared melatonin with inactive controls were identified that reported this outcome.

Melatonin Compared With Active Controls

No SR+MAs or SRs that compared melatonin with active controls were identified.

Diphenhydramine Compared With Inactive Controls

No included SR+MAs or SRs that compared diphenhydramine with inactive controls were identified that reported this outcome.

Diphenhydramine Compared With Active Controls

No SR+MAs or SRs that compared diphenhydramine with active controls were identified.

Cognitive Behavioural Therapy Compared With Inactive Controls

Three SR+MAs and two SRs that compared CBT,[49,62,73] CBT with an additional behavioural intervention,[53] or multi-component CBT[75] to inactive control, reported on fatigue severity. Two SR+MAs[49,53] and two SRs[73,75] included patients with comorbidities (cancer, kidney disease, chronic pain) and one SR+MA[62] did not include any patients with comorbidities. One SR[75] included subjective measures (sleep diary) to record fatigue symptoms, three SR+MAs[49,53,62] included questionnaires or scales to measure fatigue symptoms, and one SR[73] did not report the method used to measure fatigue.

Four MAs (in two publications)[49,62] that compared different forms of CBT with control included between six and seven studies representing between 398 and 1,098 patients found that CBT produced a statistically significant reduction in fatigue severity compared with control in two MAs with standardized mean differences of 0.45 (95% CI, 0.07 to 0.83; I^2: 76.5%) and 0.38 (95% CI, 0.08 to 0.69; I^2:71%). The other two analyses also found a reduction in fatigue severity but failed to reach statistical significance with a Cohen's *d* of 0.35 (95% CI, –0.16 to 0.86; I^2: 76.5%) and 0.36 (95% CI, –0.15 to 0.88; I^2: 76.5%). The duration and length of follow-up of the included studies was not reported. The SR[73] examining CBT included one study representing 12 patients and found a statistically significant decrease in fatigue severity at week 8 of follow-up compared with baseline scores (mean change: –0.82, [95% CI, –1.87 to -0.16]). The duration of the study was not reported.

Details of the interventions and results are available in Appendix 9, Table 84.

A possible total of 26 unique primary studies were included across the three SR+MAs and two SRs that reported on fatigue severity outcomes. Due to inadequate reporting in one SR+MA, the specific primary studies associated with this outcome could not be determined and they are not included in the following counts. One primary study was cited at least twice across two different SR+MAs and one SR, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlapping primary studies is available in Appendix 10.9, Table 128.

Cognitive Behavioural Therapy Compared With Active Controls

No included SR+MAs or SRs that compared CBT with active controls were identified that reported this outcome.

Table 62: Cognitive Behavioural Therapy — Summary of Evidence for Fatigue Severity

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
CBT vs. inactive controls[49,62,73]	+/–	NA	+	NA
CBT + relaxation vs. inactive controls[53]	–	NA	NA	NA
Multi-component CBT vs. inactive controls[75]	NA	NA	+	NA

CBT = cognitive behavioural therapy; MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Behavioural Interventions Compared With Inactive Controls

One SR+MA[62] that compared BT with inactive controls reported on fatigue severity outcomes. The SR+MA did not include any patients with comorbid conditions and included the Fatigue Severity Scale as the outcome measure.

The SR+MA included two studies representing 74 patients and found a non-statistically significant increase in fatigue severity compared with control with a difference (Cohen's *d*) of 0.09 (95% CI, –0.61 to 0.79; I^2: 76.5%). The duration and length of follow-up of the included studies was not reported.

Details of the interventions and results are available in Appendix 9, Table 84.

Behavioural Interventions Compared With Active Controls

No included SR+MAs or SRs that compared behavioural interventions with active controls were identified that reported this outcome.

Table 63: Behavioural Interventions — Summary of Evidence for Fatigue Severity

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Behavioural therapy vs. inactive controls[62]	NA	NA	–	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Mindfulness-Based Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared mindfulness-based interventions with inactive controls were identified that reported this outcome.

Mindfulness-Based Interventions Compared With Active Controls

No SR+MAs or SRs that compared mindfulness-based interventions with active controls were identified.

Combination Therapies Compared With Inactive Controls

No included SR+MAs or SRs that compared combination therapies (non-pharmacologic plus pharmacologic) with inactive controls were identified that reported this outcome.

Combination Therapies Compared With Active Controls

No SR+MAs or SRs that compared combination therapies with active controls were identified.

5.4.1.9 Health-Related Quality of Life

Benzodiazepine Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with inactive controls were identified that reported this outcome.

Benzodiazepine Drugs Compared With Active Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with active controls were identified that reported this outcome.

Non-Benzodiazepine Drugs Compared With Inactive Controls

One SR[76] that compared zopiclone with placebo reported on HRQoL in adult populations with insomnia and comorbid cancer. QoL data were collected using a 23-item questionnaire developed by sleep experts.

The SR included two studies representing 1,006 patients and found there was no difference in QoL for patients treated with zopiclone compared with placebo.

Details of the interventions and results are available in Appendix 9, Table 85.

Non-Benzodiazepine Drugs Compared With Active Controls

One SR[76] that compared nightly administration of zolpidem with occasional administration of zolpidem reported on HRQoL in adult populations with insomnia and comorbid cancer. QoL data were collected using the Short Form (36) Health Survey (SF-36).

The SR included one study representing 789 patients and found a statistically significant increase in QoL for both treatment groups ($P = 0.005$).

Details of the interventions and results are available in Appendix 9, Table 85.

Table 64: Non-Benzodiazepine Drugs — Summary of Evidence for Health-Related Quality of Life

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Zopiclone vs. placebo[76]	NA	NA	NA	–
Zolpidem nightly vs. zolpidem "as needed"[76]	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Suvorexant Compared With Inactive Controls

No included SR+MAs or SRs that compared suvorexant with inactive controls were identified that reported this outcome.

Suvorexant Compared With Active Controls

No SR+MAs or SRs that compared suvorexant with active controls were identified.

Antidepressant Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared antidepressant drugs with inactive controls were identified that reported this outcome.

Antidepressant Drugs Compared With Active Controls

No included SR+MAs or SRs that compared antidepressant drugs with active controls were identified that reported this outcome.

Antipsychotic Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared antipsychotic drugs with active controls were identified that reported this outcome.

Antipsychotic Drugs Compared With Active Controls

No SR+MAs or SRs that compared antipsychotic drugs with active controls were identified.

Melatonin Compared With Inactive Controls

One SR[84] that compared melatonin with placebo reported QoL scores. The SR did not report on comorbidities in the patient population and the QoL measure was not reported.

The SR included one study representing 42 patients and reported a statistically significant increase in QoL compared with placebo. The duration of the study and the length of follow-up were not reported.

Details of the interventions and results are available in Appendix 9, Table 85.

Melatonin Compared With Active Controls

No SR+MAs or SRs that compared melatonin with active controls were identified.

Table 65: Melatonin — Summary of Evidence for Health-Related Quality of Life

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Melatonin vs. inactive controls[c] [45,84]	NA	+/–	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes inactive controls and placebo.

Diphenhydramine Compared With Inactive Controls

No included SR+MAs or SRs that compared diphenhydramine with inactive controls were identified that reported this outcome.

Diphenhydramine Compared With Active Controls

No SR+MAs or SRs that compared diphenhydramine with active controls were identified.

Cognitive Behavioural Therapy Compared With Inactive Controls

Four SRs that compared CBT[66,73,76] and multi-component CBT[75] with inactive controls reported on HRQoL. All four SRs included patients with comorbidities (cancer and alcohol use). One SR[66] included daily sleep diaries and ISI scores as measures of HRQoL, two

SRs[73,76] included scales or questionnaires as measures of HRQoL, and one SR[75] did not report on the method used to measure HRQoL.

The three SRs[66,73,76] that compared CBT with inactive controls included between one and four studies representing between 10 and 706 patients and found that CBT resulted in statistically significant improvements in HRQoL on global, cognitive, physical, and emotional/mental health dimensions when compared with control or baseline values. One trial (72 patients) included in one SR[73] was an exception as it found a non-statistically significant increase in scores on the Functional Assessment of Cancer Therapy – Breast scale (FACT-B) with a change of 0.37 points compared with placebo (95% CI, –0.11 to 0.83). The duration of the included studies was not reported and length of follow-up ranged from two to 52 weeks.

The SR[75] that compared multi-component CBT with inactive controls included one study representing 81 patients and found a statistically significant improvement in HRQoL for the multi-component CBT group compared with baseline (values not reported). The duration of the included study was not reported and length follow-up was up to 74 weeks.

Details of the interventions and results are available in Appendix 9, Table 85.

A total of seven unique primary studies were included across the four SRs that reported HRQoL outcomes. One primary study was cited at least twice across two SRs, and there were no other apparent overlaps in primary studies. The full list of primary studies and overlapping primary studies is available in Appendix 10.9, Table 129.

Cognitive Behavioural Therapy Compared With Active Controls

One SR[76] that compared two types of CBT (individual versus group) reported on HRQoL. The SR included patients with comorbid cancer and used a questionnaire/scale to measure HRQoL.

The SR included one study representing 58 patients and found that both CBT groups experienced statistically significant improvements in HRQoL compared with baseline.

Details of the interventions and results are available in Appendix 9, Table 85.

Table 66: Cognitive Behavioural Therapy — Summary of Evidence for Health-Related Quality of Life

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
CBT vs. inactive controls[66,73,76]	NA	NA	+	+
Multi-component CBT vs. inactive controls[75]	NA	NA	+	NA
CBT (individual vs. group)[76]	NA	NA	NA	+

CBT = cognitive behavioural therapy; MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Behavioural Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared behavioural interventions with inactive controls were identified that reported this outcome

Behavioural Interventions Compared With Active Controls

No included SR+MAs or SRs that compared behavioural interventions with active controls were identified that reported this outcome.

Mindfulness-Based Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared mindfulness-based interventions with inactive controls were identified that reported this outcome.

Mindfulness-Based Interventions Compared With Active Controls

No SR+MAs or SRs that compared mindfulness-based interventions with active controls were identified.

Combination Therapies Compared With Inactive Controls

No included SR+MAs or SRs that compared combination therapies (non-pharmacologic plus pharmacologic) with inactive controls were identified that reported this outcome

Combination Therapies Compared With Active Controls

No SR+MAs or SRs that compared combination therapies with active controls were identified.

5.4.2 Harms

a) Hangover/Morning Sedation

Benzodiazepine Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with inactive controls were identified that reported this outcome.

Benzodiazepine Drugs Compared With Active Controls

One SR compared zopiclone with flurazepam and reported hangover or morning sedation effects. Results are detailed in the next section of the report and in Appendix 9, Table 77.

Non-Benzodiazepine Drugs Compared With Active and Inactive Controls

One SR[68] that compared zopiclone, flurazepam, and placebo reported hangover or morning sedation effects. The SR did not report the occurrence of comorbidities in the sample population and did not report the method for collecting outcome data.

The SR included one study representing 24 patients and found that after three weeks of treatment zopiclone had no effect on morning activity and no residual sedative activity. Results for the flurazepam and placebo treatment arms were not reported.

Details of the interventions and results are available in Appendix 9, Table 77.

Table 67: Non-Benzodiazepine Drugs — Summary of Evidence for Hangover/Morning Sedation

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Zopiclone [68]	NA	NA	NA	–
Flurazepam[68]	NA	NA	NA	Not reported
Placebo[68]	NA	NA	NA	Not reported

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Suvorexant Compared With Inactive Controls

Two SR+MAs[39,41] that compared suvorexant with placebo reported hangover or morning sedation effects, the two SR+MAs only included patients with insomnia. One SR+MA[39] did not report the specific definition of hangover/morning sedation included in the review, the other SR+MA[41] defined the outcome as “excessive daytime sleepiness.”

Three primary studies reporting data from four RCTs (3,076 patients) were included across the two SR+MAs resulting in complete overlap between the included reviews for this outcome. The two MAs both found a statistically significant increase in the risk of hangover or morning sedation with use of suvorexant compared with placebo with a risk ratio of 3.34 (95% CI, 1.08 to 10.32; I^2:0%) and relative risk of 3.05 (95% CI, 1.10 to 8.48; I^2:0%), respectively. Length of follow-up for the included trials ranged from four to 52 weeks and study duration was not reported.

Details of the interventions and results are available in Appendix 9, Table 77.

The same three primary studies (reporting data from four RCTs) were cited by the two SR+MAs for this treatment comparison, resulting in complete overlap across all seven outcomes reported for this treatment comparison. The full list of primary studies and overlaps is available in Appendix 10.3, Tables 96 to 102.

Suvorexant Compared With Active Controls

No SR+MAs or SRs that compared suvorexant with active controls were identified.

Table 68: Suvorexant — Summary of Evidence for Hangover/Morning Sedation

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Suvorexant vs. placebo[39,41]	+	NA	NA	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Antidepressant Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared antidepressant drugs with inactive controls were identified that reported this outcome.

Antidepressant Drugs Compared With Active Controls

No included SR+MAs or SRs that compared antidepressant drugs with active controls were identified that reported this outcome.

Antipsychotic Drugs Compared With Inactive Controls

One SR[63] that compared quetiapine with placebo reported the occurrence of morning sedation; the SR did not include any patients with comorbidities.

The SR included two trials and did not report the sample size for this outcome. The occurrence of morning sedation was found to be statistically significantly more common in the quetiapine group compared with placebo. The duration of the included studies and the length of follow-up were not reported.

Details of the interventions and results are available in Appendix 9, Table 77.

Antipsychotic Drugs Compared With Active Controls

No SR+MAs or SRs that compared antipsychotic drugs with active controls were identified.

Table 69: Antipsychotic Drugs — Summary of Evidence for Hangover/Morning Sedation

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Quetiapine vs. inactive controls[c] [63]	NA	NA	NA	+

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes placebo and no comparator (pre- and post-measures).

Melatonin Compared With Inactive Controls

No included SR+MAs or SRs that compared melatonin with inactive controls were identified that reported this outcome.

Melatonin Compared With Active Controls

No SR+MAs or SRs that compared melatonin with active controls were identified.

Diphenhydramine Compared With Inactive Controls

No included SR+MAs or SRs that compared diphenhydramine with inactive controls were identified that reported this outcome.

Diphenhydramine Compared With Active Controls

No SR+MAs or SRs that compared diphenhydramine with active controls were identified.

Cognitive Behavioural Therapy Compared With Inactive Controls

No included SR+MAs or SRs that compared CBT with inactive controls were identified that reported this outcome.

Cognitive Behavioural Therapy Compared With Active Controls

No included SR+MAs or SRs that compared CBT with active controls were identified that reported this outcome.

Behavioural Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared behavioural interventions with inactive controls were identified that reported this outcome.

Behavioural Interventions Compared With Active Controls

No included SR+MAs or SRs that compared behavioural interventions with active controls were identified that reported this outcome.

Mindfulness-Based Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared mindfulness-based interventions with inactive controls were identified that reported this outcome.

Mindfulness-Based Interventions Compared With Active Controls

No SR+MAs or SRs that compared mindfulness-based interventions with active controls were identified.

Combination Therapies Compared With Inactive Controls

No included SR+MAs or SRs that compared combination therapies (non-pharmacologic plus pharmacologic) with inactive controls were identified that reported this outcome.

Combination Therapies Compared With Active Controls

No SR+MAs or SRs that compared combination therapies with active controls were identified.

b) Accidental Injuries

Benzodiazepine Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with inactive controls were identified that reported this outcome.

Benzodiazepine Drugs Compared With Active Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with active controls were identified that reported this outcome.

Non-Benzodiazepine Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared non-benzodiazepine drugs with inactive controls were identified that reported this outcome.

Non-Benzodiazepine Drugs Compared With Active Controls

No included SR+MAs or SRs that compared non-benzodiazepine drugs with active controls were identified that reported this outcome.

Suvorexant Compared With Inactive Controls

Two SR+MAs[39,41] that compared suvorexant with placebo reported the occurrence of accidental injuries. The two SR+MAs[39,41] only included patients with insomnia. One SR+MA[39] did not report the occurrence of "motor vehicle accidents/violations," and the other SR+MA[41] reported the occurrence of falls.

Three primary studies reporting data from four RCTs (3,076 patients) were included across the two SR+MAs, resulting in complete overlap between the included reviews for this outcome. The two MAs both found a non-statistically significant increase in the risk of accidental injury (motor vehicle accidents) compared with placebo, with a risk ratio of 1.16 (95% CI, 0.52 to 2.60; I^2: 0%) and one MA[41] found a non-significant decrease in the risk of

falls for suvorexant compared with placebo, with a relative risk of 0.84 (95% CI, 0.44 to 1.62; I^2: 0%). Length of follow-up for the included trials ranged from four weeks to 52 weeks, and study duration was not reported.

Details of the interventions and results are available in Appendix 9, Table 87.

The same three primary studies (reporting data from four RCTs) were cited by the two SR+MAs, resulting in complete overlap across all seven outcomes reported for this treatment comparison. The full list of primary studies and overlaps is available in Appendix 10.3, Tables 96 to 102.

Suvorexant Compared With Active Controls

No SR+MAs or SRs that compared suvorexant with active controls were identified.

Table 70: Suvorexant — Summary of Evidence for Accidental Injuries

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Suvorexant vs. placebo[39,41]	+	NA	NA	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Antidepressant Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared antidepressant drugs with inactive controls were identified that reported this outcome.

Antidepressant Drugs Compared With Active Controls

No included SR+MAs or SRs that compared antidepressant drugs with active controls were identified that reported this outcome.

Antipsychotic Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared antipsychotic drugs with active controls were identified that reported this outcome.

Antipsychotic Drugs Compared With Active Controls

No SR+MAs or SRs that compared antipsychotic drugs with active controls were identified.

Melatonin Compared With Inactive Controls

No included SR+MAs or SRs that compared melatonin with inactive controls were identified that reported this outcome.

Melatonin Compared With Active Controls

No SR+MAs or SRs that compared melatonin with active controls were identified.

Diphenhydramine Compared With Inactive Controls

No included SR+MAs or SRs that compared diphenhydramine with inactive controls were identified that reported this outcome.

Diphenhydramine Compared With Active Controls

No SR+MAs or SRs that compared diphenhydramine with active controls were identified.

Cognitive Behavioural Therapy Compared With Inactive Controls

No included SR+MAs or SRs that compared CBT with inactive controls were identified that reported this outcome.

Cognitive Behavioural Therapy Compared With Active Controls

No included SR+MAs or SRs that compared CBT with active controls were identified that reported this outcome.

Behavioural Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared behavioural interventions with inactive controls were identified that reported this outcome.

Behavioural Interventions Compared With Active Controls

No included SR+MAs or SRs that compared behavioural interventions with active controls were identified that reported this outcome.

Mindfulness-Based Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared mindfulness-based interventions with inactive controls were identified that reported this outcome.

Mindfulness-Based Interventions Compared With Active Controls

No SR+MAs or SRs that compared mindfulness-based interventions with active controls were identified.

Combination Therapies Compared With Inactive Controls

No included SR+MAs or SRs that compared combination therapies (non-pharmacologic plus pharmacologic) with inactive controls were identified that reported this outcome.

Combination Therapies Compared With Active Controls

No SR+MAs or SRs that compared combination therapies with active controls were identified.

c) Additional Health Care Utilization Related to Harms of the Intervention

No SR+MAs or SRs that examined relevant interventions and reported this outcome were identified.

d) Delirium Related to the Intervention

No SR+MAs or SRs that examined relevant interventions and reported this outcome were identified.

e) Sleep-Disordered Breathing Related to the Intervention

No SR+MAs or SRs that examined relevant interventions and reported this outcome were identified.

f) Addiction, Dependence, or Diversion

Benzodiazepine Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared benzodiazepine drugs with inactive controls reported this outcome.

Benzodiazepine Drugs Compared With Active Controls

One SR compared zopiclone with triazolam and temazepam and reported effects of addiction or dependence. Results are detailed in the next section of the report and Appendix 9, Table 88.

Non-Benzodiazepine Drugs Compared With Inactive Controls

No SR+MAs that compared non-benzodiazepine drugs with inactive controls that reported symptoms of dependence were included in this review. One SR[68] that compared pre- and post-effects of zopiclone on reported symptoms of dependence in adult populations with insomnia was included. The SR did not report the occurrence of comorbidities in the sample population and did not report the method for collecting outcome data.

The SR examining zopiclone included three studies representing 119 patients and found mixed results ranging from no carryover effect to rebound insomnia and withdrawal effects up to three months after treatment.

Details of the interventions and results are available in Appendix 9, Table 88.

Non-Benzodiazepine Drugs Compared With Active Controls

No SR+MAs that compared non-benzodiazepine drugs with active controls and that reported symptoms of dependence were included in this review. One SR[68] that compared zopiclone, zolpidem, temazepam, and triazolam included four studies (a mix of RCTs and NRCTs) representing 331 patients. The SR found inconsistent results, with two trials that compared zopiclone with triazolam and zopiclone to zolpidem reporting that a small minority of patients taking zopiclone suffered from rebound insomnia or anxiety after withdrawing from the medication. The other two trials that compared zopiclone with temazepam, reported no effects of rebound insomnia or anxiety.

Details of the interventions and results are available in Appendix 9, Table 88.

Table 71: Non-Benzodiazepine Drugs — Summary of Evidence for Addiction, Diversion, or Dependence

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Zopiclone vs. inactive control[c] [68]	NA	NA	NA	+/–
Zopiclone vs. triazolam[68]	NA	NA	NA	+/–
Zopiclone vs. zolpidem[68]	NA	NA	NA	+/–
Zopiclone, temazepam, and placebo[68]	NA	NA	NA	+/–

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.

Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.

– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.

+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.

[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).

[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

[c] Includes placebo and no comparator (pre- and post-measures).

Suvorexant Compared With Inactive Controls

Two SR+MAs[39,41] that compared suvorexant to placebo reported the potential for abuse of the drug. The two SR+MAs only included patients with insomnia.

Three primary studies reporting data from four RCTs (3,076 patients) were included across the two SR+MAs, resulting in complete overlap between the included reviews for this outcome. The two MAs both found a statistically significant increase in the potential for abuse compared with placebo, with a risk ratio of 1.05 (95% CI, 0.67 to 1.65; I^2: 0%) and a relative risk of 1.05 (95% CI, 0.66 to 1.65; I^2: 0%). Length of follow-up for the included trials ranged from four weeks to 52 weeks, and study duration was not reported.

Details of the interventions and results are available in Appendix 9, Table 77.

The same three primary studies (reporting data from four RCTs) were cited by the two SR+MAs, resulting in complete overlap across all seven outcomes reported for this treatment comparison. The full list of primary studies and overlaps is available in Appendix 10.3, Tables 96 to 102.

Suvorexant Compared With Active Controls

No SR+MAs or SRs that compared suvorexant with active controls were included in this review.

Table 72: Suvorexant — Summary of Evidence for Addiction, Diversion, or Dependence

Treatment Comparison	SRs With MA		SRs Without MA	
	High/Moderate Quality[a]	Low/Critically Low Quality[b]	High/Moderate Quality[a]	Low/Critically Low Quality[b]
Suvorexant vs. placebo[39,41]	+	NA	NA	NA

MA = meta-analysis; NA = no reviews available; SR = systematic review; vs. = versus.
Note: + (Effective) = statistically significant difference from comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
– (No Difference) = no statistically significant difference between interventions and comparator for effectiveness outcomes (intended treatment effects) and harms outcomes (unintended treatment effects). Font size indicates amount of available evidence.
+/– (Unclear) = mixed or conflicting evidence between MAs and SRs. Font size indicates amount of available evidence.
[a] Rated high or moderate quality using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2):[28] no or one weakness and no critical flaws (high quality); few weaknesses and no critical flaws (moderate quality).
[b] Rated low or critically low quality using AMSTAR 2:[28] one critical flaw with or without additional weaknesses (low quality); more than one critical flaw with or without additional weaknesses (critically low quality).

Antidepressant Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared antidepressant drugs with inactive controls reported this outcome.

Antidepressant Drugs Compared With Active Controls

No included SR+MAs or SRs that compared antidepressant drugs with active controls reported this outcome.

Antipsychotic Drugs Compared With Inactive Controls

No included SR+MAs or SRs that compared antipsychotic drugs with active controls reported this outcome.

Antipsychotic Drugs Compared With Active Controls

No SR+MAs or SRs that compared antipsychotic drugs with active controls were included in this review.

Melatonin Compared With Inactive Controls

No included SR+MAs or SRs that compared melatonin with inactive controls reported this outcome.

Melatonin Compared With Active Controls

No SR+MAs or SRs that compared melatonin with active controls were included in this review.

Diphenhydramine Compared With Inactive Controls

No included SR+MAs or SRs that compared diphenhydramine with inactive controls reported this outcome.

Diphenhydramine Compared With Active Controls

No SR+MAs or SRs that compared diphenhydramine with active controls were included in this review.

Cognitive Behavioural Therapy Compared With Inactive Controls

No included SR+MAs or SRs that compared CBT with inactive controls reported this outcome.

Cognitive Behavioural Therapy Compared With Active Controls

No included SR+MAs or SRs that compared CBT with active controls reported this outcome.

Behavioural Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared behavioural interventions with inactive controls reported this outcome.

Behavioural Interventions Compared With Active Controls

No included SR+MAs or SRs that compared behavioural interventions with active controls reported this outcome.

Mindfulness-Based Interventions Compared With Inactive Controls

No included SR+MAs or SRs that compared mindfulness-based interventions with inactive controls reported this outcome.

Mindfulness-Based Interventions Compared With Active Controls

No SR+MAs or SRs that compared mindfulness-based interventions with active controls were included in this review.

Combination Therapies Compared With Inactive Controls

No included SR+MAs or SRs that compared combination therapies (non-pharmacologic plus pharmacologic) with inactive controls reported this outcome.

Combination Therapies Compared With Active Controls

No SR+MAs or SRs that compared combination therapies with active controls were included in this review.

All-Cause Mortality Related to the Intervention

No SR+MAs or SRs that examined relevant interventions and reported this outcome were identified.

5.4.3 Overall Summary of Results

a) Effectiveness Outcomes

Based on evidence from moderate- to high-quality SR+MAs, the following pharmacological interventions were consistently effective for SOL:

1. Flurazepam versus placebo (based on one SR+MA, see Table 4).
2. Triazolam versus placebo (based on two SR+MAs, see Table 4).
3. Zolpidem versus placebo (based on four SR+MAs, see Table 5).
4. Zopiclone versus placebo (based on two SR+MAs, see Table 5).
5. Suvorexant versus placebo (based on three SR+MAs, see Table 6).
6. Melatonin versus inactive control (based on four SR+MAs, see Table 9).

Based on evidence from moderate- to high-quality SR+MAs, the following non-pharmacological interventions were consistently effective for SOL:

1. CBT versus inactive control (based on 12 SR+MAs, see Table 11).
2. CBT combined with relaxation techniques versus inactive control (based on two SR+MAs, see Table 11).
3. CBT including multiple components versus inactive control (based on five SR+MAs, see Table 11).
4. Behavioural interventions including multiple components versus inactive control (based on one SR+MA, see Table 12).

Based on evidence from moderate- to high-quality SR+MAs, the following pharmacological interventions were consistently effective for TST:

1. Zolpidem versus placebo (based on three SR+MAs, see Table 16).
2. Suvorexant versus placebo (based on three SR+MAs, see Table 17).
3. Doxepin versus placebo (based on four SR+MAs, see Table 18).

Based on evidence from moderate- to high-quality SR+MAs, none of the non-pharmacological interventions were consistently effective for TST.

Based on evidence from moderate- to high-quality SR+MAs, the following pharmacological interventions were consistently effective for WASO:

1. Temazepam versus placebo (based on one SR+MA, see Table 26).
2. Triazolam versus placebo (based on one SR+MA, see Table 26).
3. Zolpidem versus placebo (based on two SR+MAs, see Table 27).
4. Suvorexant versus placebo (based on two SR+MAs, see Table 28).

Based on evidence from moderate- to high-quality SR+MAs, the following non-pharmacological interventions were consistently effective for WASO:

1. CBT versus inactive control (based on 12 SR+MAs, see Table 32).
2. CBT including multiple components versus inactive control (based on four SR+MAs, see Table 32).
3. Behavioural interventions including multiple components versus inactive control (based on one SR+MA, see Table 33).

Based on evidence from moderate- to high-quality SR+MAs, the following pharmacological interventions were consistently effective for SQ:

1. Zolpidem versus placebo (based on two SR+MAs, see Table 35).
2. Suvorexant versus placebo (based on one SR+MA, see Table 36).

Based on evidence from moderate- to high-quality SR+MAs, the following non-pharmacological interventions were consistently effective for SQ:

1. CBT versus inactive control (based on nine SR+MAs, see Table 41).
2. CBT including multiple components versus inactive control (based on three SR+MAs, see Table 41).

Based on evidence from moderate- to high-quality SR+MAs, none of the pharmacological interventions were consistently effective for SS.

Based on evidence from moderate- to high-quality SR+MAs, none of the non-pharmacological interventions were consistently effective for SS.

Based on evidence from moderate- to high-quality SR+MAs, the only pharmacological intervention that was consistently effective for SE was melatonin versus inactive control (based on five SR+MAs, see Table 52).

Based on evidence from moderate- to high-quality SR+MAs, the following non-pharmacological interventions were consistently effective for SE:

1. CBT versus inactive control (based on 11 SR+MAs, see Table 54)
2. CBT including multiple components versus inactive control (based on four SR+MAs, see Table 54).

Based on evidence from moderate- to high-quality SR+MAs, the following pharmacological interventions were consistently effective on the ISI:

1. Suvorexant versus placebo (based on two SR+MAs, see Table 57)
2. Doxepin versus placebo (based on one SR+MA, see Table 58).

Based on evidence from moderate- to high-quality SR+MAs, the following non-pharmacological interventions were consistently effective on the ISI:

1. CBT versus inactive control (based on eight SR+MAs, see Table 61).

Based on evidence from moderate- to high-quality SR+MAs, none of the pharmacological interventions were consistently effective on fatigue severity.

Based on evidence from moderate- to high-quality SR+MAs, the only non-pharmacological intervention that was consistently effective on fatigue severity was CBT versus inactive control (based on one SR+MA, see Table 63).

Based on evidence from moderate- to high-quality SR+MAs, none of the pharmacological interventions were consistently effective on HRQoL.

Based on evidence from moderate- to high-quality SR+MAs, none of the non-pharmacological interventions were consistently effective on HRQoL.

b) Harms Outcomes

Based on evidence from moderate- to high-quality SR+MAs, suvorexant caused more hangover or morning sedation (based on two SR+MAs, see Table 68), accidental injuries (based on two SR+MAs, see Table 70), and addiction, dependence, or diversion than placebo (based on two SR+MAs, see Table 72).

6. Discussion

6.1 Summary of Evidence

We conducted a review of reviews including 64 SRs and 801 unique primary studies. We found that several pharmacological interventions had consistent evidence of effectiveness based on data from moderate- to high-quality SR+MAs. For pharmacological interventions, there was evidence of effectiveness across more than one outcome for the interventions zolpidem, triazolam, suvorexant, doxepin, and melatonin, despite variation across treatment regimens. However, there was evidence suggesting that suvorexant caused more harms than placebo, such as hangover or morning sedation, accidental injuries, and addiction or dependence. Furthermore, very few SRs reported the important harms examined here for zolpidem, triazolam, doxepin, and melatonin. Also, most of the studies examined these pharmacological interventions for the short-term (less than 12 weeks) with a duration of intervention ranging from 24 hours to 16 weeks and duration of follow-up ranging from one week to 52 weeks. Very few patients were included across the primary studies in the reviews, which is concerning given the fact that such a high proportion of the general population use these medications.

For the non-pharmacological interventions, there was evidence of effectiveness across more than one outcome for CBT (alone or multi-component) and behavioural interventions (multi-component). Most of the studies examined these interventions in the short-term, ranging from two weeks to 16 weeks and with a duration of follow-up ranging from one week to 104 weeks. Although one SR+MA[47] examined CBT administered online, it did not compare the effectiveness of online CBT with CBT delivered in person. Due to the high cost of in-person CBT and the lack of accessibility of this important intervention in Canada, we believe this is a topic worthy of future research. Specifically, a realist review considering what type of cognitive behavioural intervention might be the most effective and in which setting, would likely provide clarity to the field.

As noted in the summary of evidence tables, we identified a high-quality SR without MA that reported positive conclusions for the following treatment comparisons:

- Doxepin versus placebo for WASO and SE.
- Sleep restriction versus inactive control for WASO, SQ, and SE.
- CBT versus inactive control for SS and HRQoL.
- CBT versus CBT combined with relaxation for SE.
- Multi-component CBT versus inactive control for HRQoL.

However, a moderate- to high-quality SR+MA was not identified for any of these. As such, we suggest that a future SR+MA be conducted on these interventions and outcomes to provide more definitive conclusions, if appropriate.

In addition, there are several data gaps that our review of reviews identified in the insomnia field. The biggest gap is related to the safety of the pharmacological interventions included here. Despite widespread use, there is a dearth of data on the harms outcomes of pharmacological interventions. This is quite concerning given the amount spent on benzodiazepine drugs and z-drugs, which was more than $330 million in 2013 in Canada, and likely even higher today.[5] Furthermore, zopiclone was the leading drug for insomnia, accounting for 38% of spending,[5] yet this medication was not consistently effective across outcomes from moderate- or high-quality SR+MAs. None of the SR+MAs focused on

examining differences in dosing of the pharmacological interventions. As well, there was very little evidence available examining the effectiveness of sequencing drug and non-drug interventions, or combinations of drug and non-drug interventions, which are areas warranting future research. Furthermore, head-to-head studies comparing pharmacological versus pharmacological; non-pharmacological versus non-pharmacological; and pharmacological versus non-pharmacological comparisons are required. The effectiveness outcomes with the fewest reviews were SS, fatigue severity, and HRQoL, suggesting that future RCTs or SRs should include these important outcomes. In addition, the clinical significance of symptomatic changes in insomnia disorder (e.g., the minimal clinically important difference) are poorly understood and standards are lacking to help researchers evaluate whether a statistically significant improvement in outcomes translates into a clinically significant one. Furthermore, adherence to treatment was not a focus of this review of reviews and may impact the effectiveness of some of the interventions examined here, particularly, non-pharmacological interventions. As well, we did not identify any SRs that focused on patients in long-term care or individuals in correctional facilities. These are areas where future reviews are warranted. Although we attempted to identify harms for the non-pharmacological interventions examined here, no studies reported the harms outcomes, likely because they were more relevant to pharmacological interventions (e.g., addiction, hangover effect, etc.).

6.2 Interpretation of the Results

Based on these results, it is expected that CBT will demonstrate consistent effectiveness across a number of insomnia-related outcomes while being associated with few, or possibly no, serious harms. However, there is insufficient data to evaluate what the true benefit-to-harm ratio is for CBT. If CBT is not effective, then other behavioural interventions may be considered. If non-drug interventions are not effective, short durations of melatonin, zolpidem, triazolam, or doxepin may be considered. However, these agents have only been tested in the short-term and there is very little evidence on their effectiveness and safety beyond 16 weeks of treatment.

6.3 Strengths and Limitations of the Systematic Review

6.3.1 Strengths

There are several strengths of our review of reviews that are worth noting. The Cochrane Handbook was used to guide the conduct of our review, as well as the AMSTAR 2 tool. We used a protocol to guide our review conduct, which was registered with the PROSPERO registry. We conducted a comprehensive literature search, which was not restricted by publication date, language of publication, or publication status (i.e., grey literature was eligible for inclusion). We included 15 outcomes that were of greatest interest, according to the clinical content experts and stakeholders consulted. We calibrated all screening, charting, data abstraction, and risk of bias appraisal forms. Two independent team members screened both title and abstract and full-text articles, whereas one team member conducted data abstraction and risk of bias appraisal, which was verified by another team member. We also closely reviewed the 64 included SRs for overlap between the 801 primary studies included in the systematic reviews and found overlap across most of the reviews, as highlighted in our Results section.

6.3.2 Limitations

There are some limitations of the included SRs worth noting. More than 50% of the 64 included SRs were appraised as being low quality. This suggests that substantial improvements are required in the knowledge syntheses that are being produced within the insomnia field and that current results should be interpreted with caution. Areas where the SRs process could improve include the use of a protocol, providing a rationale for study design inclusion, providing a list of excluded studies with reasons for exclusion, and transparently reporting the source of funding of the studies included in the SR.

There are also some limitations to the process we followed for our review of reviews. We were unable to conduct targeted literature searches for primary research on safety outcomes due to time and resource constraints. Although we originally intended to include sleep hygiene/patient education interventions, we decided to exclude these if they were delivered as a stand-alone treatment after consultation with our clinical experts. As well, although we attempted to identify unpublished reviews and reviews written in languages other than English, we were only able to include one unpublished review and two reviews written in languages other than English. This suggests that our results are likely only generalizable to published SRs written in English. As well, only one team member conducted the data charting exercise, which allowed us to tailor the selection of outcomes according to clinician input. Furthermore, one person abstracted and appraised risk of bias, while another verified these responses; this was conducted to increase the feasibility of this project, yet may have led to inaccuracies in the data. In addition, our definitions of non-drug interventions and inactive controls were quite inclusive and as such, some interventions (such as sleep restriction) might not have been found to be effective because they were being compared with active interventions, such as sleep hygiene and education. This is contrary to pharmacological interventions, which, in most cases, were compared with a placebo. As such, the results of some non-pharmacological interventions should be interpreted with caution, as their effectiveness might be higher than that observed here. Furthermore, variation across the interventions was apparent regarding the dose, duration, intensity, and frequency, which may have influenced the results reported here. Also, due to time and staff constraints we were unable to refine the list of outcome measures to include only standardized or validated measures, further adding to the variability of the results. Finally, we were unable to provide interpretations of the clinical or symptomatic significance of the results of the included reviews due to a lack of standards to interpret them (i.e., minimal clinically important difference) and that the impact of symptomatic changes in insomnia disorder are currently poorly understood.

7. Conclusions

Short-duration treatment (less than and equal to 16 weeks on average) with zolpidem, triazolam, suvorexant, doxepin, and melatonin appear to improve sleep outcomes in adult patients with insomnia disorder. Clinical expert input indicated that use of these drugs is frequently for longer durations than the evidence supports. The comparative and long-term effectiveness of these and other pharmacological interventions for insomnia disorder is poorly understood and associated with a high degree of uncertainty. This fact needs to be balanced with the lack of robust safety evidence — especially for serious harms including mortality — for these interventions.

These results may be used to update clinical practice guidelines on insomnia. As well, funding agencies may use these results to fund high-quality research in the areas where data gaps were identified (e.g., comparative effects of interventions on HRQoL, long-term effectiveness and safety). In particular, more primary studies and reviews are required to examine the harms associated with pharmacological treatment of insomnia. Future SRs should include important effectiveness outcomes, such as SS, fatigue severity, and HRQoL. As well, SRs on the effectiveness of interventions for patients in certain age groups (e.g., 65 years and older), those in long-term care facilities, or individuals in correctional facilities will help decision-makers tailor policy specifically for these settings.

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Appendix 1: Literature Search Strategy

OVERVIEW

Interface:	Ovid
Databases:	Ovid MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily Embase Classic+Embase PsycINFO **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 14, 2017
Alerts:	None
Study Types:	Systematic reviews; meta-analyses; network meta-analyses; technology assessments.
Limits:	None

SYNTAX GUIDE

/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.jw	Journal word
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.tw	Text word
emczd	Embase Classic+Embase database code
ppez	Ovid MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily database code

MULTI-DATABASE STRATEGY

1. exp "Sleep Initiation and Maintenance Disorders"/
2. (insomni* or hyposomni*).tw,kw.
3. (sleep* adj3 initiat* adj3 (disorder* or dysfunction* or problem*)).tw,kw.
4. (sleep* adj3 (mainten* or maintain*) adj3 (disorder* or dysfunction* or problem*)).tw,kw.
5. ((difficult* or disturb* or inabilit* or unable* or problem* or reduced) adj3 (asleep or sleep*)).tw,kw.
6. sleepless*.tw,kw.
7. (early adj1 (awake* or wake or wakes or waking)).tw,kw.
8. or/1-7 [INSOMNIA]
9. exp Child/ not (exp Adult/ and exp Child/)
10. exp Infant/ not (exp Adult/ and exp Infant/)
11. 8 not (9 or 10) [CHILD-ONLY REMOVED]

MULTI-DATABASE STRATEGY

12. exp Animals/ not (exp Animals/ and Humans/)
13. 11 not 12 [ANIMAL-ONLY REMOVED]
14. (comment or editorial or interview or news).pt.
15. (letter not (letter and randomized controlled trial)).pt.
16. 13 not (14 or 15) [OPINION PIECES REMOVED]
17. limit 16 to systematic reviews
18. meta analysis.pt.
19. exp meta-analysis as topic/
20. (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative review* or research integration or research review* or collaborative review*).tw,kw.
21. (systematic review* or systematic review* or evidence-based review* or evidence-based review* or (evidence adj3 (review* or review*)) or meta-review* or meta-review* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw,kw.
22. exp Technology assessment, biomedical/
23. (cochrane or health technology assessment or evidence report).jw.
24. (network adj (MA or MAs)).tw,kw.
25. (NMA or NMAs).tw,kw.
26. indirect comparison?.tw,kw.
27. (indirect treatment* adj1 comparison?).tw,kw.
28. (mixed treatment* adj1 comparison?).tw,kw.
29. (multiple treatment* adj1 comparison?).tw,kw.
30. (multi-treatment* adj1 comparison?).tw,kw.
31. simultaneous comparison?.tw,kw.
32. mixed comparison?.tw,kw.
33. or/18-32
34. 16 and 33
35. 17 or 34 [SYSTEMATIC REVIEWS]
36. 35 use ppez [MEDLINE RECORDS]
37. exp insomnia/
38. (insomni* or hyposomni*).tw,kw.
39. (sleep* adj3 initiat* adj3 (disorder* or dysfunction* or problem*)).tw,kw.
40. (sleep* adj3 (mainten* or maintain*) adj3 (disorder* or dysfunction* or problem*)).tw,kw.
41. ((difficult* or disturb* or inabilit* or unable* or problem* or reduced) adj3 (asleep or sleep*)).tw,kw.
42. sleepless*.tw,kw.
43. (early adj1 (awake* or wake or wakes or waking)).tw,kw.
44. or/37-43 [INSOMNIA]
45. exp juvenile/ not (exp juvenile/ and exp adult/)
46. exp Child/ not (exp Adult/ and exp Child/)
47. exp Infant/ not (exp Adult/ and exp Infant/)
48. or/45-47
49. 44 not 48 [CHILD-ONLY REMOVED]
50. exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
51. exp human/ or exp human experimentation/ or exp human experiment/
52. 50 not 51
53. 49 not 52 [ANIMAL-ONLY REMOVED]
54. editorial.pt.
55. letter.pt. not (letter.pt. and randomized controlled trial/)

MULTI-DATABASE STRATEGY

56. 53 not (54 or 55) [OPINION PIECES REMOVED]
57. meta-analysis/
58. "systematic review"/
59. "meta analysis (topic)"/
60. (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative review* or research integration or research review* or collaborative review*).tw,kw.
61. (systematic review* or systematic review* or evidence-based review* or evidence-based review* or (evidence adj3 (review* or review*)) or meta-review* or meta-review* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw,kw.
62. biomedical technology assessment/
63. (cochrane or health technology assessment or evidence report).jw.
64. (network adj (MA or MAs)).tw,kw.
65. (NMA or NMAs).tw,kw.
66. indirect comparison?.tw,kw.
67. (indirect treatment* adj1 comparison?).tw,kw.
68. (mixed treatment* adj1 comparison?).tw,kw.
69. (multiple treatment* adj1 comparison?).tw,kw.
70. (multi-treatment* adj1 comparison?).tw,kw.
71. simultaneous comparison?.tw,kw.
72. mixed comparison?.tw,kw.
73. or/57-72
74. 56 and 73 [SYSTEMATIC REVIEWS]
75. 74 use emczd [EMBASE RECORDS]
76. Insomnia/
77. (insomni* or hyposomni*).tw,kw.
78. (sleep* adj3 initiat* adj3 (disorder* or dysfunction* or problem*)).tw,kw.
79. (sleep* adj3 (mainten* or maintain*) adj3 (disorder* or dysfunction* or problem*)).tw,kw.
80. ((difficult* or disturb* or inabilit* or unable* or problem* or reduced) adj3 (asleep or sleep*)).tw,kw.
81. sleepless*.tw,kw.
82. (early adj1 (awake* or wake or wakes or waking)).tw,kw.
83. or/76-82 [INSOMNIA]
84. Meta Analysis/
85. (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative review* or research integration or research review* or collaborative review*).tw,kw.
86. (systematic review* or systematic review* or evidence-based review* or evidence-based review* or (evidence adj3 (review* or review*)) or meta-review* or meta-review* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw,kw.
87. (network adj (MA or MAs)).tw,kw.
88. (NMA or NMAs).tw,kw.
89. indirect comparison?.tw,kw.
90. (indirect treatment* adj1 comparison?).tw,kw.
91. (mixed treatment* adj1 comparison?).tw,kw.
92. (multiple treatment* adj1 comparison?).tw,kw.
93. (multi-treatment* adj1 comparison?).tw,kw.
94. simultaneous comparison?.tw,kw.
95. mixed comparison?.tw,kw.
96. or/84-95

MULTI-DATABASE STRATEGY
97. 83 and 96 [SYSTEMATIC REVIEWS]
98. 97 use ppez
99. 97 use emczd
100. 97 not (98 or 99) [PSYCINFO RECORDS]
101. 36 or 75 or 100 [ALL DATABASES]

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane Library	Same MeSH and keywords used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Cochrane Library databases.	

Grey Literature

Dates for Search:	June 14-18, 2017
Keywords:	Insomnia, sleep, sleeping, sleepless, sleeplessness, asleep
Limits:	No restrictions

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Joanna Briggs Institute EBP Database
- Databases (free)
- Internet Search.

Appendix 2: List of Ineligible Complementary and Alternative Medicine Therapies

Name	Definition
Acupressure	Applying pressure to certain meridian points, similar to acupuncture, but without the use of needles.
Acupuncture	The Chinese art of stimulating the pathways of energy (14 main meridians plus branches) by puncturing, pressing, heating, using electrical current, or using herbal medicines.
Alexander Technique	Originally a technique used for respiratory re-education, now a comprehensive technique of psychophysical re-education to improve physical functioning.
Anthroposophy	A health care system defined by Rudolf Steiner. The study of the wisdom of the human being, inner development, and careful observation to more accurately reflect the patient as a whole and unique human being.
Apitherapy (Bee Venom)	The use of bee products from the European honey-bee to promote health and healing.
Applied Biomechanics	The use of biomechanical principals of human motion and structure of the human body as well as the laws of mechanics to prevent and treat injuries. Most commonly used in sports medicines.
Applied Kinesiology	A form of patient biofeedback. A muscle is tested to discover allergies, weaknesses in the body. Any muscle in the body may be used to test when the patient is exposed to a substance or a thought.
Aromatherapy	The skilled and controlled use of essential oils, volatile liquids distilled from plants, shrubs, trees, flowers, roots, and seeds. They contain oxygenating molecules that transport the nutrients to cells of the body.
Art Therapy	Increase awareness of self; cope with symptoms, stress, and traumatic experiences; and enhance cognitive abilities through the practice of creating art. Includes talking about it with a trained art therapist.
Autogenic Therapy	The practice of “passive concentration,” a state of alert but detached awareness which allows the trainee to break through whatever excess stress is present. Western form of meditation.
Aversion Therapy	Exposure to unpleasant stimuli while engaged in the targeted behaviour. Usually associated with alcoholism and smoking.
Ayurvedic Medicine	A traditional health care system practised in India. The “Science of Life.” People are categorized into three basic constitutional types, Pitta, Kapha, Vata, with many different subdivisions. Treatment of the same illness will be different based on the type determined by the physician.
Bach Flower Remedies	Restoration of balance to disrupted states of mind, addresses the underlying emotional causes of disease using flowering plants.
Balneotherapy	Practice of healing using bath preparations. Essential oils in a preparation that will dilute in water.
Biofeedback	A treatment technique in which people train their bodies to respond to specific signals in their body. Used often to lower blood pressure and to slow heart rates.
Body Electronics	Preparing a client nutritionally and then using a specialized form of sustained acupressure.
Bowen Therapy	Gentle moves on the skin or through light clothing designed to result in overall relaxation, allowing the body to recharge, and cleanse itself.
Breathwork	Holotropic Experiential method combining deep relaxation, expanded breathing, music, art, and focused energy work. Transformational Directed breathing exercises to massage internal organs and tone diaphragm and abdominal muscles. The high volume of oxygen absorbed by the lungs cleanses and revitalizes the organ systems.
Cell Therapy (not done in US)	Injection of healthy cellular material into the body to assist the body in its natural ability to heal.
Cheirology (Palmistry)	The art of hand analysis. A combination of the ancient Chinese Buddhist hand analysis and the best of traditional Western palmistry. A dialogue and touch therapy.
Chelation Therapy	A slow drip IV injection of a synthetic amino acid used for the purpose of removing plaque and calcium deposits from arteries.

Name	Definition
Chiropractic	Based on a procedure that evaluates causative factors in the biomechanical and structural derangements of the spine that may affect the nervous system and organs.
Chromatotherapy	See Colour Therapy.
Luminous	The use of colours of the light spectrum to treat illness at three levels, at the ailment, at the eye level, and at the acupuncture point level.
Molecular	Using the same wavelength as luminous, but derived from matter. Used on the skin or orally.
Coaching	The art of working with individuals to eliminate barriers in reaching their personal and professional goals, includes dialogue and “homework assignments.”
Colon Hydrotherapy	The cleansing of the entire large intestine with a gentle enema-type system using filtered water and gentle abdominal massage.
Colour Therapy	Known also as chromatotherapy, based on the concept that colours vibrate at different frequencies and can stimulate different responses in a person and the use of specific colours in a person's environment may promote balance and healing.
Contact Reflex Analysis (CRA)	A natural system for analyzing the body's structural, physical, and nutritional needs. Most commonly used by chiropractors.
Craniosacral Therapy	This therapy focuses on the eight bones of the cranial vault in conjunction with the spine and sacrum, and the cerebrospinal fluid. Light touch creates relaxation and a sense of energy moving within your body.
Crystal Therapy (Gemstone Therapy)	The practice of using crystals of different minerals to treat various disharmonies in the body.
Cupping (Moxibustion)	The placement of burning mugwort, a plant containing complex volatile oils such as camphor, at acupuncture points to stimulate qi and healing.
Detoxification Therapy	The various processes used to rid the body of toxins absorbed from the atmosphere, food, soil, and water.
Didgeridoo	A form of sound therapy, this aboriginal wind instrument has been used for healing for 40,000 years. Circular breathing supported by the sound frequency reaches deep into the subconscious.
Dream Therapy	The interpretation of dreams to assist in addressing problems and support resolution.
Ear Candling	Ear candles or cones of unbleached cotton or linen strips dipped in paraffin, beeswax, or herbs are burned, sending smoke and warmth inside the ear creating a vacuum effect to loosen buildup of wax and other debris.
Electrotherapy (TENS)	Transcutaneous electrical nerve stimulation (TENS). A form of medical treatment that uses electricity as a cure or relief. For example, as a way of stimulating nerves and connected muscles.
Emotional Freedom Technique (Tapping)	Also called Thought Field Therapy. A brief, effective psychotherapy for the rapid resolution of negative emotions; tapping with the fingertips on the acupuncture meridian points while repeating some specific phrases.
Energy Field Medicine	Seven major chakras (vortices of energy within the human body) serve as a network of mind-body-spiritual energies.
Enzyme Therapy	Diet supplemented with plant-derived enzymes and pancreatic enzymes either independent of each other or in combinations determined by the prescriber.
Essences Therapy	Similar to Bach flower remedies. Water-based infusion activated by natural sunlight, stabilized usually with brandy.
Eye Movement Desensitization and Reprocessing (EMDR)	The treatment of patients using guided eye movement while mentally focused on whatever mental image, negative thought, or body sensation the client wishes to address.
Fasting (Cleansing)	The complete abstinence from all substances except purified water in an environment of total rest. Benefits include the promotion of detoxification and it gives the digestive system a rest.
Feldenkrais Method	A blend of science and aesthetics, uses two approaches to healing. “Awareness Through Movement,” directing students to move in specific ways related to early basic movements, and “Functional Integration,” movement custom tailored to the unique needs of each student.
Gerson Therapy	Combination of vigorous detoxification with nutrition aimed at restoring the body's natural immunity and healing power.

Name	Definition
Gestalt Therapy	Challenging a client with questions that increase awareness of feelings and so develop a stronger ability to face day-to-day situations and problems.
Guided Imagery	The use of relaxation and mental visualization to improve mood and or physical well-being.
Healing Touch	An energy-based therapeutic approach to healing. Using hands-on and energy-based techniques to balance and align the human energy field.
Hellerwork	Similar to Rolfing. Stress-reducing body realignment, which adds verbal dialogue and emotional release to connective tissue bodywork and body movement education.
Herbal Medicine	The use of any plants, seeds, berries, roots, leaves, bark, or flowers for medicinal purposes.
Homeopathy	A philosophy of treatment “That which is similar ends suffering.” Toxic remedies from raw materials and plants are administered in a highly diluted form to stimulate the body's own healing mechanisms.
Humour Therapy	Using laughter to release endorphins, increasing the body's ability to heal itself.
Huna	The exploration of body, mind, and spirit through shamanism and ancient Hawaiian healing. Increasing the individual’s spirituality and healing powers.
Hydrogen Peroxide Therapy	Based on the theory that, when injected into the veins, hydrogen peroxide is converted to water and singlet oxygen, an oxidizing agent that inhibits growth of bacteria and viruses and enhances enzymatic metabolism.
Hydrotherapy	The placement of alternating hot and cold water on the skin in order to redirect the flow of blood.
Hyperbaric Oxygen Therapy	The delivery of pure oxygen at two to three times that of sea level. Among its uses is the treatment of leg ulcers that do not respond to other therapies.
Hyperthermia	Heat treatment to selectively destroy cancer cells using heating rods, microwaves, ultrasound, thermal blankets, lasers, or pyrogens to induce fever.
Hypnotherapy	Intense focused concentration with partial or complete exclusion of awareness of peripheral phenomenon. Among its clinical uses are the treatment of pain, habit disorders, nausea, relaxation, and anxiety.
Iridology	The iris of the eye reveals abnormal conditions of the tissues, organs, and glands of the body. Diagnosis of disease is not made, but conditions of various parts of the body are revealed.
Jaffe-Mellor Technique (JMT)	A bioenergetic technique utilizing kinesiology and acupressure to relieve pain and symptoms associated with osteoarthritis, rheumatoid arthritis, and other complex health disorders.
Jin Shin Jyutsu	A gentle oriental art practised by placing fingertips (over clothing) on 26 designated “safety energy locks” to harmonize and restore balance.
Juice Therapy	The use of raw vegetables and fruits turned into juice to make it easier to assimilate. Taken on an empty stomach, it is absorbed within 15 minutes.
Kegel Exercises	A form of biofeedback exercise. Pelvic floor exercises focus on women's abdominal organs and muscles.
Kirlian Photography	Photography of the body's auras and energy flow.
Light Therapy	Use of light, from natural sun exposure to high-tech sophisticated forms of light-assisted psychotherapy, to treat physical and psychological disorders.
Macrobiotics	Changing or managing your diet for spiritual and healthful ends. Diet excludes meats and emphasizes whole grains.
Magnet Therapy	Use of natural and man-made magnets to enhance energy fields around and within the body to enhance healing.
Manual Lymphatic Drainage (MLD)	A highly systematic method of stimulating lymph flow through the entire body using a range of specialized and gentle rhythmic pumping techniques. This stimulates the lymphatic vessels that carry substances vital to the defence of the body and removes waste products.
Marma Therapy	A form of healing massage focusing on 108 points on the body where vein, artery, tendon, bone, and flesh meet.
Massage Therapy	A general term for a wide range of therapeutic techniques involving the manipulation of muscles and soft tissues, including kneading, rubbing, tapping, and friction; vigorous or relaxing; deep or superficial.

Name	Definition
Medical Intuitive	The utilization of a focused, intuitive instinct to “diagnose” or “read” energetic and frequency information in and around the human body.
Mind-Body Medicine	A philosophy and a system of health practices that is based on the concept that the mind and the body work together for healing.
Music Therapy	The prescribed use of music by a qualified person to effect positive changes in the psychological, physical, cognitive, or social functioning of individuals with health or educational problems.
NAET (Nambudripad's Allergy Elimination Therapy)	A combination of disciplines including kinesiology and acupressure designed to identify and eliminate allergies. The treatment stimulates acupuncture points along the spine while patient holds an allergen.
Naprapathy	Manipulation, mobilization, and soft tissue methods similar in some ways to chiropractic, but specializing in health problems that originate in the muscles, tendons, and ligaments.
Nasal Irrigation	Saline solution (noniodized salt, baking soda, and water) inhaled through the nostrils to clear mucus and reduce cough caused by post nasal drip.
Naturopathic Medicine	A system of primary health care which uses a holistic natural approach to health and healing, emphasizing the treatment of disease through stimulation, enhancement, and support of the inherent healing capacity of the person.
Naturopathy	The basic philosophy of naturopathic medicine, practised by both licensed naturopathic doctors and other complementary and alternative medicine (CAM) practitioners.
Neuro-Linguistic Programming (NLP)	The study of the structure of subjective experience and what can be calculated from that, predicated upon the belief that all behaviour has structure.
Neuromuscular Therapy (Trigger Point Myotherapy)	Consists of alternating levels of concentrated pressure on the areas of muscle spasm using fingers, knuckles, or elbows.
Nutritional Therapy	Use of food and supplements to encourage the body's own natural healing.
Orthomolecular Medicine	The prescription of large doses of vitamins and minerals, based on the philosophy that each individual is biochemically unique and therefore nutritional deficiencies affect certain people more than others.
Ozone-Oxygen Therapy (Bio-oxidative Therapy)	Small amounts of hydrogen peroxide and ozone are administered into the body as medicine.
Panchakarma Therapy	Ayruvedic herbal remedies designed to balance and cleanse, restore harmony.
Past Life Therapy	Treatment and release of phobias and emotional blockages through a regression process that explores past life traumas.
Pet Therapy	Animals of all sizes and breeds respond well to CAM therapies that stimulate their own natural powers; sometimes they are more responsive than human beings.
Pilates	Systematic practice of specific exercises coupled with focused breathing patterns.
Polarity	A system based on the belief that the flow and balance of energy in the body is the underlying foundation of health. The body's own electrical flow to muscles and organs is opened through a process of bodywork, diet, exercise, and self-awareness.
Pranic Healing	Comprehensive system of subtle energy healing that utilizes “prana” in balancing, harmonizing, and transforming the body's energy process.
Prayer	Some cultures and religions believe that prayer is the most powerful medicine.
Prolotherapy	Non-surgical ligament reconstruction, treatment for chronic pain. Dextrose solution is injected into ligament or tendon where it attaches to the bone; inflammation increases blood supply and stimulates body's natural healing ability.
QiGong	Literally means “energy cultivation;” refers to exercises aimed at bringing about harmony, as well as improving health and longevity. Healing methods involve breathing, movement, the mind, and the eyes.
Radiance Technique (TRT)	Seven-degree transcendental energy system similar to Reiki.
Rapid Eye Technology	A transformational technology that facilitates healing on all levels. The client follows a lighted wand with their eyes, while the therapist gives verbal clues designed to release physical, emotional, or mental stress.

Name	Definition
Reflexology	Non-invasive acupressure of the hands and feet. Points on the feet and hands correspond to various zones and organs throughout the body. Precise pressure on these reflex points stimulates energy and releases blockages to the specific area of pain or illness.
Reiki	An ancient Tibetan tradition. Hand symbols and breathing draw in and manipulate energy forces to effect a balance. Power source energy travels through the Reiki practitioner into the client's body.
Rolfing (Somatic Ontology, Structural Integration)	The Rolfer slowly stretches and repositions the body's supportive wrappings, called fascia, with firm and gently directed pressure, to restore normal length and elasticity to the network of deep connective fibres.
Rosen Method	Mind, bodywork, and movement; combines emotional psychotherapy with physical awareness.
Rubenfeld Synergy	A holistic therapy that integrates body, mind, spirit, and emotions using gentle touch, along with verbal dialogue, active listening, Gestalt Process, imagery, metaphor, movement, and humour.
Shamanism	Traditional native healing systems practised throughout the world. Archaic magico-religious phenomenon in which the shaman may use fire, wind, or magical flight as part of a healing ceremony.
Shiatsu	A type of bodywork from Japan that uses acupuncture energy meridians to activate and balance the body's energy (chi).
Spiritual Healing	A healing philosophy incorporating the concept of spiritual energy as a healing force; using prayer, meditation, individual, or group spiritual resources and other methods of focusing thought energy.
Stress Management	Based on the belief that stress creates a “dis-ease” climate within the body, by reducing stress, the body's own natural healing resources are enhanced, such as the immune system.
Tai Chi	Balanced gentle movements, incorporating a combination of meditation and breathing, are designed to dissolve physical and karmic layers of tension in both the physical body and the energy body, and to open up the spiritual space inside.
Tao	A philosophy often related to CAM practices. The definition of Tao is “the way,” “the law;” the rule of Tao is living in total harmony with the natural world.
Therapeutic Touch	Hands do not touch the body, but perform smoothing and soothing movements above it, “massaging” the human energy field surrounding the body; involving mind, body, emotion, and spirit.
Traditional Chinese Medicine (Oriental Medicine)	The ancient (and modern) theory of medicine with unique diagnostic methods and systematic approach includes medication, pharmacology, herbology, acupuncture, massage, and QiGong.
Transsage	The use of therapeutic massage, deep relaxation (hypnosis), guided imagery, metaphors, and affirmations with the goal of increasing mental focus.
Trager Method	Based on the theory that patterns of stiffness and aging exist more in the unconscious mind than in the tissues, this method re-educates the body/mind to release old holding patterns that limit us physically and mentally. Rhythmic movement and soothing rocking are used.
Transpersonal Psychology	The extension of psychological studies into consciousness studies, spiritual inquiry, body-mind relationships, and transformations.
Trepanation	A small hole is drilled in the skull (solely in the bone, not entering the brain), to allow an expansion window in the brain to permanently regain its youth.
Tuina Massage	A 2000-year-old Chinese massage technique, like acupuncture without needles. Tuina works with the Qi (chi) energy of patients.
Unani Medicine	Traditional herbal healing system of ancient Persia and modern India, Australia, and other countries.
Urine Therapy	Using (one’s own) urine externally and internally to provide nutrients, purify blood and tissue, and signal what is out of balance.
Visualization	Similar to Guided Imagery. Creative visualization is the art of sending an image to the subconscious mind, where the subconscious mind will begin to create what it “sees.”
Visceral Manipulation	Based on the specific placement of soft manual force to encourage normal mobility, tone, and inherent tissue motion of the viscera and connective tissues.
Vitamin Therapy	Use of vitamins, minerals, enzymes, amino acids, fatty acids, and other nutritional support.
Watsu	A creative blend of meridian stretches, Indian chakra work, acupressure, Zen Shiatsu, and yoga movements performed in warm water.

Name	Definition
Wave Work	A psycho-spiritual process for integration, based on deeper teachings of Yoga. Using breath and awareness of sensation to allow an organic shift in consciousness.
Yoga	A general term for a wide range of body-mind exercise practices, traditionally referred to as the art of “yoking” or hooking up the lower consciousness with the higher consciousness. Combines breathing, movement, meditation, and a sequence of sound to align, purify, and promote a healthy flexible body.
Zero Balancing	Hands-on body-mind system to align body energy with the body's physical structure.

Appendix 3: List of Excluded Studies

Companion Reports of Included Studies

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Erratum

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Overlaps Completely with Included Systematic Review – No New Evidence

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Appendix 4: Data Abstraction Items

Table 73: Data Abstraction Items for Systematic Reviews With Meta-Analysis

Review and Participant Characteristics	
Item	**Description**
Review Characteristics	
Title	Copy-paste the full title of the article (will be filled in for you on this tab)
Author	The Last Name of the first author (will be filled in for you on this tab)
Year	The year of the publication (will be filled in for you on this tab)
Country	The country where the review was conducted. If not reported enter the country of the corresponding author (will be filled in for you on this tab)
Review type	The review type will be filled in for you, please verify and change if you feel it is incorrect
# of Included studies	Enter the total number of studies included in the review, as reported if possible; if not clearly reported please enter 'NR.'
# of RCTs	Enter the total number of **Randomized controlled trials (RCTs)** included in the review, as reported if possible; if not clearly reported please enter 'NR.'
# of NRCTs	Enter the total number of **Non-Randomized controlled trials (NRCTs)** included in the review, as reported if possible; if not clearly reported please enter 'NR.'
# of Quasi-experimental	Enter the total number of **Quasi-experimental studies** (e.g., controlled before and after, interrupted time series) included in the review, as reported if possible; if not clearly reported please enter 'NR.'
# of Observational	Enter the total number of **Observational studies** (e.g., cohort study, case-control study) included in the review, as reported if possible; if not clearly reported please enter 'NR.'
Overall Sample Size	Enter the total number of participants in the review, as reported; if not clearly reported please enter 'NR'
Overall Age (mean; SD)	Enter the mean age and standard deviation of the participants in the review, as reported; if not clearly reported please enter 'NR,' DO NOT calculate yourself
% female overall	Enter the proportion of participants in the review that are female, as reported; if not clearly reported please enter 'NR,' DO NOT calculate yourself* ***EXCEPTION:** If the proportion of male participants is reported please calculate the % female by subtracting the % male from 100 and enter the result in this column
Participant Characteristics	
Intervention Sample Size	Enter the total number of participants receiving an intervention in the review, as reported or if it can be easily calculated (e.g., from a study characteristics table) If not clearly reported please enter 'NR'
Intervention Age (mean; SD)	Enter the mean age and standard deviation of the participants receiving an intervention, as reported; if not clearly reported please enter 'NR,' DO NOT calculate yourself
% female Intervention	Enter the proportion of participants receiving the intervention that are female, as reported; if not clearly reported please enter 'NR,' DO NOT calculate yourself
Control Sample Size	Enter the total number of participants in the control group in the review, as reported or if it can be easily calculated (e.g., from a study characteristics table) If not clearly reported please enter 'NR'
Control Age (mean; SD)	Enter the mean age and standard deviation of the participants in a control group, as reported; if not clearly reported please enter 'NR,' DO NOT calculate yourself
% female Control	Enter the proportion of participants in a control group that are female, as reported; if not clearly reported please enter 'NR,' DO NOT calculate yourself

Diagnostic Criteria for Insomnia/Sleep disorder	Copy and paste (from the methods section) the eligibility criteria or diagnostic criteria used to define the insomnia population in the review
Includes comorbidities	Identify whether the review includes only insomnia patients or patients with insomnia and a comorbidity
Comorbidities	List any comorbidities present in the patient population
Exclusion criteria	Copy and paste (from the methods section) any exclusion criteria related to the populations or interventions included in the review
COMMENTS	Please record here any observations or issues you would like to bring to the attention of the RCs

Treatment Comparison	
Treatment Comparison Characteristics	
Item	**Description**
Comparison Type	Select from the following comparisons: ☐pharma vs. control ☐pharma vs. pharma ☐pharma vs. non-pharma ☐pharma vs. combo ☐non-pharma vs. control ☐non-pharma vs. pharma ☐non-pharma vs. non-pharma ☐non-pharma vs. combo ☐combo vs. control ☐combo vs. pharma ☐combo vs. non-pharma ☐combo vs. combo **NOTES:** • pharma = pharmacological; non-pharma = non-pharmacological, combo = combination • Depending on the type of comparison you select, certain cells in the row will be highlighted grey. You DO NOT need to enter anything in the grey cells as they are irrelevant to that particular comparison
Control(s)	**NOTE:** If you selected a comparison type with an active comparator (e.g., pharma v pharma), this cell will be greyed out, DO NOT enter anything here Enter any relevant *inactive control groups* in this column • Inactive controls include: Placebo, wait-list, symptom- or self- monitoring, delayed treatment, usual care (includes sleep education, sleep hygiene, or stimulus control) If there is more than one kind of control combined in the comparison enter each one in the 'Control(s)' column followed by the number of studies using that control in brackets and separated by a semicolon • **EXAMPLE:** placebo (3); wait-list (2); sleep hygiene (5)
Intervention Category 1 or 2	
Category	Please select from the following: ☐ Antidepressants ☐ Antihistamine ☐ Antipyschotics ☐ Benzodiazepines ☐ Melatonin ☐ Non-benzodiazepines ☐ Suvorexant ☐ Behavioural Therapy (BT) ☐ BT + single component ☐ CBT (cognitive behavioural therapy)

	☐ CBT + single component ☐ Combination ☐ Medication withdrawal ☐ Meditation techniques ☐ Mindfulness techniques ☐ Multi-component behavioural intervention ☐ Multi-component Behavioural Therapy ☐ Multi-component CBT ☐ Single behavioural intervention ☐ Sleep-disordered breathing treatment
Pharmacologic Intervention 1 or 2	
Name	Please select from the dropdown menu
Dose	Enter dose information as reported • if multiple dosages of a medication lumped together please enter each dose separated by a semicolon (e.g., 5mg; 10mg) • if multiple doses of a medication are being examined in different meta-analyses please abstract each on a separate row
Delivery method/Formulation	Enter any information on the formulation of the intervention (e.g., fast release, long duration, etc.) or delivery method (e.g., pill, patch, sublingual) as reported
Frequency	Enter any information on the frequency of the intervention (e.g., daily, twice daily, etc.) as reported
Setting	Select from the following: ☐ in-patient (e.g., hospital based) ☐ outpatient (e.g., clinic, therapist's office) ☐ home ☐ community (e.g., community centre, halfway house) ☐ long-term care (e.g., nursing home) ☐ institution (e.g., prison, adult care facility) ☐ NR (e.g., not reported)
Shortest Follow-up (weeks)	Enter the shortest follow-up duration, in weeks*, in the studies included in the review *if it is reported in a unit other than weeks use Google to convert: type '[X] months in weeks' in the Google search bar and enter the result in the form
Longest follow-up (weeks)	Enter the longest follow-up duration, in weeks*, in the studies included in the review *if it is reported in a unit other than weeks use Google to convert: type '[X] months in weeks' in the Google search bar and enter the result in the form
Non-Pharmacologic Intervention 1 or 2	
Components	Enter the specific components of the intervention, as reported. If individual components of a multi-component intervention are not clearly reported please enter 'unspecified'
Delivery Method	Enter any information on how the intervention was delivered (e.g., group therapy, self-help, individual, etc.), as reported
Frequency	Enter any information on the frequency of the intervention (e.g., weekly, monthly, etc.) as reported
Setting	Select from the following: ☐ in-patient (e.g., hospital based) ☐ outpatient (e.g., clinic, therapist's office) ☐ home ☐ community (e.g., community centre, halfway house) ☐ long-term care (e.g., nursing home) ☐ institution (e.g., prison, adult care facility) ☐ NR (e.g., not reported)
Shortest Follow-up (weeks)	Enter the shortest follow-up duration, in weeks*, in the studies included in the review *if it is reported in a unit other than weeks use Google to convert: type '[X] months in weeks' in the Google search bar and enter the result in the form

Longest follow-up (weeks)	Enter the longest follow-up duration, in weeks*, in the studies included in the review *if it is reported in a unit other than weeks use Google to convert: type '[X] months in weeks' in the Google search bar and enter the result in the form

Results	
If the data are analyzed with multiple time points and you are unsure which to abstract please use the following decision rule: • If available, always abstract the '*overall*' results (e.g., combines all time points/all relevant studies) • If 'overall' results are not available abstract the results based on the *longest duration of follow-up* • If 'longest duration' results are not available, abstract the *post-treatment results*	
Treatment Comparison	
Item	**Description**
Comparison Type	Will be automatically filled in from previous items
Pharma Intervention 1	Will be automatically filled in from previous items
Non-pharma Intervention 1	Will be automatically filled in from previous items
Pharma Intervention 2	Will be automatically filled in from previous items
Non-pharma Intervention 2	Will be automatically filled in from previous items
Meta-analysis results (repeated for up to 10 outcomes, add more as needed)	
Outcome	Select from the dropdown menu: ☐ Insomnia Severity Index ☐ Sleep Efficiency ☐ Sleep Latency (e.g., sleep onset latency, latency to sleep onset) ☐ Sleep Quality ☐ Sleep Satisfaction ☐ Total Sleep Time ☐ Wake after sleep onset ☐ Quality of Life ☐ Fatigue Severity ☐ Accidental Injury ☐ Addiction, Dependence, Diversion ☐ Additional Health care Utilization ☐ Delirium ☐ Hangover/Morning Sedation ☐ Sleep-Disordered Breathing ☐ Mortality
Questionnaire/scale/method	Enter the questionnaire, scale, or method (e.g., sleep diary, polysomnography) used to collect outcome data, as reported
# of Studies	Number of studies included in the meta-analysis for this intervention and outcome
# participants in intervention	Number of participants receiving the intervention for this outcome
# participants in comparator	Number of participants in the comparator group for this outcome
Effect measure value	Enter the value for the meta-analysis result
Effect measure	Enter the type of effect measure (e.g., odds ratio, relative risk, mean difference) for the meta-analysis result
Variance value	Enter the value of the variance for the meta-analysis result
Variance type	Enter the variance type (e.g., standard deviation, standard error, range) for the meta-analysis result
Heterogeneity value	Enter the value of the heterogeneity for the meta-analysis of this outcome
Heterogeneity type	Enter the type of heterogeneity estimation (e.g., I-squared, Chi-squared) for the meta-analysis of this outcome

Table 74: Data Abstraction Items for Systematic Reviews Without Meta-Analysis

Review and Participant Characteristics	
Item	**Description**
Review Characteristics	
Title	Copy-paste the full title of the article (will be filled in for you on this tab)
Author	The Last Name of the first author (will be filled in for you on this tab)
Year	The year of the publication (will be filled in for you on this tab)
Country	The country where the review was conducted. If not reported enter the country of the corresponding author (will be filled in for you on this tab)
Review type	The review type will be filled in for you, please verify and change if you feel it is incorrect
# of Included Studies	Enter the total number of studies included in the review, as reported if possible; if not clearly reported please enter 'NR.'
# of RCTs	Enter the total number of **Randomized controlled trials (RCTs)** included in the review, as reported if possible; if not clearly reported please enter 'NR.'
# of NRCTs	Enter the total number of **Non-Randomized controlled trials (NRCTs)** included in the review, as reported if possible; if not clearly reported please enter 'NR.'
# of Quasi-experimental	Enter the total number of **Quasi-experimental studies** (e.g., controlled before and after, interrupted time series) included in the review, as reported if possible; if not clearly reported please enter 'NR.'
# of Observational	Enter the total number of **Observational studies** (e.g., cohort study, case-control study) included in the review, as reported if possible; if not clearly reported please enter 'NR.'
Overall Sample Size	Enter the total number of participants included in the review, as reported or if it can be easily calculated (e.g., from a study characteristics table) If not clearly reported please enter 'NR'
Overall Age (mean; SD)	Enter the mean age and standard deviation of the participants in the review, as reported; if not clearly reported please enter 'NR,' DO NOT calculate yourself
% female overall	Enter the proportion of participants in the review that are female, as reported; if not clearly reported please enter 'NR,' DO NOT calculate yourself* ***EXCEPTION:** If the proportion of male participants is reported please calculate the % female by subtracting the % male from 100 and enter the result in this column
Participant Characteristics	
Intervention Sample Size	Enter the total number of participants receiving an intervention in the review, as reported or if it can be easily calculated (e.g., from a study characteristics table) If not clearly reported please enter 'NR'
Intervention Age (mean; SD)	Enter the mean age and standard deviation of the participants receiving an intervention, as reported; if not clearly reported please enter 'NR,' DO NOT calculate yourself
% female Intervention	Enter the proportion of participants receiving the intervention that are female, as reported; if not clearly reported please enter 'NR,' DO NOT calculate yourself
Control Sample Size	Enter the total number of participants in the control group in the review, as reported or if it can be easily calculated (e.g., from a study characteristics table) If not clearly reported please enter 'NR'
Control Age (mean; SD)	Enter the mean age and standard deviation of the participants in a control group, as reported; if not clearly reported please enter 'NR,' DO NOT calculate yourself
% female Control	Enter the proportion of participants in a control group that are female, as reported; if not clearly reported please enter 'NR,' DO NOT calculate yourself
Diagnostic Criteria for Insomnia/Sleep disorder	Copy and paste (from the methods section) the eligibility criteria or diagnostic criteria used to define the insomnia population in the review

Includes comorbidities	This will be filled in for you, please verify
Comorbidities	This will be filled in for you, please verify
Exclusion criteria	Copy and paste (from the methods section) any exclusion criteria related to the populations or interventions included in the review
COMMENTS	Please record here any observations or issues you would like to bring to the attention of the RCs

Treatment comparison	
Treatment Comparison Characteristics	
Item	**Description**
Comparison Type	Select from the following comparisons: ☐No comparison* ☐pharma v control** ☐pharma v pharma ☐pharma v non-pharma ☐pharma v combo ☐non-pharma v control ☐non-pharma v pharma ☐non-pharma v non-pharma ☐non-pharma v combo ☐combo v control ☐combo v pharma ☐combo v non-pharma ☐combo v combo **NOTES:** • pharma = Pharmacological; non-pharma = Non-pharmacological, combo = Combination • Depending on the type of comparison you select, certain cells in the row will be highlighted grey. You DO NOT need to enter anything in the grey cells as they are irrelevant to that particular comparison • *if 'No comparison' is selected please use the appropriate columns for 'Intervention 1' to record the details of the interventions examined in the review • **control includes ANYTHING the *review authors* have classified or analyzed as a control group (details of the controls will be entered in column E)
Control(s)	**NOTE:** If you selected a comparison type with an active comparator (e.g., pharma v pharma), this cell will be greyed out, DO NOT enter anything here Enter any relevant *inactive control groups* in this column • Inactive controls include: Placebo, wait-list, symptom- or self- monitoring, delayed treatment, usual care (includes sleep education, sleep hygiene, or stimulus control) If there is more than one kind of control combined in the comparison enter each one in the 'Control(s)' column followed by the number of studies using that control in brackets and separated by a semicolon **EXAMPLE:** placebo (3); wait-list (2); sleep hygiene (5)

Intervention 1 or 2	
Category	Please select from the following: ☐ Antidepressants ☐ Antihistamine ☐ Antipyschotics ☐ Benzodiazepines ☐ Melatonin ☐ Non-benzodiazepines ☐ Suvorexant ☐ Behavioural Therapy (BT) ☐ BT + single component ☐ CBT (cognitive behavioural therapy) ☐ CBT + single component ☐ Combination ☐ Medication withdrawal ☐ Meditation techniques ☐ Mindfulness techniques ☐ Multi-component behavioural intervention ☐ Multi-component Behavioural Therapy ☐ Multi-component CBT ☐ Single behavioural intervention ☐ Sleep-Disordered breathing treatment
Pharma Intervention 1 or 2	
Name	Please select from the dropdown menu.
Dose	Enter dose information as reported • if multiple dosages of a medication lumped together please enter each dose separated by a semicolon (e.g., 5mg; 10mg) • if multiple doses of a medication are being compared in separate syntheses please abstract each on a separate row
Delivery method/Formulation	Enter any information on the formulation of the intervention (e.g., fast release, long duration, etc.) or delivery method (e.g., pill, patch, sublingual) as reported
Frequency	Enter any information on the frequency of the intervention (e.g., daily, twice daily, etc.) as reported
Setting	Select from the following: ☐ in-patient (e.g., hospital based) ☐ outpatient (e.g., clinic, therapist's office) ☐ home ☐ community (e.g., community centre, halfway house) ☐ long-term care (e.g., nursing home) ☐ institution (e.g., prison, adult care facility) ☐ NR (e.g., not reported)
Shortest Follow-up (weeks)	Enter the shortest follow-up duration, in weeks, in the studies included in the review
Longest follow-up	Enter the longest follow-up duration, in weeks, in the studies included in the review
Non-Pharma Intervention 1 or 2	
Components	Enter the specific components of the intervention, as reported. If individual components of a multi-component intervention are not clearly reported please enter 'unspecified'
Delivery Method	Enter any information on how the intervention was delivered (e.g., group therapy, self-help, individual, etc.), as reported
Frequency	Enter any information on the frequency of the intervention (e.g., weekly, monthly, etc.) as reported
Setting	Select from the following: ☐ in-patient (e.g., hospital based)

	☐ outpatient (e.g., clinic, therapist's office) ☐ home ☐ community (e.g., community centre, halfway house) ☐ long-term care (e.g., nursing home) ☐ institution (e.g., prison, adult care facility) ☐ NR (e.g., not reported)
Shortest Follow-up (weeks)	Enter the shortest follow-up duration, in weeks, in the studies included in the review
Longest follow-up (weeks)	Enter the longest follow-up duration, in weeks, in the studies included in the review

Results

If the data are reported with multiple time points and you are unsure which to abstract please use the following decision rule:

- If available, always abstract the '*overall*' results (e.g., combines all time points/all relevant studies)
- If 'overall' results are not available abstract the results based on the *longest duration of follow-up*

If 'longest duration' results are not available, abstract the *post-treatment results*

Treatment Comparison	
Item	**Description**
Comparison Type	Will be automatically filled in from previous cells
Pharma Intervention 1	Will be automatically filled in from previous cells
Non-pharma Intervention 1	Will be automatically filled in from previous cells
Pharma Intervention 2	Will be automatically filled in from previous cells
Non-pharma Intervention 2	Will be automatically filled in from previous cells
Outcome Results (repeated for up to 10 outcomes, add more as needed)	
Outcome	Select from the dropdown menu: ☐ Insomnia Severity Index ☐ Sleep Efficiency ☐ Sleep Latency ☐ Sleep Quality ☐ Sleep Satisfaction ☐ Total Sleep Time ☐ Wake after sleep onset ☐ Quality of Life ☐ Fatigue Severity ☐ Accidental Injury ☐ Addiction, Dependence, Diversion ☐ Additional Health care Utilization ☐ Delirium ☐ Hangover/Morning Sedation ☐ Sleep-Disordered Breathing ☐ Mortality
Questionnaire/scale/method	Enter the questionnaire/scale used to collect outcome data, as reported
# of Studies	Number of studies included in the results for this intervention and outcome
# participants	Overall number of participants included in this outcome. If the number of participants is broken down according to intervention and control enter the values like so: 35 (intervention); 45 (control)
Change in outcome	Enter any pooled/summary quantitative measure of change reported for this outcome. If multiple time points are reported abstract the results from the longest duration of follow-up. Example:

	• mean change from baseline • mean difference compared with placebo
Significance (*P* value)	Enter the significance of the change as reported in the review. Some reviews may report the *P* value directly (e.g., *P* = 0.34) or indicate whether a result reached significance (e.g., *P* < 0.05 or NS [not significant]). If no *P* value is reported or the significance level is not indicated enter NR
Proportion of respondents	Enter any pooled/summary quantitative measure of the proportion of respondents for this outcome. If multiple time points are reported abstract the results from the longest duration of follow-up. Example: • percentage of patients showing improvement* • number of patients responding to treatment* ***NOTE:** if a threshold or cut-off value is used to define treatment response please add this information to the '*Questionnaire/scale*' column Example: • Insomnia Severity Index; decrease ≥3 points considered improvement • Polysomnography; total sleep time increase ≥15 minutes considered improvement
Significance (*P* value)	Enter the significance of the change as reported in the review. Some reviews may report the *P* value directly (e.g., *P* = 0.34) or indicate whether a result reached significance (e.g., *P* < 0.05 or NS [not significant]). If no *P* value is reported or the significance level is not indicated enter NR
Conclusion	If no pooled or synthesized results are reported, copy and paste any conclusions the authors have drawn regarding this intervention and outcome pair (either from the abstract or the 'conclusions' section)

Appendix 5: List of Included Studies

1. Anderson SL, Vande Griend JP. Quetiapine for insomnia: A review of the literature. *Am J Health-Syst Pharm.* 2014;71(5):394-402.
2. Ballesio A, Aquino M, Feige B, et al. The effectiveness of behavioural and cognitive behavioural therapies for insomnia on depressive and fatigue symptoms: A systematic review and network meta-analysis. *Sleep Med Rev.* 2018;37:114-129.
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6. Brooks AT, Wallen GR. Sleep Disturbances in Individuals with Alcohol-Related Disorders: A Review of Cognitive-Behavioral Therapy for Insomnia (CBT-I) and Associated Non-Pharmacological Therapies. *Subst Abus.* 2014;8:55-62.
7. Buscemi N, Vandermeer B, Friesen C, et al. Manifestations and management of chronic insomnia in adults. *Evid Rep Technol Assess (Summ).* 2005(125):1-10.
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15. Costello RB, Lentino CV, Boyd CC, et al. The effectiveness of melatonin for promoting healthy sleep: a rapid evidence assessment of the literature. *Nutr J.* 2014;13:106.
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18. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. *PLoS ONE.* 2013;8(5):e63773.
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20. Hellström A, Willman A. Promoting sleep by nursing interventions in health care settings: a systematic review. *Worldviews Evid Based Nurs.* 2011;8(3):128-142.
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Appendix 6: Review and Participant Characteristics

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
Systematic Reviews with Meta-Analysis, n = 35							
Ballesio, 2017[62]	Germany	Total: 47 47 RCTs	Total: 4,317 Intervention: 2,448 Control: 1,869	Overall: 51.9 (NR); 62.8%	None	NR	Uncontrolled studies; studies of CBT-I combined with other therapies; no adult insomnia patients; no measures of depression or fatigue.
Brasure, 2015[29]	US	Total: 46 46 RCTs	Total: 5764	NR	Pain, chronic low back pain, hearing impairment	DSM and/or ICSD (both in current or previous versions)	(1) Lack of randomization. (2) Inadequate study duration. (3) Drugs not approved for use in the US. (4) Insomnia not clinically diagnosed. (5) Not available in English.
Buscemi, 2004[31]	Canada	Total: 139	NR	NR	NR	NR	(1) Individuals were required to be free of any type of sleep disorder in the case of the question relating to the effect of melatonin on normal sleepers, and to suffer from a sleep disorder in the case of the question relating to the effect of melatonin on people with sleep disorders. (2) For questions pertaining to the administration of exogenous melatonin to a study population, any formulation, dosage, timing, frequency, and duration of melatonin administration was acceptable. (3) Melatonin is required to be the primary intervention, and in the case of controlled trials,

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
							compared with placebo.
Buscemi, 2005[30]	Canada	Total: 97 97 RCTs	NR	NR	NR	Persistent sleep disturbance for at least 4 weeks, regardless of symptom severity	(1) Reported in a language other than English. (2) A review/ commentary/ practice parameter. (3) Did not examine an adult population (4) Study population did not suffer from chronic insomnia. (5) Not a randomized controlled trial. (6) Did not have a placebo arm. (7) Not double-blind. (8) Did not report on any outcomes relevant to review. (9) Data relevant to the study outcomes were not adequately reported.
Cheng, 2012[32]	Hong Kong	Total: 6 6 RCTs	Total: 431	NR	Cancer-related insomnia	(1) DSM-IV or ICD-10 (2) Insomnia secondary to or comorbid with anxiety or depression (3) Subjective complaint of insomnia without a clinical diagnosis	(1) Participants had shift work that interfered with the establishment of regular sleep patterns. (2) Participants had an acute psychotic disorder or manic disorder. (3) Suffered from head injury and/or were unable to read.
Ferracioli-Oda, 2013[33]	US	Total: 19 19 RCTs	Total: 1,683	NR	Delayed sleep phase disorder, REM sleep behaviour disorder	DSM-IV	(1) Not randomized placebo-controlled trials. (2) Did not examine sleep disorders or primary sleep disorders. (3) Did not examine the effects of melatonin. (4) Sample size of less than 10

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
							participants for parallel designs or 5 participants for crossover designs. (5) Follow-up studies. (6) Manuscripts that were not in a peer-reviewed journal. (7) Retracted study.
Gong, 2016[34]	China	Total: 6 6 RCTs	Total: 330	NR	Depression, cancer	(1) Diagnosed with insomnia or sleep disorders (2) Subjective complaint of sleep without clinical diagnosis	(1) Non-randomized or uncontrolled trials. (2) Qualitative report including literature review. (3) Case reports or trials with fewer than 20 subjects. (4) Incomplete articles after contacting the authors.
Ho, 2015[36]	Hong Kong	Total: 20 20 RCTs	Total: 2,411	Overall: 49.3 (NR); 74.2%	None	DSM-IV, DSM-V, ICD-10, ICSD, or research diagnostic criteria	Self-help CBT given in addition to pharmacotherapy or conventional form of psychological treatment.
Ho, 2016[35]	Hong Kong	Total: 11 11 RCTs	Total: NR Intervention: 303 Control: 290	Overall: 45.3 (NR); 35.6%	PTSD, depression	NR	Studies with CBT for sleep disturbances as control group were excluded.
Hwang, 2016[61]	South Korea	Total: 37 13 RCTs 24 Quasi-experimental	Total: 2,150	NR	NR	NR	Studies were university-owned research, thesis papers, duplicate publications, animal studies, presentations, announcements, and literature reviews.
Irwin, 2006[37]	US	Total: 23 23 RCTs	NR	NR	None	NR	(1) No participants were children. (2) Data were not markedly abnormal (mean was larger than the standard deviation, per criterion from Montgomery &

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
							Dennis, 2003).
Johnson, 2016[38]	Canada	Total: 8 8 RCTs	Total: 752 Intervention: 434 Control: 318	NR	Cancer	DSM, ICSD, or ISI with a clinical cut-off score of eight	(1) Did not evaluate CBT-I. (2) Not RCT. (3) Secondary data analysis. (4) No sleep diary data. (5) Not cancer survivors. (6) Conference abstracts, repeat citation.
Kishi, 2015[39]	Japan	Total: 4 4 RCTs	Total: 3,076	Overall: 56.6 (NR); 61.8%	None	DSM-IV	NR
Koffel, 2015[40]	US	Total: 8 8 RCTs	NR	NR	Chronic pain, cancer, fibromyalgia, chronic illness, arthritis	DSM-IV-TR and ICSD criteria for insomnia, including both primary and secondary insomnia diagnoses	NR
Kuriyama, 2017[41]	Japan	Total: 4 4 RCTs	Total: 3,076	Overall: 56.3 (15.3); 61.5%	None	DSM-IV-TR	Trials examining efficacy of suvorexant for any entities other than primary insomnia.
Lee, NA [unpublished][58]	South Korea	Total: 18 18 RCTs	NR	NR	None	NR	NR
Liu, 2017[42]	China	Total: 7 7 RCTs	Total: NR Intervention: 743 Control: 733	NR	None	NR	(1) Uncontrolled, non-randomized, or quasi-randomized trials. (2) Insomnia accompanied by other significant medical disorders. (3) Participants consisted of healthy adults and the study was using a model of transient insomnia. (4) No placebo condition. (5) Data included in the study was incomplete or unavailable.

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
McCleery, 2016[43]	UK	Total: 3 3 RCTs	Total: 222	NR	Dementia	A sleep problem diagnosed either subjectively or objectively. Sleep problems include difficulty initiating sleep, problems with sleep maintenance, the sundowning phenomenon, and daytime napping.	(1) Patients with obstructive sleep apnea syndrome. (2) No sleep problem at baseline. (3) No primary sleep aim. (4) Older studies with uncertain diagnostic participant status. (5) Incomplete studies. (6) Not RCT.
Montgomery, 2003[44]	US	Total: 6 6 RCTs	Total: 282 224 in MA	NR	Parasomnia, sleep apnea	(1) Standardized measure including polysomnography (2) Objective measure including self/caregiver/ nurse report	(1) Patients with sleep apnea. (2) Secondary insomnia . (3) Sleep disturbance caused by psychiatric/ medical disorder. (4) Patients with dementia and/or depression.
Navarro-Bravo, 2015[56]	Spain	Total: 9 9 RCTs	Total: 699 Intervention: 352 Control: 347	NR	Cancer survivor, depression, restless leg syndrome, osteoarthritis	DSM-IV, ICD-10	NR
Okajima, 2011[57]	Japan	Total: 14 14 RCTs	Total: NR Intervention: 454 Control: 384	NR	None	ICSD-1, DSM-IV, DSM-III-R, ICSD-R; DSM-IV-TR	(1) Statistical values not described. (2) Results not in English. (3) Not RCT. (4) CBT implemented not using previously indicated treatment techniques.
Sateia, 2017[45]	US	Total: 129 129 RCTs 46 in MA	NR	NR	None	Diagnosis of primary chronic insomnia	(1) Not a drug treatment. (2) Pediatric population. (3) Sample size < 20.

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
							(4) Significant comorbidity. (5) Not chronic insomnia and/or normal/healthy subjects. (6) Other subpopulation (hospitalized patients, etc.). (7) Wrong publication type (i.e., review).
Seda, 2015[46]	US	Total: 8 8 RCTs	NR	NR	PTSD, nightmares	NR	(1) Not RCTs. (2) Reviews or theoretical articles, single case studies, included adolescent or child treatment samples (3) Used treatments other than IRT or prazosin.
Seyffert, 2016[47]	US	Total: 15 15 RCTs	Total: 2,392	NR	Major depression	NR	(1) Studies involving children less than 16 years of age. (2) Trials targeting specific patients were excluded as the causes and treatment of insomnia maybe different in these populations.
Soldatos et al., 1999[48]	Greece	Total: 75	Total: 1,276	NR	None	NR	(1) Unconventional timing of sleep or conditions/procedures that may interfere with sleep. (2) Non-standard sleep recording or scoring procedures. (3) No placebo control. (4) Individuals suffering from concurrent medical or psychiatric disorders. (5) Inadequate or no washout period. (6) Inadequate documentation of blindness or randomization.

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
							(7) No adaptation night in a single group study. (8) Unconventional placebo comparator.
Tang, 2015 [49]	UK	Total: 11 11 RCTs	Total: 1,066 965 in MA	Overall: 45 - 61 (NR); 55 -100%	Chronic pain, cancer, back pain, arthritis	DSM diagnostic criteria	(1) Not sleep intervention. (2) Not chronic pain conditions. (3) No sleep measure and/or no health measure. (4) Not original.articles/multiple publications/poster abstracts with preliminary findings.
Trauer, 2015[50]	Australia	Total: 20 20 RCTs	Total: 1,162	Overall: 55.6 (NR); 64.3%	None	DSM-IV, ICSD, DSM-III, RDC	Studies of insomnia comorbid with medical, sleep, or psychiatric disorders.
van Straten, 2009[93]	Netherlands	Total: 10 10 RCTs 9 in MA	Total: 1,000 Intervention: 580 Control: 420	NR	Alcohol dependence, chronic disease	NR	(1) No control group. (2) Loss to follow-up of more than 50%. (3) No post-test data but only 1-year follow-up data.
van Straten, 2007[51]	Netherlands	Total: 87 87 RCTs	Total: 6,303 Intervention: 3,724 Control: 2,579	NR	chronic pain; cancer; alcohol dependence; hearing problems; post-traumatic stress disorder; chronic obstructive pulmonary disease	NR	(1) Other therapies such as interpersonal therapy, bright light therapy, exercise biofeedback, and cognitive distraction. (2) Studies aimed at children or adolescents. (3) Studies looking at tapering medication, which used outcomes such as fatigue instead of sleep. (4) Studies treating another mental illness.
Xu, 2015[52]	China	Total: 6	Total: 484	NR	Dementia	NR	(1) Animal studies, case reports,

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
		6 RCTs					non-randomized trials, and trials without eligible outcome measurements.
Yang, 2014[53]	China	Total: 3 3 RCTs	Total: 184	NR	Dialysis-dependent patients with end-stage renal disease	Sleep quality evaluated before and after intervention	(1) patients with renal cell carcinoma (2) patients with unstable or acute clinical situations (3) presence of psychiatric disorders
Ye, 2016[54]	China	Total: 14 14 RCTs	Total: 1,604 Intervention: 1,013 Control: 591	NR	Cancer, depression	Clinical diagnosis of insomnia based on DSM-V, DSM-IV, or ICSD-2; sleep difficulty occurring three or more nights per week and lasting more than 4 weeks	(1) not in English; duration of therapy < 4 weeks (2) insufficient data to calculate the effect size (3) duplicate publications (4) not an RCT (5) below 18 years
Yuan, 2010[59]	China	Total: 4 4 RCTs	Total: 171 Intervention: 171 Control: 169	NR	None	DSM-IV	(1) studied other sleep, mental disorders and physical illness, alcohol or drugs and other medical problems caused by insomnia (2) secondary insomnia patients
Zachariae, 2016[55]	Denmark	Total: 11 11 RCTs	Total: 1,460 Intervention: 790 Control: 670	NR	Cancer	DSM-IV, DSM-V	(1) did not include an Internet-based program (2) did not include results on sleep-related outcomes, (3) did not include non-intervention control group, did (4) not include quantitative sleep data
Zhang, 2016[60]	China	Total: 9 9 RCTs	NR	NR	Alzheimer disease, Parkinson disease, REM	NR	NR

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
					sleep behaviour disorder		
Systematic Reviews Without Meta-Analysis, n = 29							
Anderson, 2014[63]	US	Total: 12 4 RCTs	NR	NR	depression/major depressive disorder, bipolar disorder, breast cancer, Parkinson disease, schizophrenia, poly-substance abuse (withdrawal)	NR	Participants did not have a diagnosis of insomnia at baseline.
Bellon, 2006[64]	US	Total: 15 15 RCTs	Total: 452	NR	Schizophrenia, dementia, medically ill patients, Alzheimer disease	NR	NR
Bogdanov, 2017[65]	Australia	Total: 4 1 RCT 3 Quasi-experimental	NR	Mean age ranged between 27 – 54	Traumatic brain injury	NR	(1) traumatic brain injury sample mixed with other sample and outcomes not reported separately (2) pre- and/or post-sleep data not reported (3) sleep hygiene combined with medication and relative Effects not examined separately
Brooks, 2014[66]	US	Total: 4 3 RCTs 1 Quasi-experimental	NR	NR	Alcohol use	NR	NR

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
Chase, 1997[67]	US	Total: 4 5 RCTs	Total: 66	NR	Patients with at least one chronic disease	NR	NR
Chiesa, 2009[88]	Italy	Total: 3 3 Observational	Total: 63	NR	NR	NR	NR
Cimolai, 2007[68]	Canada	Total: 8 2 RCTs 6 NRCTs	Total: 474	NR	NR	NR	NR
Citrome, 2014[69]	US	Total: 4 4 RCTs	Total: NR Intervention: 1,279 Control: 1,274	NR	None	NR	NR
Coe, 2012[70]	US	Total: 2 1 RCT 1 NRCT	Total: 34	NR	None	NR	NR
Costello, 2014[71]	US	Total: 4 4 RCTs	Total: 845	NR	None	NR	(1) Any study design other than a RCT (2) Population with pre-existing conditions or diseases other than insomnia; (3) Focus of article was on an intervention other than melatonin (4) Intervention was a combination of melatonin and other supplements or drugs; article (5) Did not have at least one sleep outcome of interest
Culpepper, 2015[72]	US	Total: 11 11 RCTs	Total: 1,590	NR	None	Diagnosed insomnia (using established diagnostic classification criteria) or occasional disturbed sleep	Studies conducted in populations with underlying serious medical conditions (physical or psychiatric diseases or sleep disorders other than insomnia) and studies exclusively on sedative or cognitive effects following daytime

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
						(generally defined as mild symptoms of insomnia occurring 2 to 3 times per week) that included objective or subjective (i.e., participant reported) sleep-related end points	administration (without an intervening period of bedtime).
Dickerson, 2014[73]	US	Total: 7 7 RCTs	Total: 352 Intervention: 220 Control:132	NR	Cancer	QoL and sleep-wake disturbance measures that demonstrated an association between sleep-wake disturbance and QoL	(1) Did not include QoL measures (2) Sleep measurement issues (3) Described caregivers only (4) Reviews, theses, editorials, cross-sectional studies
Hellström, 2011[74]	Sweden	Total: 3 3 RCTs	Total: 209 Intervention: 103 Control: 106	NR	NR	NR	(1) Studies concerning shift workers, health care personnel (2) Pharmacological treatment including herbal remedies (3) Children (< 19 years.) were excluded (4) Studies that did not involve patients in health care settings
Howell, 2014[75]	Canada	Total: 7 7 RCTs	NR	NR	Cancer	NR	(1) Data for cancer in general population studies are not analyzed/reported separately or analyzed post hoc (2) Language other than English (3) Intervention studies in non-cancer populations
Ishak, 2012[76]	US	Total: 7	NR	NR	Breast, prostate gynecological, bowel cancer	NR	NR

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
Kolla, 2011[77]	US	Total: 4 2 RCTs 2 NRCTs	Total: 240	NR	Alcohol recovery	NR	NR
Mayers, 2005[78]	UK	Total: 6 6 RCTs	Total: 466	NR	Depression, dysthymia	NR	(1) Mixed population (2) Did not explicitly mention insomnia patients
McCurry, 2007[79]	US	Total: 11	NR	NR	Medical Illness	ICSD, ICD, DSM-IV	NR
Mendelson, 2005[80]	US	Total: 18	Total: 1,667 Intervention: 1,195 Control: 472	NR	Depression	NR	Studies that did not measure any end point for insomnia efficacy.
Miller, 2014[81]	UK	Total: 9 4 RCTs 1 NRCT 4 Observational	Total: 380	Overall: 53.3 (10.2); NR	None	NR	Reviews, duplicates and studies that implemented sleep compression therapy or SRT as a treatment package (CBT-I).
Swainston Harrison, 2005[91]	New Zealand	Total: 3 3 RCTs	Total: 145 Intervention: 102 Control: 43	NR	None	Patients with insomnia who received zolpidem; large, well-controlled trials with appropriate statistical methodology were preferred	Patients with psychiatric disorders.
Tamrat, 2013[89]	US	Total: 8 4 RCTs 2 NRCTs 2 Observational	Total: 508	NR	Cancer, post-coronary artery bypass grafting, psychiatric disease (all hospitalized patients)	NR	(1) Non-English articles (2) Not in-patients (3) ICU/Critical care (4) Pediatric patients (5) No comparison group
Taylor, 2014[82]	US	Total: 16 16 RCTs	Total: 571	NR	Depression, post- traumatic	NR	(1) Studies with primarily co- morbid medical disorders (e.g., pain,

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
					stress disorder, alcohol dependence, hypnotic		cancer, fibromyalgia) were excluded from these analyses (2) Studies which did not report data using a sleep diary or validated symptom questionnaire or weekly hypnotic use
Vande Griend, 2012[83]	US	Total: 16 16 RCTs	NR	NR	Alcohol detoxification, methadone-maintained	NR	NR
Venables, 2014[90]	UK	Total: 22 16 RCTs 5 Quasi-experimental 1 Observational	Total: 1,794	NR	Adult cancer patients undergoing curative treatment	NR	(1) Non-curative/palliative patients (2) Children and adolescents (3) Qualitative and non-primary research
Vural, 2014[84]	Netherlands	Total: 5 4 RCTs 1 NRCTs	Total: 207	NR	NR	Elderly aged ≥ 55 years with sleep maintenance insomnia; older adults with insomnia; insomniacs aged 55 years to 80 years; adults with primary insomnia; elderly with nocturia	(1) Articles only measuring endogenous levels without administration of melatonin (2) Treatment with agomelatine (3) Animal studies (4) Mean age < 55 years (5) "Add-on" effect of melatonin on another treatment (6) No melatonin concentrations mentioned (7) Group comparison not conducted after therapy
Wang, 2005[85]	Taiwan	Total: 6 6 RCTs	Total: 255	NR	NR	Primary insomnia/ psychophysiological insomnia according to DSM-IV/ICSD-R/ICD-10	(1) Patients with other sleep disorders (e.g., circadian rhythm sleep disorder, periodic limb movements in sleep) (2) Severe medical conditions (e.g.,

Author, Year	Country	Number and Type of Included Studies	Sample Size	Age and Sex mean (SD); % female	Comorbidities	Insomnia Diagnosis	Exclusion Criteria for Review
							cancer, dementia, end-stage renal disease) (3) Severe psychiatric disorders (e.g., major depression, anxiety disorders) (4) Substance use
Wine, 2009[86]	US	Total: 3 3 NRCTs	Total:50	NR	Post-traumatic stress disorder, Parkinson disease	Quetiapine prescribed "as needed" for insomnia, insomnia-type symptoms; primary insomnia	(1) Patients with psychiatric or nonpsychiatric condition (2) Evaluated use of quetiapine prescribed
Yeung, 2015[87]	Hong Kong	Total: 8 8 RCTs	Total:1,513	NR	Anxiety, depression	NR	(1) Did not examine doxepin or insomnia (2) Not RCT (3) Doxepin not administered orally (4) No doxepin treatment arm (5) No placebo control (6) Conference abstract

CBT = cognitive behavioural therapy; CBT-I = cognitive behavioural therapy for insomnia; DSM-III/IV/V-R/TR = Diagnostic and Statistical Manual of Mental Disorders - 3rd/4th/5th ed. - Revision/Text Revision; ICD-10 = International Statistical Classification of Diseases and Related Health Problems 10th Revision; ICSD-R/2 = International Classification of Sleep Disorders - Revised (1997)/2nd edition (2005); ISI = Insomnia Severity Index; NR = not reported; NRCT = non-randomized controlled trial; PTSD = post-traumatic stress disorder; QoL = quality of life; RCT = randomized controlled trial; RDC = Research Diagnostic Criteria; REM = rapid eye movement; SD = standard deviation.

Appendix 7: Intervention Characteristics

Author, Year	Synthesis Type	Intervention and Comparator doses (mg)	Delivery Method; Setting	Frequency; Duration of Treatment	Length of Follow-Up Range, Weeks
Benzodiazepine Drugs (3 SR+MAs, 2 SRs)					
Buscemi, 2005[30]	MA	Flurazepam (30 mg; 15 mg) Temazepam (30 mg; 20 mg; 15 mg) Triazolam (0.5 mg; 0.25 mg; 0.125 mg) Placebo	NR	NR	NR
Sateia, 2017[45]	MA	Temazepam (15 mg) Placebo	NR	5 days for 8 weeks	NR
Soldatos, 1999[48]	MA	Triazolam (0.25 mg; 0.5 mg) Placebo	NR	1 to 42 nights	NR
Kolla, 2011[77]	SR	Triazolam (0.5 mg to 1 mg) No comparator (pre- / post-intervention effect)	Oral	NR	4
Swainston, 2005[91]	SR	Triazolam (0.5 mg) Placebo	Tablet; bedtime	NR	4
Non-Benzodiazepines (z-drugs) (4 SR+MAs, 5 SRs)					
Brasure, 2015[29]	MA	Zolpidem (10 mg; 15mg) Zolpidem (10 mg) Placebo	NR; outpatient NR; outpatient	NR “as needed”	4 to 34.76 4
Buscemi, 2005[30]	MA	Zolpidem (20 mg, 15 mg, 10 mg, 5 mg) Zopiclone (7.5 mg) Placebo	NR	NR	NR
Sateia, 2017[45]	MA	Zolpidem (10 mg) Placebo	NR	2 to 32 weeks	NR
Soldatos, 1999[48]	MA	Zopiclone (7.5 mg; 10 mg; 15 mg) Zolpidem (10 mg; 15 mg; 20mg) Placebo	NR NR	5 to 113 nights 1 to 35 nights	NR
Cimolai, 2007[68]	SR	Zopiclone (7.5 mg) Zopiclone (7.5 mg) vs. Triazolam Zopiclone (7.5 mg) vs. Zolpidem Zopiclone (7.5 mg) vs. Flurazepam Zopiclone (7.5 mg) vs. Temazepam	NR	NR	NR

Author, Year	Synthesis Type	Intervention and Comparator doses (mg)	Delivery Method; Setting	Frequency; Duration of Treatment	Length of Follow-Up Range, Weeks
Ishak, 2012[76]	SR	Zopiclone (NR) vs. Placebo Zolpidem (10 mg) vs. Zolpidem (10 mg)	NR NR; NR	NR 5 nights/week + placebo 2 nights/week; once-daily	NR 2; 2
Mayers, 2005[78]	SR	Zolpidem (10 mg) Placebo	Oral	NR	NR
Mendelson, 2005[80]	SR	Zolpidem (10 mg) Placebo	NR	Nightly	NR
Swainston, 2005[91]	SR	Zolpidem (10 mg) vs. Placebo Zolpidem (10 mg) vs. Triazolam	Tablet	Bedtime	7 2 to 7
Melatonin (8 SR+MA, 5 SR)					
Buscemi, 2005[30]	MA	Melatonin (5 mg; 3 mg; 2 mg; 1 mg; 0.5 mg; 0.3 mg; 0.1 mg) Placebo	NR	NR	NR
Buscemi, 2004[31]	MA	Melatonin (0.1 mg; 0.3 mg, 0.5 mg, 1 mg; 2 mg; 3 mg; 5 mg; 6 mg) Placebo	Oral (sustained release; fast release; immediate-release)	16 days; nightly; variable number of capsules based on study	NR
Ferracioli-Oda, 2013[33]	MA	Melatonin (0.1 mg; 0.3 mg; 0.5 mg; 1 mg; 2mg; 3 mg; 5 mg) Placebo	NR	NR	1 to 26
McCleery, 2016[43]	MA	Melatonin (5 mg immediate-release; 10 mg immediate-release; 2 mg slow-release; 2.5 mg slow-release) Lactose placebo Placebo Bright light exposure	Tablet (immediate-release; slow-release); long-term care and community care	Hrs.; 1 to 2 hours before bedtime	8 to 28
Sateia, 2017[45]	MA	Melatonin (2mg) Placebo	NR	3 weeks; nightly	NR
Xu, 2015[52]	MA	Melatonin (1.5 mg; 2.5 mg; 2.9 mg; 3 mg; 5 mg; 6 mg; 8.5 mg; 10 mg) Placebo Light therapy	Melatonin (sustained release, immediate-release)	NR	1.43 to 10
Lee, NA[58]	MA	Melatonin (0.1 mg; 0.3 mg; 1 mg; 2 mg; 5 mg; 12 mg; 0.05 mg/kg; 0.1 mg/kg; 0.15 mg/kg; 75 mg) Placebo	Transbuccal (sustained release, fast release, controlled release; prolonged release)	4 days; 6 months of treatment	NR

Author, Year	Synthesis Type	Intervention and Comparator doses (mg)	Delivery Method; Setting	Frequency; Duration of Treatment	Length of Follow-Up Range, Weeks
Zhang, 2016[60]	MA	Melatonin (2 mg/d; 2.5 mg/d; 3 mg/d; 5 mg/d; 6 mg/d; 8.5 mg/d; 50 mg/d) Placebo	NR	2 to 24 weeks treatment period	NR
Beelon, 2006[64]	SR	Melatonin (0.3 mg, 0.5 mg, 1 mg, 2 mg, 2.5 mg, 5 mg, 6 mg, 10 mg, 75 mg)	Fast sustained release	Nightly/bedtime, 4 hrs. after bedtime; 1 to 4 weeks	NR
Chase, 1997[67]	SR	Melatonin (1 mg, 2 mg, 5 mg, 75 mg)	Controlled sustained release	NR	NR
Cosello, 2014[71]	SR	Melatonin (0.3 mg, 1 mg, 2 mg, 5 mg)	Oral, sustained release	Daily	NR
Culpepper, 2015[72]	SR	Melatonin (1 mg, 5 mg) Melatonin (0.3mg, 1 mg, 2 mg)	Fast-release capsule, sustained release synthetic tablet, prolong-release tablet	Daily Daily	4 to 8 1 to 29
Vural, 2014[84]	SR	Melatonin (0.5 mg, 2 mg) Melatonin (0.4 mg, 0.5 mg, 2 mg, 4 mg)	Sustained release transbuccal patch Immediate, controlled release	2 sessions, 4 nights each at 7:00 p.m.; 1 to 2 hours before bedtime 3 times daily at bedtime; 42 days	1 to 24 2 to 8
Antidepressant Drugs (5 SR+MA, 5 SR)					
Brasure, 2015[29]	MA	Doxepin (1 mg; 3 mg; 6 mg) Placebo	NR; outpatient	NR	4 to 12
Buscemi, 2005[30]	MA	Doxepin (25 mg; 25 mg to 50 mg) Trazodone (50 mg; 150 mg to 250 mg) Placebo	NR	NR	NR
Liu, 2017[42]	MA	Doxepin (6 mg; 3 mg; 1 mg) Placebo	NR	NR	NR
Sateia, 2017[45]	MA	Doxepin (3 mg) Doxepin (6 mg) Placebo	NR	2 nights to 12 weeks 2 nights to 5 weeks	NR
Yuan, 2010[59]	MA	Doxepin (1 mg) Doxepin (3 mg) Doxepin (6 mg)	NR	NR	NR

Author, Year	Synthesis Type	Intervention and Comparator doses (mg)	Delivery Method; Setting	Frequency; Duration of Treatment	Length of Follow-Up Range, Weeks
		Doxepin (25 mg) Placebo			
Kolla, 2011[77]	SR	Trazodone (50 mg to 200 mg) Placebo	Oral	NR	4 to 24
Mayers, 2005[78]	SR	Trazodone (50 mg, 75 mg, 100 mg) Doxepin (25 mg to 50 mg) vs. Placebo Trazodone (50 mg to 100 mg) vs. Placebo Trazodone (50 mg) vs. Zolpidem (10 mg)	Oral Oral Oral Oral; Oral	NR NR NR 2 week duration; 2 week duration	NR NR NR NR; NR
Mendelson, 2005[80]	SR	Trazodone (50 mg, 75 mg, 100 mg, 150 mg, 50 mg to 100 mg, 50 mg to 300 mg, 150 mg to 400 mg, 300 mg to 400 mg, 400 mg to 600 mg) Trazodone (50 mg, 100 mg, 150 mg, 50 mg to 100 mg, 100 mg to 300 mg) vs. Placebo Trazodone (50 mg) vs. Zolpidem (10 mg)	NR	NR Nightly Nightly; nightly	NR
Vande Grier, 2012[83]	SR	Trazodone (50 mg) vs. Placebo Doxepin (25 mg or 25 mg to 50 mg; 1 mg, 3 mg, and 6 mg; 1 mg and 3 mg; 6 mg; 3 mg and 6 mg) vs. Placebo Trazodone (50 mg) vs. Zolpidem (NR)	NR	1 to 4 weeks 1 night to 12 weeks (one crossover included 2 nights each with 5 to 12 day washout) 2 weeks; 2 weeks	NR
Yeung, 2015[87]	SR	Doxepin (3 mg) Doxepin (6 mg) Doxepin (25 mg to 300 mg) Placebo	Oral, low dose	NR	4 to 12 4 to 12 4
Antipsychotic Drugs (4 SR)					
Anderson, 2014[63]	SR	Quetiapine (25 mg; increased to 50 mg or 75 mg) Quetiapine (25 mg; 25 mg to 100mg; 340 mg) vs. Placebo	Oral; in-patient Oral; NR	Daily; 2 to 12 weeks Daily; 2, 4, 8 weeks	NR

Author, Year	Synthesis Type	Intervention and Comparator doses (mg)	Delivery Method; Setting	Frequency; Duration of Treatment	Length of Follow-Up Range, Weeks
Coe, 2012[70]	SR	Quetiapine (25 mg titrated up to 75 mg) Quetiapine (25 mg) vs. Placebo	NR	NR	2 to 6 2
Kolla, 2011[77]	SR	Quetiapine (300 mg to 800mg) No comparator (pre- / post- intervention)	Oral	NR	16
Wine, 2009[86]	SR	Quetiapine (25 mg to 75 mg; 12.5 mg to 50mg) Quetiapine (25 mg to 300mg) Untreated control	Tablet Tablet	HS PRN HS PRN	6 to 12 6
Suvorexant (3 SR+MA, 1 SR)					
Brasure, 2015[29]	MA	Suvorexant (15 mg; 20mg) Placebo	NR	NR	4
Kishi, 2015[39]	MA	Suvorexant (10 mg to 80mg/d) Placebo	NR; Outpatient	NR	4 to 52
Kuriyama, 2017[41]	MA	Suvorexant (10 mg/d; 15 mg/d; 20 mg/d; 30 mg/d; 40 mg/d; 80mg/d) Placebo	NR	NR	4 to 52
Citrome, 2014[69]	SR	Suvorexant (15 mg, 20 mg) Suvorexant (20 mg, 40 mg) Placebo	Oral	NR	12
Diphenhydramine (1 SR+MA, 2 SRs)					
Sateia, 2017[45]	MA	Diphenhydramine (50 mg) Placebo	NR	Nightly for 2 weeks	NR
Culpepper, 2015[72]	SR	Diphenhydramine (50 mg) Placebo	Tablet	Daily; NR	1 day to 4 weeks
Vande Grier, 2012[83]	SR	Diphenhydramine (50 mg) Placebo	NR	5 to 28 days	NR
Cognitive Behavioural Therapy (14 SR+MA, 7 SR)					
Brasure, 2015[29]	MA	CBT-I Control conditions: sham treatment/placebo, wait-list control, no treatment, or sleep hygiene/sleep education	Individual (in-person), group (in-person), phone, self-help (using books,	Once a week for 1 hour or less	4 to 104

Author, Year	Synthesis Type	Intervention and Comparator doses (mg)	Delivery Method; Setting	Frequency; Duration of Treatment	Length of Follow-Up Range, Weeks
		Placebo	handouts, or electronic resources); Outpatient		
Cheng, 2012[32]	MA	CBT-I: sleep hygiene, stimulus control, relaxation training, sleep restriction, cognitive restructuring, relapse prevention, psychoeducation Control conditions: wait-list control, sleep-monitoring	Computer or mobile phone; Home-based	5 to 9 weeks	3 to 26
Ho, 2016[35]	MA	CBT: image rehearsal therapy, exposure, re-scripting, and relaxation therapy, mind-body bridging, behavioural sleep intervention Control conditions: wait-list control, sleep hygiene, placebo	Individual, group	2 to 12 weeks	1 to 26
Irwin, 2006[37]	MA	CBT: relaxation/biofeedback/hypnosis, behavioural interventions [sleep compression/restriction, paradoxical intention] Control	NR	NR	NR
Johnson, 2016[38]	MA	CBT-I Control conditions: wait-list control, treatment as usual, sleep education, behavioural placebo, mindfulness-based stress reduction	Individual, group, video or online-based	NR	13 to 52
Koffel, 2015[40]	MA	CBT-I: behavioural strategies (stimulus control, sleep restriction) and cognitive strategies (addressing dysfunctional beliefs about sleep) Control conditions: wait-list, treatment as usual, placebo	Group; community	More than one session	13.04 to 52
Montgomery, 2003[44]	MA	CBT: sleep hygiene, stimulus control, muscle relaxation, sleep restriction, cognitive therapy, education, imagery training Control conditions: wait-list control, placebo	Group, individual	NR	13 to 104
Seyfrett, 2016[47]	MA	CBT: sleep education, stimulus control, sleep restriction, relaxation, sleep hygiene, cognitive techniques Control conditions: wait-list control, Internet control, treatment as usual	Internet-based; home	Weekly	4 to 48
Tang, 2015[49]	MA	CBT-I: psychoeducation, sleep hygiene, stimulus control, sleep restriction, cognitive therapy, relaxation Control conditions: wait-list control, treatment as usual,	Face-to-face, phone or Internet, group, individual	3 to 7 sessions totalling average of 69 to 120 minutes over 60 days	13 to 52

Author, Year	Synthesis Type	Intervention and Comparator doses (mg)	Delivery Method; Setting	Frequency; Duration of Treatment	Length of Follow-Up Range, Weeks
		active control (sleep hygiene advice, healthy eating control, nutrition control)			
Van Straten, 2007[51]	MA	CBT: relaxation, sleep restriction, stimulus control, paradoxical intention, identifying and challenging dysfunctional thought Control conditions: wait-list control, no treatment, psychoeducation, placebo	Group, individual, phone, self-help	2 to 16 sessions	NR
Van Straten, 2009[93]	MA	CBT: Self-help, stimulus control, sleep restriction, cognitive therapy, sleep hygiene, relaxation, in-bed exercises Control conditions: Wait-list control	Written materials (books), audiotapes, videotapes, Internet + support through face-to-face, telephone, or email; Home (self-help) In-person	NR Weekly	17 to 43.5 NR
Ye, 2016[54]	MA	CBT: sleep hygiene education, cognitive restructuring, stimulus control, sleep restriction, relaxation therapy, hierarchy development, imagery training, scheduled pseudo desensitization, breathing control Control conditions: wait-list control, treatment as usual, Internet +email, Internet +telephone, telephone, Internet-based control	Internet	NR	4 to 52
Navarro-Bravo, 2015[56]	MA	CBT: sleep restriction, stimulus control, sleep education/hygiene Control conditions: placebo, wait-list control, stress management and wellness training, treatment as usual, sleep hygiene/education	NR	NR	5 to 8
Ballesio, 2017[62]	MA	CBT-I group, CBT-I individual, CBT-I self-help Control conditions: sleep hygiene, wait-list control, pharmacological, placebo, psychological, CBT self-help,	Group, individual, self-help	NR	NR
Bogdanov, 2017[65]	SR	CBT	NR	60 minutes	4 to 13

Author, Year	Synthesis Type	Intervention and Comparator doses (mg)	Delivery Method; Setting	Frequency; Duration of Treatment	Length of Follow-Up Range, Weeks
Brooks, 2014[66]	SR	CBT-I CBT-I vs. control (unspecified)	Individual, in-person	8 sessions 9 sessions; 6 sessions; 5 sessions	NR 26
Dickerson, 2014[73]	SR	CBT CBT vs. Control conditions: usual treatment, wait-list crossover, wait-list control, control, usual treatment	NR	Weekly NR	4 to 8 NR
Ishak, 2012[76]	SR	CBT vs. Control conditions: placebo, no treatment, unspecified, usual care CBT group vs. CBT individual: psychoeducation, sleep hygiene, stimulus control, sleep restriction, relaxation exercises, cognitive restructuring	NR Individual; group	NR Weekly; Weekly	14 to 52 4 to 24; 4 to 24
Taylor, 2014[82]	SR	CBT: Stimulus control, sleep restriction, relaxation therapy, cognitive therapy, image rehearsal therapy + CBT, medication withdrawal + CBT Control conditions: wait-list control, usual care, sleep hygiene, placebo control, hypnotic withdrawal, medication withdrawal	In-person	2 to 10 sessions	NR
Venables, 2014[90]	SR	Self-help CBT Professionally administered CBT Group CBT	Self-help; home Professionally administered Group	Video NR NR	NR
Wang, 2005[85]	SR	CBT: stimulus control, sleep restriction, cognitive therapy, sleep hygiene education, sleep scheduling vs. Control conditions: quasi-desensitization, self-monitoring control, sleep hygiene, wait-list control CBT: stimulus control, sleep restriction, sleep hygiene education vs. Single behavioural therapy: relaxation	NR	NR	12 to 104 24
CBT + Single Component (2 SR+MAs)					
Buscemi, 2005[30]	MA	CBT + individual behavioural components (relaxation): relaxation training, cognitive control, stimulus control, group relaxation, aggressive muscle relaxation, cognitive	NR	NR	NR

Author, Year	Synthesis Type	Intervention and Comparator doses (mg)	Delivery Method; Setting	Frequency; Duration of Treatment	Length of Follow-Up Range, Weeks
		distraction Single behavioural interventions(relaxation): progressive muscle relaxation, EMG bio feedback, group relaxation CBT: cognitive therapy, sleep restriction, stimulus control, sleep hygiene Placebo			
Yang, 2014[53]	MA	CBT + single components (relaxation): sleep hygiene, relaxation CD Control conditions: sleep hygiene, treatment as usual	NR	Daily (relaxation); 3 to 4 weekly (CBT)	4 to 8
Multi-Component CBT (5 SR+MAs,34 SRs)					
Buscemi, 2005[30]	MA	Multi-component CBT, paradoxical intention, sleep compression, stimulus control Placebo	NR	NR	NR
Ho, 2015[36]	MA	Multi-CBT: stimulus control, sleep restriction, sleep hygiene, relaxation, cognitive therapy Control conditions: wait-list control, routine care, no treatment	Self-help; home	NR	4 to 52
Trauer, 2015[50]	MA	Multi-CBT: cognitive therapy, stimulus control, sleep restriction, relaxation, sleep hygiene Control conditions: wait-list control, treatment as usual, sleep hygiene, sham, placebo	Group, remainder individually with aids such as telephone, audiocassettes, written material	NR	4 to 48
Zachariae, 2016[55]	MA	Multi-CBT: stimulus control, sleep hygiene, cognitive therapy, sleep restriction, relaxation technique Control conditions: wait-list control, treatment as usual, active control	Internet; home	NR	4 to 48
Okajima, 2011[57]	MA	Multi-CBT: sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, relaxation, paradoxical intention Control conditions: placebo, wait-list control, treatment as usual, sleep hygiene education	Individual, group	1 to 8 sessions	4 to 104

Author, Year	Synthesis Type	Intervention and Comparator doses (mg)	Delivery Method; Setting	Frequency; Duration of Treatment	Length of Follow-Up Range, Weeks
Wang, 2005[85]	SR	Multi-CBT: stimulus control, relaxation therapy, sleep education Control conditions: Stimulus control	NR	NR	4
Howell, 2014[75]	SR	Multi-CBT: sleep hygiene, sleep restriction, stimulus control, cognitive restructuring, relaxation therapies Control conditions: usual care, wait-list control, health eating and nutrition, sleep education and hygiene, no treatment	Individual	Weekly	8 to 74
McCurry, 2007[79]	SR	Multi-CBT: sleep restriction, education, stimulus control Multi-CBT vs. benzodiazepine drugs (temazepam, NR mg) + CBT Multi-CBT: sleep hygiene, relaxation, sleep compression, CBT, stimulus control vs. Control conditions: delayed treatment, wait-list control, placebo, stress management	Individual Group Individual	Weekly Weekly; NR Weekly	NR
Behavioural Therapy (2 SR+MAs)					
Ballesio, 2017[62]	MA	Group behavioural therapy Control conditions: placebo, psychological	Group	NR	NR
Hwang, 2016[61]	MA	Behavioural therapy Control conditions: unspecified	NR	NR	NR
Single Behavioural Intervention (3 SR+MAs, 7 SRs)					
Brasure, 2015[29]	MA	Sleep restriction Relaxation therapy Control conditions: wait-list control, no treatment, sleep hygiene/sleep re-education, passive control	Outpatient	NR	4 to 26 4
Buscemi, 2005[30]	MA	Autogenic training, breathing process training, EMG feedback training, group relaxation, hypnotic relaxation, progressive relaxation or relaxation Placebo	NR	NR	NR
Seda, 2015[46]	MA	Imagery rehearsal therapy Multi-component CBT: CBT (stimulus control, sleep	Face-to-face, group, self-help	1 to 8 sessions	Post-treatment NR

Author, Year	Synthesis Type	Intervention and Comparator doses (mg)	Delivery Method; Setting	Frequency; Duration of Treatment	Length of Follow-Up Range, Weeks
		restriction therapy) + imagery rehearsal therapy	Face-to-face, group, self-help; outpatient	1 to 8 sessions	
Bogdanov, 2017[65]	SR	Problem-solving therapy Control conditions: education only	Phone call	Fortnightly	NR
Brooks, 2014[66]	SR	Progressive relaxation training from psychologist Control conditions: NR	Individual	10 sessions	NR
Dickerson, 2014[73]	SR	EEG biofeedback Control conditions: wait-list control	NR	NR	NR
Hellström, 2011[74]	SR	Mental imagery Control conditions: usual care	In-person; in-patient	Daily	NR
McCurry, 2007[79]	SR	Sleep restriction therapy: nap sleep restriction therapy, sleep compression, sleep compression guidance Control conditions: sleep hygiene, placebo, wait-list control	Individual	Weekly	NR
Miller, 2014[81]	SR	Sleep restriction therapy Control conditions: relaxation therapy, wait-list control, sleep hygiene instructions	NR	NR	13 to 52
Tamrat, 2013[89]	SR	Relaxation techniques, audiotape guided imagery, relaxation tapes Control conditions: usual care, solitary activity, baseline	In-patient	Nightly	NR
Multi-Component Behavioural Intervention (1 SR+MA)					
Brasure, 2015[29]	MA	Multi-component behavioural intervention or brief behavioural therapy Control conditions: information control, Placebo	Outpatient	NR	4
Mindfulness Techniques (1 SR+MA)					
Gong, 2016[34]	MA	Mindfulness-based stress reduction, mindfulness meditation, mindfulness-based therapy for insomnia Control conditions: wait-list control, sleep hygiene education, self-monitoring condition	NR	NR	6 to 8
Combination Therapy (1 SR+MA, 1 SR)					
Buscemi,	MA	Triazolam (0.25 mg); Temazepam (7.5 mg to 30 mg)	NR	NR	NR

Author, Year	Synthesis Type	Intervention and Comparator doses (mg)	Delivery Method; Setting	Frequency; Duration of Treatment	Length of Follow-Up Range, Weeks
2005[30]		CBT Placebo			
Chiesa, 2009[88]	SR	Pharmacotherapy Mindfulness	NR	NR	NR

CBT = cognitive behavioural therapy; CBT-I = cognitive behavioural therapy for insomnia; CD = compact disc; EEG = electroencephalography; EMG = electromyography; MA = meta-analysis; NR = not reported; SR = systematic review; SR+MA = systematic review plus meta-analysis; vs. = versus.

Appendix 8: AMSTAR Results

Table 75: Results of AMSTAR 2 Appraisal for Systematic Reviews With Meta-Analyses

Author, Year	1. PICO Components	2. A Priori Design	3. Rationale for Study Selection	4. Literature Search	5. Duplicate Selection	6. Duplicate Abstraction	7. List of Excluded Studies	8. Description of Included Studies	9a. RoB Assessment in RCTs	9b. RoB Assessment in Non-Randomized Studies	10. Funding Sources	11. Appropriate MA Methods	12. Used RoB in MA	13. Used RoB in Interpreting Results	14. Discussion of Heterogeneity	15. Publication Bias	16. Conflict of Interest	Overall Rating
Ballesio, 2017[62]	Y	Y	Y	Partial Y	Y	Y	Y	Y	Y	Includes only RCTs	Y	Y	Y	Y	Y	Y	Y	High
Brasure, 2015[29]	Y	Y	Y	Y	Y	N	Y	Y	Y	Includes only RCTs	Y	Y	Y	Y	Y	N	Y	High
Buscemi, 2004[31]	Y	Partial Y	Y	Y	Y	Y	Y	Y	Partial Y	Includes only RCTs	Y	Y	N	Y	Y	Y	Y	High
Buscemi, 2005[30]	Y	N	N	Partial Y	Y	N	Y	Partial Y	Y	Includes only RCTs	Y	Y	Y	N	Y	Y	Y	High
Cheng, 2012[32]	Y	N	N	Y	N	N	N	Y	Y	Includes only RCTs	N	Y	Y	Y	N	N	Y	Low
Ferracioli, 2013[33]	Y	N	N	N	Y	N	N	Partial Y	N	Includes only RCTs	N	Y	N	N	Y	Y	Y	Critically Low
Gong, 2016[34]	Y	N	N	Partial Y	Y	Y	N	Partial Y	Y	Includes only RCTs	N	Y	N	N	Y	Y	Y	Low
Ho, 2015[36]	Y	N	N	Partial Y	Y	Y	N	Y	Y	Includes only RCTs	N	Y	Y	Y	N	Y	Y	Low
Ho, 2016[35]	Y	N	Y	Partial Y	Y	Y	N	Partial Y	Y	Includes only RCTs	N	Y	N	N	N	N	Y	Low
Hwang, 2016[61]	Y	N	N	Partial Y	Y	Y	N	N	Partial Y	N	N	Y	N	N	N	Y	N	Critically Low

Author, Year	1. PICO Components	2. A Priori Design	3. Rationale for Study Selection	4. Literature Search	5. Duplicate Selection	6. Duplicate Abstraction	7. List of Excluded Studies	8. Description of Included Studies	9a. RoB Assessment in RCTs	9b. RoB Assessment in Non-Randomized Studies	10. Funding Sources	11. Appropriate MA Methods	12. Used RoB in MA	13. Used RoB in Interpreting Results	14. Discussion of Heterogeneity	15. Publication Bias	16. Conflict of Interest	Overall Rating
Irwin, 2006[37]	Y	N	N	Partial Y	N	N	N	Partial Y	N	Includes only RCTs	N	Y	N	N	Y	N	N	Critically Low
Johnson, 2016[38]	Y	Y	Y	Y	Y	Y	N	Partial Y	Y	Includes only RCTs	N	Y	N	Y	Y	Y	Y	Moderate
Kishi, 2015[39]	N	N	N	Partial Y	N	Y	N	Partial Y	Y	Includes only RCTs	N	Y	Y	Y	Y	Y	Y	Moderate
Koffel, 2015[40]	N	N	Y	Partial Y	N	N	N	N	Y	Includes only RCTs	Y	N	N	N	N	Y	N	Critically Low
Kuriyama, 2017[41]	N	N	N	Y	Y	Y	N	Y	Y	Includes only RCTs	N	Y	Y	Y	N	N	Y	Moderate
Yuan, 2010[59]	Y	N	N	Y	Y	Y	N	Partial Y	Y	Includes only RCTs	N	Y	N	N	Y	N	Y	Critically Low
Liu, 2017[42]	Y	Partial Y	N	Partial Y	Y	N	N	Y	Y	Includes only RCTs	N	Y	N	N	Y	Y	Y	Critically Low
McCleery, 2016[43]	Y	Partial Y	Y	Partial Y	Y	Y	Y	Partial Y	Partial Y	Includes only RCTs	N	Y	Y	Y	Y	N	Y	High
Montgomery, 2003[44]	Y	Y	N	Y	Y	Y	Y	Y	Y	Includes only RCTs	N	Y	N	Y	Y	Y	Y	High
Navarro-Bravo, 2015[56]	Y	N	N	Partial Y	Y	Y	N	Partial Y	Y	Includes only RCTs	N	Y	N	N	Y	Y	Y	Moderate
Okajima, 2011[57]	Y	N	N	N	N	N	N	Y	N	Includes only RCTs	N	N	N	N	N	Y	N	Critically Low
Sateia, 2017[45]	Y	N	N	N	Y	N	N	Partial Y	Partial Y	Y	Y	Y	N	Y	N	Y	Y	Critically Low

Author, Year	1. PICO Components	2. A Priori Design	3. Rationale for Study Selection	4. Literature Search	5. Duplicate Selection	6. Duplicate Abstraction	7. List of Excluded Studies	8. Description of Included Studies	9a. RoB Assessment in RCTs	9b. RoB Assessment in Non-Randomized Studies	10. Funding Sources	11. Appropriate MA Methods	12. Used RoB in MA	13. Used RoB in Interpreting Results	14. Discussion of Heterogeneity	15. Publication Bias	16. Conflict of Interest	Overall Rating
Seda, 2015[46]	Y	N	N	Partial Y	N	N	N	Partial Y	N	Includes only RCTs	N	Y	N	N	Y	Y	N	Low
Seyffert, 2016[47]	Y	Partial Y	N	Y	N	Y	N	Partial Y	Y	Includes only RCTs	Y	Y	Y	Y	N	Y	Y	Low
Soldatos, 1999[48]	Y	N	N	N	N	N	Y	Partial Y	N	N	Y	Y	N	N	N	N	N	Critically Low
Tang, 2015[49]	Y	Y	N	Partial Y	Y	Y	N	Y	Y	Includes only RCTs	N	Y	N	Y	Y	Y	Y	Moderate
Trauer, 2015[50]	Y	Y	N	Y	Y	Y	N	Partial Y	Y	Includes only RCTs	Y	Y	Y	Y	Y	Y	Y	Moderate
van Straten, 2007[51]	Y	N	N	Y	Y	Y	N	Y	Y	Includes only RCTs	Y	N	Y	Y	Y	Y	Y	Low
van Straten, 2009[93]	Y	N	N	Partial Y	N	N	N	Y	Partial Y	Includes only RCTs	N	Y	N	Y	Y	Y	N	Moderate
Xu, 2015[52]	Y	N	N	Partial Y	Y	Y	N	Partial Y	Y	Includes only RCTs	N	Y	N	N	Y	Y	Y	Moderate
Yang, 2014[53]	Y	Y	N	Partial Y	Y	Y	N	Y	Partial Y	Partial Y	N	Y	N	Y	Y	Y	Y	Moderate
Ye, 2016[54]	Y	Partial Y	N	Partial Y	Y	Y	Y	Partial Y	Partial Y	Includes only RCTs	Y	Y	N	Y	Y	Y	Y	Moderate
Lee, NA [58]	Y	N	N	Partial Y	Y	Y	N	Partial Y	Y	Includes only RCTs	Y	Y	N	N	Y	Y	N	Low
Zachariae, 2016[55]	Y	Y	N	Partial Y	Y	N	Y	Partial Y	Y	Includes only RCTs	N	Y	Y	Y	Y	Y	Y	Moderate

Author, Year	1. PICO Components	2. A Priori Design	3. Rationale for Study Selection	4. Literature Search	5. Duplicate Selection	6. Duplicate Abstraction	7. List of Excluded Studies	8. Description of Included Studies	9a. RoB Assessment in RCTs	9b. RoB Assessment in Non-Randomized Studies	10. Funding Sources	11. Appropriate MA Methods	12. Used RoB in MA	13. Used RoB in Interpreting Results	14. Discussion of Heterogeneity	15. Publication Bias	16. Conflict of Interest	Overall Rating
Zhang, 2016[60]	Y	N	N	Partial Y	N	Y	N	Partial Y	Y	Includes only RCTs	N	Y	N	N	N	Y	Y	Critically Low

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; MA = meta-analysis; N = no; PICO = population, intervention, comparison, outcome; RCT = randomized controlled trial; RoB = risk of bias; Y = yes.

Table 76: Results of AMSTAR 2 Appraisal for Systematic Reviews Without Meta-Analysis

Author, Year	1. PICO Components	2. A Priori Design	3. Rationale for Study Selection	4. Literature Search	5. Duplicate Selection	6. Duplicate Abstraction	7. List of Excluded Studies	8. Description of Included Studies	9a. RoB Assessment in Rcts	9b. RoB Assessment in Non-Randomized Studies	10. Funding Sources	11. Appropriate MA Methods	12. Used RoB in MA	13. Used RoB in Interpreting Results	14. Discussion of Heterogeneity	15. Publication Bias	16. Conflict of Interest	Overall Rating
Anderson, 2014[63]	N	N	N	Partial Y	N	N	N	Partial Y	N	N	N	No MA	No MA	N	N	No MA	N	Critically Low
Bellon, 2006[64]	N	N	N	Partial Y	N	N	N	Partial Y	N	N	N	No MA	No MA	N	N	No MA	N	Critically Low
Bogdanov, 2017[65]	N	N	N	Partial Y	N	N	N	Partial Y	Y	Y	N	No MA	No MA	N	N	No MA	Y	Low
Brooks, 2014[66]	N	N	N	Partial Y	N	N	N	Partial Y	Partial Y	Partial Y	N	No MA	No MA	Y	N	No MA	Y	Low
Chase, 1997[67]	N	N	N	N	N	N	N	Partial Y	N	N	N	No MA	No MA	N	N	No MA	N	Critically Low
Chiesa, 2009[88]	Y	N	Y	Partial Y	N	N	N	Partial Y	Y	Y	N	No MA	No MA	N	N	No MA	N	Low
Cimolai, 2007[68]	N	N	N	N	N	N	N	Partial Y	N	N	N	No MA	No MA	N	N	No MA	Y	Critically Low
Citrome, 2014[69]	N	N	N	Partial Y	N	N	N	Partial Y	N	N	N	No MA	No MA	N	No MA	No MA	Y	Critically Low
Coe, 2012[70]	N	N	N	Partial Y	N	N	N	Partial Y	N	N	N	No MA	No MA	N	N	No MA	Y	Critically Low
Costello, 2014[71]	Y	N	Y	Partial Y	Y	N	N	Y	Y	Includes only RCTs	Y	No MA	No MA	Y	Y	No MA	Y	Moderate
Culpepper, 2015[72]	Y	Partial	Y	Partial	N	N	N	Partial	N	Includes only	N	No	No	N	N	No	Y	Critically

Author, Year	1. PICO Components	2. A Priori Design	3. Rationale for Study Selection	4. Literature Search	5. Duplicate Selection	6. Duplicate Abstraction	7. List of Excluded Studies	8. Description of Included Studies	9a. RoB Assessment in Rcts	9b. RoB Assessment in Non-Randomized Studies	10. Funding Sources	11. Appropriate MA Methods	12. Used RoB in MA	13. Used RoB in Interpreting Results	14. Discussion of Heterogeneity	15. Publication Bias	16. Conflict of Interest	Overall Rating
		Y		Y				Y		RCTs		MA	MA			MA		Low
Dickerson, 2014[73]	Y	Partial Y	Y	Partial Y	Y	Y	Partial Y	Partial Y	Partial Y	Includes only RCTs	N	No MA	No MA	Y	Y	No MA	Y	High
Hellström, 2011[74]	N	Partial Y	N	Partial Y	N	N	Y	Y	Y	Includes only RCTs	N	No MA	No MA	Y	N	No MA	N	Moderate
Howell, 2014[75]	N	Partial Y	N	Partial Y	Y	N	N	Partial Y	Y	Partial Y	Y	No MA	No MA	N	N	No MA	Y	Moderate
Ishak, 2012[76]	N	Partial Y	N	Partial Y	Y	N	N	Partial Y	N	N	N	No MA	No MA	N	N	No MA	Y	Low
Kolla, 2011[77]	N	N	N	Partial Y	N	N	N	Partial Y	N	N	N	No MA	No MA	N	N	No MA	N	Critically Low
Mayers, 2005[78]	Y	N	Y	Partial Y	N	N	N	Partial Y	N	Includes only RCTs	N	No MA	No MA	N	N	No MA	N	Critically Low
McCurry, 2007[79]	Y	N	N	N	N	Y	N	Partial Y	N	N	N	No MA	No MA	N	N	No MA	N	Critically Low
Mendelson, 2005[80]	N	N	N	Partial Y	N	N	N	Partial Y	N	N	N	No MA	No MA	N	N	No MA	N	Critically Low
Miller, 2014[81]	Y	N	Y	Partial Y	N	N	Y	Partial Y	Y	Y	N	No MA	No MA	Y	N	No MA	Y	High
Swainston Harrison, 2005[91]	Y	Partial Y	Y	Partial Y	N	N	N	Partial Y	N	N	N	No MA	No MA	N	N	No MA	N	Critically Low
Tamrat, 2013[89]	Y	Partial	N	N	Y	Y	N	Partial	Y	Y	N	No	No	Y	Y	No	Y	Low

Author, Year	1. PICO Components	2. A Priori Design	3. Rationale for Study Selection	4. Literature Search	5. Duplicate Selection	6. Duplicate Abstraction	7. List of Excluded Studies	8. Description of Included Studies	9a. RoB Assessment in Rcts	9b. RoB Assessment in Non-Randomized Studies	10. Funding Sources	11. Appropriate MA Methods	12. Used RoB in MA	13. Used RoB in Interpreting Results	14. Discussion of Heterogeneity	15. Publication Bias	16. Conflict of Interest	Overall Rating
		Y						Y				MA	MA			MA		
Taylor, 2014[82]	N	N	N	Partial Y	N	N	N	Partial Y	N	Includes only RCTs	N	No MA	No MA	N	N	N	Y	Critically Low
Vande Griend, 2012[83]	N	N	N	Partial Y	N	N	N	Partial Y	N	Includes only RCTs	N	No MA	No MA	N	N	N	Y	Critically Low
Venables, 2014[90]	N	N	N	Partial Y	N	N	N	Y	N	N	N	No MA	No MA	N	N	No MA	N	Critically Low
Vural, 2014[84]	Y	N	N	Partial Y	N	N	Partial Y	N	N	N	N	No MA	No MA	N	N	No MA	Y	Critically Low
Wang, 2005[85]	Y	Partial Y	Y	Partial Y	Y	Y	N	Partial Y	Partial Y	Includes only RCTs	N	No MA	No MA	Y	Y	No MA	N	Moderate
Wine, 2009[86]	N	N	N	Partial Y	N	N	N	Partial Y	N	N	N	No MA	No MA	N	N	No MA	N	Critically Low
Yeung, 2015[87]	Y	Partial Y	N	Y	Y	Y	N	Y	Y	Includes only RCTs	Y	No MA	No MA	Y	Y	No MA	Y	Moderate

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; MA = meta-analysis; N = no; PICO = population, intervention, comparison, outcome; RCT = randomized controlled trial; RoB = risk of bias; Y = yes.

Appendix 9: Tables of Results

Table 77: Detailed Results for Sleep Onset Latency / Sleep Latency

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Benzodiazepine Drugs vs. Inactive Controls; 3 SR+MAs						
Buscemi, 2005[30] MA	High	Flurazepam: 317 Placebo: 215	10	sleep diary, PSG	Mean difference (95% CI): **–23.21 (–34.26 to –12.16)** I^2: 51.8%	
Buscemi, 2005[30] MA	High	Temazepam: 128 Placebo: 78	4	sleep diary, PSG	Mean difference (95% CI): –11.61 (–23.64 to 0.42) I^2: 84%	
Sateia, 2017[45] MA	Critically Low	Temazepam: 36 Placebo: 36	2	subjective measure	Mean difference (95% CI): **–20.06 (–39.05 to –1.07)** I^2: 68%	
Buscemi, 2005[30] MA	High	Triazolam: 290 Placebo: 249	8	sleep diary, PSG	Mean difference (95% CI): **–19.69 (–28.36 to –11.01)** I^2: 69.2%	
Soldatos, 1999[48] MA	Critically Low	Triazolam: NR Placebo: NR	28	sleep laboratory	Mean difference (95% CI): **–15.5 (–19.5 to –11.4)** I^2: NR	
Non-Benzodiazepines vs. Inactive Controls; 4 SR+MAs, 3 SRs						
Brasure, 2015[29] MA	High	Zolpidem: 181 Placebo: 192	4	subjective sleep latency, min	Mean difference (95% CI): **–14.95 (–22.10 to –7.80)** I^2: 0%	
		Zolpidem: 177 Placebo: 178	2	subjective report, min	Mean difference (95% CI): **–14.8 (–23.41 to –6.19)** I^2: 0%	
Buscemi, 2005[30]	High	Zolpidem: 997 Placebo: 808	17	sleep diary, PSG	Mean difference (95% CI): **–12.75 (–16.42 to –9.08)** I^2: 4.5%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
MA		Zopiclone: 178 Placebo: 178	5	sleep diary, PSG	Mean difference (95% CI): **–30.91 (–49.37 to –12.44)** I^2: 73.9%	
Sateia, 2017[45] MA	Critically Low	Zolpidem: 181 Placebo: 185	5	PSG	Mean difference (95% CI): **–11.65 (–19.15 to –4.15)** I^2: 78%	
		Zolpidem: 543 Placebo: 558	10	subjective measure	Mean difference (95% CI): **–19.55 (–24.90 to –14.20)** I^2: 95%	
Soldatos, 1999[48] MA	Critically Low	Zolpidem: NR Placebo: NR	29	sleep laboratory	Mean difference (95% CI): **–17.6 (–23.2 to –12)** I^2: NR	
		Zopiclone: NR Placebo: NR	14	sleep laboratory	Mean difference (95% CI): **–19.1 (–26.7 to –11.5)** I^2: NR	
Mayers, 2005[78] SR	Critically Low	Zolpidem Placebo Total sample: 306	1	NR		**Significant decrease** in sleep latency compared with placebo **(*P* < 0.05).**
Mendelson, 2005[80] SR	Critically Low	Zolpidem Placebo Total sample: 306	1	self-reported		The zolpidem group demonstrated **significant improvement** compared with placebo for sleep latency **(*P* = 0.037).**
Non-Benzodiazepine Drugs vs. Other Pharmacological Interventions; 1 SR						
Swainston Harrison, 2005[91] SR	Critically Low	Zolpidem Triazolam Total sample: 22	1	NR	Change in outcome (*P* value): –23 mins vs. –15 mins (*P* = NS)	NR
Suvorexant vs. Inactive Controls; 3 SR+MAs, 1 SR						
Kishi, 2015[39] MA	Moderate	Suvorexant: 936 Placebo: 953	3	sleep diary	Mean difference (95% CI): **–7.62 (–11.03 to –4.21)** I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
		Suvorexant: 349 Placebo: 659	3	PSG	Mean difference (95% CI): **–10.82 (–16.72 to –4.93)** I^2: 35%	
Kuriyama, 2017[41] MA	Moderate	Suvorexant: NR Placebo: NR	3	sleep diary, PSG	Mean difference (95% CI): **–9.45 (–13.26 to –5.65)** I^2: 13.3%	
		Suvorexant: NR Placebo: NR	3	PSG	Mean difference (95% CI): –6.39 (–12.85 to 0.07) I^2: 67.1%	
Brasure, 2015[29] MA	High	Suvorexant: 425 Placebo: 664	2	subjective report	Mean change (95% CI): **–5.97 (–10.01 to –1.92)** I^2: 0%	
Citrome, 2014[69] SR	Critically Low	Suvorexant 15 mg, 20 mg: 425 Placebo: 688	2	sleep diary	Change in outcome (least squares mean difference (*P* value)): **–5.9 mins (*P* < 0.01)** Proportion of respondents with > 15% improvement: 69.9% vs. 66%; NNT: 26 (*P* = NS)	Suvorexant was **superior to placebo** for sleep latency both through patient-assessed and PSG means.
		Suvorexant 15 mg, 20 mg: 343 Placebo: 585	2	PSG	Change in outcome (least squares mean difference (*P* value)): –4.6 mins (*P* = NS)	
		Suvorexant 30 mg, 40 mg: 688 Placebo: 664	2	sleep diary	Change in outcome (least squares mean difference (*P* value)): **–10.8 mins (*P* < 0.001)** Proportion of respondents with > 15% improvement: 76.5% vs. 66%; NNT 10 (95% CI, 7 to 18)	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
		Suvorexant 30 mg, 40 mg: 590 Placebo: 585	2	PSG	Change in outcome (least squares mean difference (*P* value)): **–6.4 mins (*P* < 0.01)**	
Antidepressant Drugs vs. Inactive Controls; 3 SR+MAs, 4 SRs						
Buscemi, 2005[30] MA	High	Doxepin 25 mg: 40 Placebo: 40	3	sleep diary, PSG	Mean difference (95% CI): **–6.65 (–10.68 to –2.63)** I^2: 49.3%	
Sateia, 2017[45] MA	Critically Low	Doxepin 3 mg: 282 Placebo: 276	4	PSG	Mean difference (95% CI): –2.3 (–6.22 to 1.62) I^2: 0%	
		Doxepin 3 mg: 148 Placebo: 143	2	subjective measure	Mean difference (95% CI): –9.35 (–21.89 to 3.19) I^2: 55%	
		Doxepin 6 mg: 209 Placebo: 206	3	PSG	Mean difference (95% CI): **–5.29 (–9.25 to –1.34)** I^2: 0%	
Yuan, 2010[59] MA	Low	Doxepin 1 mg: 140 Placebo: 139	2	NR	Mean difference (95% CI): –0.85 (–5.82 to 4.13) I^2: NR	
		Doxepin 3 mg: 140 Placebo: 139	2	NR	Mean difference (95% CI): 0.37 (–0.66 to 1.40) I^2: NR	
		Doxepin 6 mg: 141 Placebo: 139	2	NR	Mean difference (95% CI): 0.37 (–0.66 to 1.40) I^2: NR	
		Doxepin 25 mg: 30 Placebo: 30	2	NR	Mean difference (95% CI): **–8.69 (–13.72 to –3.67)** I^2: NR	
Buscemi, 2005[30] MA	High	Trazodone 50 mg, 150 mg to 250 mg: 100 Placebo: 108	2	sleep diary, PSG	Mean difference (95% CI): **–12.21 (–22.26 to –2.15)** I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Mayers, 2005[78] SR	Critically Low	Doxepin Placebo Total sample: 10	1	NR		Doxepin **significantly improved** sleep latency compared with placebo (*P* value not reported).
Vande Griend, 2012[83] SR	Critically Low	Doxepin: NR Placebo: NR	6	PSG questionnaire (7-point Likert scale)		Mixed results: PSG and questionnaire data showed **significant improvement** compared with placebo in some trials (***P* < 0.05**); non-significant change found in other trials.
Yeung, 2015[87] SR	Moderate	Doxepin: NR Placebo: NR	NR	self-report		Adults < 65 years: 3 mg doxepin had negative impact on sleep latency in short-term (1 to 2 nights) results; 6 mg doxepin had positive impact on sleep latency in the short-term (1 to 2 nights). Adults > 65 years: 3 mg doxepin had negative impact on sleep latency in both short- and long-term (4 weeks) treatment; 6 mg doxepin had positive results in the short-term but negative results in the long-term.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
		Doxepin: NR Placebo: NR	NR	PSG		Adults < 65 years: 3 mg and 6 mg had mixed results in the short-term and negative results in the long-term. Adults > 65 years: 3 mg doxepin had mixed results in the short-term and negative results in the long-term; 6 mg doxepin had negative results in the short-term, no assessment of long-term effect.
Mayers, 2005[78] SR	Critically Low	Trazodone Placebo Total sample: 323	2	NR		**Significant decrease** in sleep latency for one trial **(*P* < 0.05)**, almost significant change in the other (*P* = 0.06).
Mendelson, 2005[80] SR	Critically Low	Trazodone Placebo; unspecified control Total sample: 306	1	self-reported		Relative to placebo, patients reported **significant improvement** during week 1 **(*P* < 0.02)**; during week 2, the trazodone group did not differ significantly from the placebo group.
		Trazodone placebo; unspecified control Total sample: 29	2	PSG		No significant changes in sleep latency found between groups.
		Trazodone: 39 No comparator (pre- / post-intervention)	5	PSG		Mixed results: 3 trials found **significant improvement** compared with baseline **(*P* < 0.05)**; 2 trials found non-significant change.
Vande Griend, 2012[83] SR	Critically Low	Trazodone: NR Placebo: NR	3	sleep diaries; PSG		No significant difference found between groups.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Antidepressant Drugs vs. Other Pharmacological Interventions; 3 SRs						
Mayers, 2005[78] SR	Critically Low	Trazodone Zolpidem Total sample: 306	1	NR		Sleep latency was **significantly shorter** for the zolpidem vs. placebo group compared with trazodone vs. placebo group **(*P* = 0.037).**
Mendelson, 2005[80] SR	Critically Low	Trazodone Zolpidem Total sample: 306	1	self-reported		Sleep latency for zolpidem compared with placebo was **significantly shorter** than that for trazodone compared with placebo **(*P* < 0.037).**
Vande Griend, 2012[83] SR	Critically Low	Trazodone Zolpidem Total sample: 306	1	daily questionnaire		Sleep latency was **significantly shorter** for zolpidem compared with placebo **(*P* < 0.005)** but not for trazodone compared with placebo; no significant difference between zolpidem and trazodone.
Antipsychotic Drugs vs. Inactive Controls; 3 SRs						
Anderson, 2014[63] SR	Critically Low	Quetiapine No comparator (pre- / post-intervention) Total sample: 70	2	PSG; Spiegel Sleep Questionnaire	Change in outcome (*P* value): 24.2 ± 19.0 mins (*P* = NS);	Improvement in Spiegel Sleep Questionnaire score (*P* value not reported).
		Quetiapine Placebo; no therapy Total sample: 52	2	PSG or actigraphy	Change in outcome (*P* value): 66.5 ± 51.2 mins vs. 47.4 ± 30.4 min (*P* = NS); **15.6 ± 18.1 min vs. 24.5 ± 30.2 min (*P* < 0.05)**	
Coe, 2014[70] SR	Critically Low	Quetiapine: 8 Placebo: 8	1	patient-recorded sleep logs	Change in outcome (*P* value): –96.16 mins vs. –23.72 mins (*P* = 0.07)	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Wine, 2009[86] SR	Critically Low	Quetiapine: 32 No comparator (pre- / post-intervention)	2	NR	Change in outcome (*P* value): 22 ± 17 mins vs. 24 ± 19 mins (*P* = NS); **82 ± 65 mins vs. 29 ± 23 mins (*P* < 0.05)**	Significant reduction in sleep latency scores compared with baseline with quetiapine use.
Melatonin vs. Inactive Controls; 4 SR+MAs, 3 SRs						
Buscemi, 2005[30] MA	High	Melatonin: 103 Placebo: 103	8	sleep diary, PSG	Mean difference (95% CI): **–8.25 (–14.45 to –2.04)** I^2: 44.2%	
Buscemi, 2004[31] MA	High	Melatonin: 178 Placebo: 167	12	NR	Mean difference (95% CI): **–10.66 (–17.61 to –3.72)** I^2: 81.5%	
Ferracioli-Oda, 2013[33] MA	Critically Low	Melatonin: NR Placebo: NR	8	PSG or actigraphy	Mean difference (95% CI): **5.5 (2.29 to 7.81)** I^2: NR	
Lee, NA[58] MA	Critically Low	Melatonin: NR Placebo: NR	12	sleep diary, PSG, or actigraphy	Mean difference (95% CI): **–3.71 (–6.78 to –0.63)** I^2: 39%	
Bellon, 2006[64] SR	Critically Low	Melatonin: NR Placebo: NR	13	subjective PSG actigraphy		Adults: 3 studies **significant improvement (*P* < 0.05);** 1 study non-significant improvement; 1 study improved subjectively and non-significant change on PSG. Elderly: 2 studies non-significant improvement; 2 studies no change; 1 study **significant improvement (*P* < 0.05).** Schizophrenia, dementia, and medically ill patients: 3 studies, non-significant improvement.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Culpepper, 2015[72] SR	Critically Low	Melatonin Placebo Total sample: 772	3	PSG actigraphy sleep diary		No significant difference between groups (melatonin vs. placebo).
Vural, 2014[84] SR	Critically Low	Melatonin Control Total sample: 14	1	NR		**Significant decrease** in sleep latency with morning and nighttime melatonin doses; **significant decrease** in sleep latency to 10 min of persistent sleep with early and continuous melatonin doses.
Diphenhydramine vs. Inactive Controls; 1 SR+MAs, 2 SRs						
Sateia, 2017[45] MA	Critically Low	Diphenhydramine: 79 patients Placebo: 84 patients	2	subjective measure	Mean difference (95% CI): –2.47 (–8.17 to 3.23) I^2: 0%	
Culpepper, 2015[72] Systematic Review	Critically Low	Diphenhydramine Placebo Total sample: 226	3	sleep diary	Change in outcome (*P* value): 34.2 *vs.* 36.8 mins (*P* = NS); 21.6 *vs.* 23.8 mins (*P* = NS); **138.5 vs. 99.9 mins (*P* < 0.05)**	
Vande Griend, 2012[83] SR	Critically Low	Diphenhydramine Placebo Total sample: 332	4	sleep diaries questionnaire PSG		Overall, the outcomes analyzed from all 4 trials provided mixed results, with the majority not being statistically different than placebo (*P* > 0.05); 3 studies found no difference compared with placebo, and 2 studies found the drug was **superior to placebo.**

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Cognitive Behavioural Interventions vs. Inactive Controls; 18 SR+MAs, 7 SRs						
Brasure, 2015[29] **CBT** MA	High	CBT-I: 626 Sham treatment/ placebo, wait-list control, no treatment, or sleep hygiene/sleep education: 620	15	subjective report	Mean difference (95% CI): **–12.7 (–18.23 to –7.18)** I^2: 78%	
		CBT-I: 108 (older adults) Placebo, wait-list control, no treatment, or sleep hygiene/sleep education: 83	3	subjective report	Mean difference (95% CI): **–9.98 (–16.48 to –3.48)** I^2: 0%	
		CBT-I: 61 (adults with chronic pain) Passive control (placebo or sham treatment or wait-list): 61	3	subjective report	Mean difference (95% CI): **–26.5 (–43.25 to –9.75)** I^2:77%	
Cheng, 2012[32] **CBT** MA	Low	CBT: sleep hygiene, stimulus control, relaxation training, sleep restriction, cognitive restructuring: NR Wait-list control: NR	4	sleep diary	Standardized mean difference (95% CI): **–0.55 (–0.80 to –0.30)** I^2: 0%	
Ho, 2016[35] **CBT** MA	Low	CBT: image rehearsal therapy, exposure, re-scripting and relaxation therapy, mind-body bridging, behavioural sleep intervention: NR Wait-list control; sleep hygiene: NR	4	sleep diary	Standardized mean difference (95% CI): **–0.83 (–1.19 to –0.47)** I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Irwin, 2006[37] **CBT** MA	Critically Low	CBT: relaxation, biofeedback, hypnosis, sleep compression/ restriction, paradoxical intention: NR Control: NR	21	self-report	Cohen's *d* (95% CI): **–0.52 (–0.68 to –0.82)** Q-statistic: 74.66	
Johnson, 2016[38] **CBT** MA	Moderate	CBT-I with both cognitive and behavioural components: 423 Wait-list control, treatment as usual, sleep education, behavioural placebo, mindfulness-based stress reduction: 297	8	sleep diary	Cohen's *d* (95% CI): **0.27 (0.11 to 0.44)** I^2: 0.2%	
Koffel, 2015[40] **CBT** MA	Critically Low	Group CBT-I: stimulus control, sleep restriction, and addressing dysfunctional beliefs about sleep: NR Wait-list, treatment as usual, placebo: NR	6	sleep diary	Mean effect size (95% CI): **0.47 (0.27 to 0.66)** I^2: NR	
Montgomery, 2003[44] **CBT** MA	High	CBT: sleep hygiene, stimulus control, muscle relaxation, sleep restriction, cognitive therapy, education, imagery training: 86 Wait-list control, placebo: 49	3	sleep Diary	Mean difference (95% CI): **–3 (–8.92 to 2.92)** I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Navarro-Bravo, 2015[56] **CBT** MA	Moderate	CBT: sleep restriction, stimulus control, sleep education/hygiene: NR Placebo, wait-list control, stress management and wellness training, treatment as usual, sleep hygiene/education: NR	7	sleep diary; actigraphy; sleep evaluation (4-item questionnaire);	Cohen's *d* (95% CI): **–0.46 (–0.76 to –0.15)** Chi square:19.88; 0.003	
Seyffert, 2016[47] **CBT** MA	Low	Internet-based CBT: sleep education, stimulus control, sleep restriction, relaxation, sleep hygiene, cognitive techniques: NR Wait-list control, Internet control, treatment as usual: NR	7	sleep diary	Mean difference (95% CI): **–10.68 (–16.00 to –5.37)** I^2: 4.3%	
van Straten, 2007[51] **CBT** MA	Low	CBT: relaxation, sleep restriction, stimulus control, paradoxical intention, identifying and challenging dysfunctional thoughts: NR Wait-list control, no treatment, placebo, psychoeducation: NR	108	sleep diary	Hedges' *g* (95% CI): **0.57 (0.50 to 0.65)** I^2: 48%	
van Straten, 2009[93] **CBT** **MA**	Moderate	CBT (self-help): stimulus control, sleep restriction, cognitive therapy, sleep hygiene, relaxation, in-bed exercises: NR Waiting list: NR	8	sleep diary	Cohen's *d* (95% CI): **0.29 (0.15 to 0.43)** I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Ye, 2016[54] **CBT** MA	Moderate	CBT: sleep hygiene education, cognitive restructuring, stimulus control, sleep restriction, relaxation therapy, hierarchy development, imagery training, scheduled pseudo desensitization, breathing control: 1,006 Wait-list control, treatment as usual, Internet + email, Internet + telephone, telephone, Internet-based control: 1,004	15	NR	Mean difference (95% CI): **–18.41 (–23.21 to 13.60)** I^2: 62%	
Brooks, 2014[66] **CBT** SR	Low	CBT-I (unspecified) Control (unspecified) Total sample: 60	1	daily sleep diary; PSQI; actigraphy		Improved self-reported sleep latency maintained for 6 months post-treatment; not corroborated by actigraphy.
Ishak, 2012[76] **CBT** SR	Low	CBT (unspecified) Placebo, no treatment, usual care Total sample: 209	1	SF-36		**Significant reductions** in sleep latency for CBT compared with placebo **(*P* < 0.01).**
Dickerson, 2014[73] **CBT** SR	High	CBT (unspecified): Control: usual treatment, wait-list crossover, wait-list control, control, usual treatment Total sample: 150	1	actigraphy	Mean change (95% CI): **–0.42 (–0.80 to –0.01)**	CBT moderate effect in decreasing insomnia symptoms.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Venables, 2014[90] CBT SR	Critically Low	Group CBT: 660 No comparator (pre- / post-intervention)	8	NR		The group CBT studies obtained improvements in all sleep parameters; group-delivered CBT sessions may be slightly more effective than individual sessions.
		Professionally administered CBT: 615 No comparator (pre- / post-intervention)	8	actigraphy; sleep diary		Seven of 8 studies that used CBT found a reduction in sleep latency (values not reported).
Wang, 2005[85] CBT SR	Moderate	CBT: stimulus control, sleep restriction, cognitive therapy, sleep hygiene education, sleep scheduling Control: quasi-desensitization, self-monitoring control, sleep hygiene recommendations, waiting-list control Total sample: 109	1	sleep diary; wrist actigraphy	Change in outcome: CBT: 61 mins to 28 mins; Control: 74 mins to 70 mins	CBT **significantly improved** sleep latency compared with control with sustained mean reduction by 50% in CBT group **(*P* < 0.05).**
Yang, 2014[53] CBT+ Behavioural MA	Moderate	CBT + relaxation: sleep hygiene, relaxation CD: 13 Sleep hygiene education, treatment as usual: 13	1	NR	Standardized mean difference (95% CI): **1.33 (0.46 to 2.19)** I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Buscemi, 2005[30] CBT+ Behavioural MA	High	CBT + relaxation: relaxation training, cognitive control, stimulus control, group relaxation, aggressive muscle relaxation, cognitive distraction: 45 Placebo: 46	4	sleep diary	Mean difference (95% CI): **–21.5 (–42.2 to –0.8)** I^2: 74.4%	
Ho, 2015[36] Multi-CBT MA	Low	Multi-component CBT: stimulus control, sleep restriction, sleep hygiene, relaxation and/or cognitive therapy: NR Waiting-list control; routine care or no treatment: NR	8	sleep diary	Hedges' *g* (95% CI): **–0.70 (–1.0 to –0.4)** I^2: 77%	
Trauer, 2015[50] Multi-CBT MA	Moderate	Multimodal CBT: cognitive therapy, stimulus control, sleep restriction, relaxation, sleep hygiene: NR Wait-list control, treatment as usual, sleep hygiene, sham, placebo: NR	16	sleep diary	Mean difference (95% CI): **–19.03 (–23.93 to 14.12)** I^2: 41.9%	
Buscemi, 2005[30] Multi-CBT MA	High	Multi-component CBT: paradoxical intention, sleep compression, stimulus control:152 Placebo: 124	9	sleep diary	Mean difference (95% CI): **–4.57 (–9.75 to 0.61)** I^2: 12.5%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Okajima, 2011[57] **Multi-CBT** MA	Critically Low	Multi-component CBT: sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, relaxation, paradoxical intention: NR Wait-list control, placebo, sleep hygiene education, control(unspecified), treatment as usual: NR	7	sleep diary	Cohen's *d* (95% CI): **0.4 (0.21 to 0.57)** I^2: NR	
			2	PSG; actigraphy	Cohen's *d* (95% CI): **0.59 (0.08 to 1.02)** I^2: NR	
Zachariae, 2016[55] **Multi-CBT** MA	Moderate	Multi-component CBT: stimulus control, sleep hygiene, cognitive therapy, sleep restriction, relaxation techniques: NR Wait-list control, treatment as usual: NR	10	NR	Hedges' *g* (95% CI): **0.41 (0.29 to 0.53)** I^2: 0%	
Howell, 2014[75] **Multi-CBT** SR	Moderate	Multi-component CBT: sleep hygiene, sleep restriction, stimulus control, cognitive restructuring, and relaxation therapies Usual care, wait-list control, healthy eating and nutrition, sleep education and hygiene only, no treatment Total sample: 235	3	sleep diary		Sleep latency had **significant improvement** in all studies post CBT intervention (values not reported).

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
McCurry, 2007[79] Multi-CBT SR	Critically Low	Multi-component CBT: sleep hygiene, relaxation, sleep compression, cognitive behavioural therapy, stimulus control Delayed treatment; wait-list control, placebo; stress management Total sample: 92	1	sleep logs		CBT **significantly decreased** sleep latency compared with stress management (*P* values not reported).
Cognitive Behavioural Interventions vs. Active Controls; 2 SR+MAs						
van Straten, 2009[93] CBT	Moderate	CBT (self-help): stimulus control, sleep restriction, cognitive therapy, sleep hygiene, relaxation, in-bed exercises: NR CBT (face-to-face)	3	sleep diary	Cohen's *d* (95% CI): **–0.37 (–0.73 to –0.02)** I^2: 0%	
Buscemi, 2005[30] CBT+ behavioural MA	High	CBT + relaxation: relaxation training, cognitive control, stimulus control, group relaxation: 18 Progressive muscle relaxation, EMG biofeedback, group relaxation: 16	2	sleep diary	Mean difference (95% CI): –9.2 (–37.9 to 19.5) I^2: 37.1%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
		CBT + relaxation: relaxation training, stimulus control, aggressive muscle relaxation, cognitive distraction: 23 CBT: cognitive therapy, sleep restriction, stimulus control, sleep hygiene: 24	2	sleep diary	Mean difference (95% CI): –4.6 (–20.7 to 11.5) I^2: 0%	
Behavioural Interventions vs. Inactive Controls; 2 SR+MAs, 2 SRs						
Brasure, 2015[29] MA	High	Sleep restriction: 68 wait-list control, no treatment, or sleep hygiene/sleep education: 73	2	subjective report	Mean difference (95% CI): –11.38 (–27.74 to 4.99) I^2: 87%	
Miller, 2014[81] SR	High	Sleep restriction therapy: 98 Wait-list control; sleep hygiene instructions: 94	4	sleep diary; actigraphy	Change in outcome (effect size; SD): *intervention (pre- / post-):* –19.34 min (0.64; 0.37); *control (pre- / post-)*: –3.64 min (0.06; 0.36)	Sleep restriction arm: sleep latency decreased in all studies, the weighted effect size was medium (0.64).
Buscemi, 2005[30] MA	High	Relaxation training (autogenic, breathing process, EMG feedback); Relaxation exercises (group, hypnotic, progressive): 199 Placebo: 185	13	sleep diary	Mean difference (95% CI): –14.56 (–29.33 to 0.20) I^2: 96.1%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Brasure, 2015[29] MA	High	Multi-component behavioural interventions or brief behavioural therapy: 70 Information control or placebo: 76	3	subjective report	Mean difference (95% CI): **–10.43 (–16.31 to –4.55)** I^2: 0%	
Wang, 2005[85] SR	Moderate	Multifactor intervention: stimulus control, relaxation response, sleep education Stimulus control Total sample: 18	1	sleep diary	Change in outcome (*P* value): Multifactor intervention: **77.3 mins to 17.5 mins (*P* < 0.001);** Stimulus control: **74.9 mins to 28 mins (*P* < 0.001)** Patients achieving SOL ≤ 20 mins: Multifactor: **6/9** Stimulus control: **2/9** **(*P* < 0.05 between groups)**	Both groups had a statistically and clinically significant change in mean SOL; significantly greater proportion of patients receiving multifactor intervention achieved "good sleeper status" (SOL ≤ 20 mins).
Mindfulness vs. Inactive Controls; 1 SR+MA						
Gong, 2016[34] MA	Low	Mindfulness-based stress reduction, mindfulness meditation, mindfulness-based therapy for insomnia Wait-list control, sleep hygiene education, self-monitoring condition Total sample: 83	2	sleep diary	Standardized mean difference (95% CI): **–0.53 (–0.97 to –0.09)** I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Weeks
Combination Therapy vs. Inactive Controls; 1 SR						
Chiesa, 2009[88] SR	Low	Pharmacotherapy (general) and mindfulness-based cognitive therapy, mindfulness-based stress reduction: 14 No comparator (pre- / post- intervention)	1	NR	NR	Median sleep latency reduced from 30 mins to 26 mins per night.

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CBT = cognitive behavioural therapy; CD = compact disc; CI = confidence interval; EMG = electromyography; MA = meta-analysis; min = minutes; NNT = number needed to treat; No. = number; NR = not reported; NS = not significant; PSG = polysomnography; PSQI = Pittsburgh Sleep Quality Index; SOL = sleep onset latency; SR = systematic review; SR+MA = systematic review plus meta-analysis; vs. = versus.

Table 78: Detailed Results for Total Sleep Time

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Benzodiazepine Drugs vs. Inactive Controls; 2 SR+MAs, 2 SRs						
Sateia, 2017[45] MA	Critically Low	Temazepam: 36 Placebo: 36	2	subjective measure	Mean difference (95% CI): **64.41 (8.07 to 120.76)** I^2: 59%	
Soldatos, 1999[48] MA	Critically Low	Triazolam: NR Placebo: NR	12	sleep laboratory	Mean difference (95% CI): **49.2 (36 to 62.5)** I^2: NR	
Kolla, 2011[77] SR	Critically Low	Triazolam: 23 (enrolled); 12 (analysis) No comparator (pre- and post-intervention)	1	sleep diaries		**Significant improvement** in depth and duration of sleep
Swainston Harrison, 2005[91] SR	Critically Low	Triazolam Placebo Total sample: 16	1	NR	Change in outcome (*P* value): **+41 min vs. +25 min** **(*P* < 0.05)**	NR

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Non-Benzodiazepines vs. Inactive Controls; 3 SR+MAs, 2 SRs						
Brasure, 2015[29] MA	High	Zolpidem: 82 Placebo: 85	3	subjective report	Mean difference (95% CI): **22.95 (2.01 to 43.88)** I^2: 0%	
Sateia, 2017[45] MA	Critically Low	Zolpidem: 55 Placebo: 57	2	PSG	Mean difference (95% CI): **28.91 (10.85 to 46.97)** I^2: 49%	
		Zolpidem: 435 Placebo: 455	8	subjective measure	Mean difference (95% CI): **30.04 (15.12 to 44.96)** I^2: 71%	
Soldatos, 1999[48] MA	Critically Low	Zolpidem: NR Placebo: NR	23	sleep laboratory	Mean difference (95% CI): **32 (21.7 to 42.3)** I^2: NR	
		Zopiclone: NR Placebo: NR	13	sleep laboratory	Mean difference (95% CI): **56.3 (37.3 to 75.4)** I^2: NR	
Mayers, 2005[78] SR	Critically Low	Zolpidem Placebo Total sample: 306	1	NR		**Significant increase** in TST compared with placebo **(*P* < 0.05)**
Swainston Harrison, 2005[91] SR	Critically Low	Zolpidem Placebo Total sample: 16	1	NR	Change in outcome (*P* value): **+35 min vs +29 min (*P* < 0.05)**	NR
Non-Benzodiazepine Drugs vs. Other Pharmacological Interventions; 1 SR						
Swainston Harrison, 2005[91] SR	Critically Low	Zolpidem Triazolam Total sample: 16	1	NR	Change in outcome (*P* value): +35 min vs. –112 min (*P* < 0.05)	NR
Suvorexant vs. Inactive Controls; 3 SR+MAs, 1 SRs						
Kishi, 2015[39] MA	Moderate	Suvorexant: 936 Placebo: 953	3	sleep diary	Mean difference (95% CI): **–20.16 (–25.01 to –15.30)** I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Kuriyama, 2017[41] MA	Moderate	Suvorexant: NR Placebo: NR	3	sleep diary, PSG	Mean difference (95% CI): **18.55 (12.52 to 24.58)** I^2: 0%	
Brasure, 2015[29] MA	High	Suvorexant: 425 Placebo: 664	2	subjective report	Mean change (95% CI): **15.97 (4.73 to 27.22)** I^2: 63%	
Citrome, 2014[69] SR	Critically Low	Suvorexant (15 mg, 20 mg): 425 Placebo: 664	2	sleep diary	Change in outcome (least squares mean difference [*P* value]): **16 (*P* < 0.001)** Proportion of respondents with > 15% increase: 50.1% vs. 41.9%; NNT 13 (95% CI, 17 to 46)	Suvorexant was also **superior to placebo** for sleep maintenance, as assessed subjectively by patient-estimated TST.
		Suvorexant (30, 40 mg): 688 Placebo: 664	2	sleep diary	Change in outcome: (least squares mean difference [*P* value]): **22.1 min (*P* < 0.0001)** Proportion of respondents with > 15% increase: 54.7% vs. 41.9%; NNT 8 (95% CI, 6 to 14)	
Antidepressant Drugs vs. Inactive Controls; 4 SR+MAs, 4 SRs						
Brasure, 2015[29] MA	High	Doxepin: 289 Placebo: 205	2	subjective report, in min	Mean change (95% CI): **23.85 (12.04 to 35.65)** I^2: 0%	
Liu, 2017[42] MA	Critically Low	Doxepin: 743 Placebo: 733	7	PSG	Standardized mean difference (95% CI): **0.61 (0.50 to 0.71)** I^2: 15%	
Sateia, 2017[45] MA	Critically Low	Doxepin (3 mg): 282 Placebo: 276	4	PSG	Mean difference (95% CI): **26.14 (18.49 to 33.79)** I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
		Doxepin (3 mg): 148 Placebo: 143	2	subjective measure	Mean difference (95% CI): **43.57 (5.16 to 81.98)** I^2: 82%	
		Doxepin (6 mg): 209 Placebo: 206	3	PSG	Mean difference (95% CI): **32.27 (24.24 to 40.30)** I^2: 0%	
		Doxepin (6 mg): 204 Placebo: 197	2	subjective measure	Mean difference (95% CI): 18.84 (-1.65 to 39.34) I^2: 56%	
Yuan, 2010[59] MA	Low	Doxepin (1 mg): 140 Placebo: 139	2	NR	Mean difference (95% CI): **17.24 (7.43 to 27.05)** I^2: NR	
		Doxepin (25 mg): 30 Placebo: 30	2	NR	Mean difference (95% CI): **70.74 (42.61 to 98.88)** I^2: NR	
		Doxepin (3 mg): 140 Placebo: 139	2	NR	Mean difference (95% CI): **27.95 (17.99 to 37.90)** I^2: NR	
		Doxepin (6 mg): 141 Placebo: 139	2	NR	Mean difference (95% CI): **33.78 (24.44 to 43.11)** I^2: NR	
Mayers, 2005[78] SR	Critically Low	Doxepin Placebo Total sample: 10	1	NR		Doxepin **significantly improved** TST compared with placebo (*P* value not reported).
Vande Griend, 2012[83] SR	Critically Low	Doxepin: NR Placebo: NR	7	PSG questionnaire (Likert-type scale)		Doxepin increased TST by 25 to 51 min across the trials; 6 of the found studies a **significant difference** compared with placebo **(*P* < 0.05).**

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Yeung, 2015[87] SR	Moderate	Doxepin: NR Placebo: NR	NR	self-report		Adults < 65 years: mixed results for 3 mg doxepin over 1 to 2 nights; a single trial showed improvement at 4 weeks. Multiple trials showed positive improvement for 6 mg doxepin over 1 to 2 nights; a single trial showed improvement at 4 weeks. Adults > 65 years: 3 mg and 6 mg doxepin showed positive results over 1 to 2 nights; results were maintained for 3 mg doxepin only.
		Doxepin: NR Placebo: NR	NR	PSG		Adults < 65 years: multiple trials found positive results for 3 mg and 6 mg doxepin over 1 to 2 nights, the effect was maintained at 4 weeks for 6 mg doxepin only. Adults > 65 years: positive results for 3 mg and 6 mg doxepin over 1 to 2 nights, the effect was maintained at 4 weeks for 3 mg doxepin; no long-term data on 6 mg doxepin was available.
Mayers, 2005[78] SR	Critically Low	Trazodone Placebo Total sample: 323	2	NR		Both trials found a **significant increase** in TST compared with placebo **(*P* < 0.05; *P* = 0.003).**

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
		Trazodone (50 *vs.* 75 *vs.* 100mg): 75 No comparator (multiple doses)	1	self-rated		TST was **significantly longer** with 50 mg and 75 mg doses compared with 100 mg (*P* value not reported); no significant difference was found between 50 mg and 75 mg doses (*P* value not reported).
Mendelson, 2005[80] SR	Critically Low	Trazodone placebo; unspecified control Total sample: 63	3	PSG		Mixed results: 2 trials found **significant improvement** in TST compared with placebo **(*P* < 0.05)**; 1 trial found no significant change between groups.
		Trazodone: 39 No comparator (pre- / post-intervention)	5	PSG		Mixed results: 2 trials found **significant increase** in TST compared with baseline **(*P* < 0.05)**; trials found no significant change from baseline.
Vande Griend, 2012[83] SR	Critically Low	Trazodone: NR Placebo: NR	2	sleep diaries PSG		No significant differences between groups.
Antidepressant Drugs vs. Other Pharmacological Interventions; 2 SRs						
Mayers, 2005[78] SR	Critically Low	Trazodone Zolpidem Total sample: 306	1	NR		No significant differences found between zolpidem and trazodone.
Vande Griend, 2012[83] SR	Critically Low	Trazodone Zolpidem Total sample: 306	1	daily questionnaire		No significant differences found between zolpidem and trazodone.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Antipsychotic Drugs to Inactive Controls; 3 SRs						
Anderson, 2014[63] SR	Critically Low	Quetiapine: 18 No comparator (pre- / post-intervention)	1	PSG	Change in outcome: **395.6 ± 62.3** **(*P* < 0.05 compared with baseline)**	
		Quetiapine Placebo; no therapy Total sample: 52	2	PSG actigraphy	Change in outcome: 347.5 ± 100.9 *vs.* 361.9 ± 85.4 (*P* = NS); 432 ± 66 *vs.* 390 ± 54 (*P* = NS)	
Coe, 2014[70] SR	Critically Low	Quetiapine: 8 Placebo: 8	1	patient-recorded sleep logs	Change in outcome (*P* value): +124.92 mins vs. +72.24 min (*P* = 0.193)	
		Quetiapine: 18 No comparator (pre- / post-intervention)	1	objective; from baseline to week 6		TST **significantly improved** from baseline compared with week 6 **(*P* = 0.03).**
Wine, 2009[86] SR	Critically Low	Quetiapine: 18 No comparator (pre- / post-intervention)	1	NR	Change in outcome (*P* value): **396 ± 62 to 358 ± 61mins (*P* < 0.05)**	**Significant decrease** in TST vs baseline for quetiapine.
		Quetiapine Untreated control (pre- / post- intervention) Total sample: 18	1	NR	Change in outcome (*P* value): **240 mins ± 60 mins to 360 mins ± 120 mins** **(*P* < 0.05)**; Control group values not reported	Quetiapine **improved** TST compared with control.
Melatonin to Inactive Controls; 6 SR+MAs, 4 SRs						
Buscemi, 2004[31] MA	High	Melatonin: NR Placebo: NR	11	NR	Mean difference (95% CI): 4 (–10.5 to 18.5) I^2: 67.6%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Ferracioli-Oda, 2013[33] MA	Critically Low	Melatonin: NR Placebo: NR	10	PSG actigraphy	Mean change (95% CI): 0.34 (–11.19 to 11.87) I^2: NR	
McCleery, 2016[43] MA	High	Melatonin: 119 Placebo: 65	2	actigraphy	Mean difference (95% CI): 10.68 (–16.22 to 37.59) I^2: 0%	
Xu, 2015[52] MA	Moderate	Melatonin: 257 Placebo; light therapy: 240	8	actigraphy	Mean difference (95% CI): **24.36 (3.26 to 45.46)** I^2: 59%	
Lee, NA[58] MA	Critically Low	Melatonin: NR Placebo: NR	11	sleep diary PSG, actigraphy	Mean difference (95% CI): **3.3 (7.04 to 13.65)** I^2:12%	
Zhang, 2016[60] MA	Critically Low	Melatonin: 101 Placebo: 96	4	PSG actigraphy	Mean difference (95% CI): 12.38 (–10.38 to 35.15) I^2: 34%	
Bellon, 2006[64] SR	Critically Low	Melatonin: NR Placebo: NR	15	subjective PSG, actigraphy		Adult patients: 2 studies report no change; 2 report decrease; 2 report **significant improvement**; 1 reports subjective improvement but no change on PSG. Elderly patients: 4 studies report no change. Schizophrenia, dementia, Alzheimer patients: 3 studies, non-significant improvement. Medically ill patients: 1 study, **significant improvement.**
Chase, 1997[67] SR	Critically Low	Melatonin Placebo Total sample: 25	2	wrist actigraphy; subjective report		One study found no change in TST; 1 study found melatonin treatment resulted in a **significant effect** on reported time asleep.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Costello, 2014[71] SR	Moderate	Melatonin Placebo Total sample: 791	1	National Sleep Foundation diary; PSQI		Melatonin (Circadin) **significantly increased** sleep time compared with placebo **(*P* = 0.035).**
Culpepper, 2015[72] SR	Critically Low	Melatonin Placebo Total sample: 50	2	sleep diary PSG, actigraphy	Change in outcome (*P* value): **–15.4 min vs. –5.5 min (*P* < 0.01)** (1 study)	One study no significant difference between groups (melatonin vs placebo); one study: **significant reduction** in sleep latency **(*P* < 0.01).**
Antihistamine Drugs vs. Inactive Controls; 1 SR+MA, 2 SRs						
Sateia, 2017[45] MA	Critically Low	Diphenhydramine: 77 patients Placebo: 84 patients	2	subjective measure	Mean difference (95% CI): 17.86 (–3.79 to 39.51) I^2: 0%	
Culpepper, 2015[72] SR	Critically Low	Diphenhydramine Placebo Total Sample: 204	2	sleep diary	Change in outcome (*P* value): 6.6 mins vs 6.3 min (*P* = NS); No change (*P* = NS);	No significant changes in TST compared with placebo.
Vande Griend, 2012[83] SR	Critically Low	Diphenhydramine Placebo Total sample: 332	4	sleep diaries, PSG, questionnaire (unspecified)		Overall, the outcomes analyzed from all four trials provided mixed results, with the majority not being statistically different than placebo (*P* > 0.05); 4 studies found no significant difference between groups; 1 study found drug to be **superior.**
Cognitive Behavioural Interventions vs. Inactive Controls; 15 SR+MAs, 3 SRs						
Brasure, 2015[29] **CBT** MA	High	CBT-I: 621 Sham treatment/ placebo, wait-list control, no treatment, or sleep hygiene/sleep education): 612	15	subjective report	Mean difference (95% CI): **14.24 (2.08 to 26.39)** I^2: 56%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Cheng, 2012[32] **CBT** MA	Low	CBT: sleep hygiene, stimulus control, relaxation training, sleep restriction, cognitive restructuring: NR Wait-list control: NR	4	sleep diary	Standardized mean difference (95% CI): 0.22 (–0.03 to 0.46) I^2: 0%	
Ho, 2016[35] **CBT** MA	Low	CBT: image rehearsal therapy, exposure, re-scripting and relaxation therapy, mind-body bridging, behavioural sleep intervention: NR Wait-list control, sleep hygiene: NR	4	sleep diary	Standardized mean difference (95% CI): 0.39 (–0.05 to 0.84) I^2: 38%	
Irwin, 2006[37] **CBT** MA	Critically Low	CBT: relaxation, biofeedback, hypnosis, sleep compression/restriction paradoxical intention: NR Control: NR	16	self-report	Cohen's *d* (95% CI): 0.17 (–0.13 to 0.48) Q-statistic: 50.27	
Koffel, 2015[40] **CBT** MA	Critically Low	Group CBT-I: stimulus control, sleep restriction, and addressing dysfunctional beliefs about sleep: NR Wait-list, treatment as usual, placebo: NR	6	sleep diary	Mean effect size (95% CI): –0.04 (–0.32 to 0.23) I^2: NR	
Montgomery, 2003[44] **CBT** MA	High	CBT: sleep hygiene; stimulus control; muscle relaxation; sleep restriction; cognitive therapy; education; imagery training: 76 Wait-list control, placebo: 67	4	sleep diary	Mean difference (95% CI): –14.56 (–36.13 to 7.01) I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
		CBT: sleep hygiene, stimulus control, muscle relaxation, sleep restriction, cognitive therapy, education, imagery training: 30 Wait-list control, placebo: 29	2	PSG	Mean difference (95% CI): 18.93 (–2.74 to 40.60) I^2: 0%	
Navarro-Bravo, 2015[56] **CBT** MA	Moderate	CBT: sleep restriction, stimulus control, sleep education/hygiene: NR Placebo, wait-list control, stress management and wellness training, treatment as usual, sleep hygiene/education: NR	8	sleep diary, PSG actigraphy, sleep evaluation (4-item questionnaire)	Cohen's *d* (95% CI): 0.11 (–0.15 to 0.37) Chi square: 17.56; 0.014	
Seyffert, 2016[47] **CBT** MA	Low	Internet-based CBT: sleep education, stimulus control, sleep restriction, relaxation, sleep hygiene, cognitive techniques: NR Wait-list control, Internet control, Treatment as usual: NR	8	sleep diary	Mean difference (95% CI): **19.57 (8.56 to 30.58)** I^2: 24.7%	
van Straten, 2007[51] **CBT** MA	Low	CBT: relaxation, sleep restriction, stimulus control, paradoxical intention, identifying and challenging dysfunctional thoughts: NR Wait-list control, no treatment, placebo, psychoeducation: NR	91	sleep diary	Hedges' *g* (95% CI): **0.16 (0.08 to 0.24)** I^2: 47%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
van Straten, 2009[93] CBT MA	Moderate	CBT: self-help: stimulus control, sleep restriction, cognitive therapy, sleep hygiene, relaxation, in-bed exercises: NR Waiting list: NR	8	sleep diary	Cohen's *d* (95% CI): –0.01 (–0.14 to 0.14) I^2: 18.8%	
Ye, 2016[54] CBT MA	Moderate	CBT: sleep hygiene education, cognitive restructuring, stimulus control, sleep restriction, relaxation therapy, hierarchy development, imagery training, scheduled pseudo desensitization, breathing control: 1,006 Wait-list control, treatment as usual, Internet + email, Internet + telephone, telephone, Internet-based control: 1,003	15	sleep diary	Mean difference (95% CI): **22.3 (16.38 to 28.23)** I^2: 12%	
Dickerson, 2014[73] CBT SR	High	CBT Usual treatment, wait-list crossover, wait-list control, control, usual treatment Total sample: 150	1	actigraphy	Change in outcome: CBT vs placebo **–0.81 (–1.21 to –0.42)**	CBT had a **moderate effect** in decreasing insomnia symptoms.
		CBT: 12 No comparator (pre- / post-intervention)	1	sleep diary	Change in outcome: Pre-/post scores 0.47 (–0.27 to 1.350)	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Venables, 2014[90] CBT SR	Critically Low	Group CBT: 660 No comparator (pre- / post-intervention)	8	NR		Seven of 8 studies obtained improvements in TST; group-delivered CBT sessions may be slightly more effective than individual sessions.
		Professionally administered CBT: 615 No comparator (pre- / post-intervention)	8	actigraphy sleep diary		Four of 8 studies reported increased TST in the intervention group, 4 of 8 found no significant increase in TST in the intervention or control groups.
Ho, 2015[36] Multi-CBT MA	Low	Multi-component CBT: stimulus control, sleep restriction, sleep hygiene, relaxation and/or cognitive therapy: NR Wait-list control; routine care or no treatment: NR	8	sleep diary	Hedges' *g* (95% CI): **0.31 (0.0 to 0.6)** I^2: 78%	
Okajima, 2011[57] Multi-CBT MA	Critically Low	Multi-component CBT: sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, relaxation, paradoxical intention: NR Wait-list control, placebo, sleep hygiene education, control(unspecified), treatment as usual: NR	7	sleep diary	Cohen's *d* (95% CI): **0.21 (0.03 to 0.39)** I^2: NR	
			2	PSG, actigraphy	Cohen's *d* (95% CI): **0.71 (0.21 to 1.12)** I^2: NR	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Trauer, 2015[50] Multi-CBT MA	Moderate	Multi-component CBT: cognitive therapy, stimulus control, sleep restriction, relaxation, sleep hygiene: NR Wait-list control, treatment as usual, sleep hygiene, sham, placebo: NR	16	sleep diary	Mean difference (95% CI): 7.61 (–0.51 to 15.74) I^2: 3.1%	
Zachariae, 2016[55] Multi-CBT MA	Moderate	Multi-component CBT: stimulus control, sleep hygiene, cognitive therapy, sleep restriction, relaxation techniques: NR Wait-list control; treatment as usual: NR	10	NR	Hedges' *g* (95% CI): **0.29 (0.17 to 0.42)** I^2: 5.4%	
Howell, 2014[75] Multi-CBT SR	Moderate	Multi-component CBT: sleep hygiene, sleep restriction, stimulus control, cognitive restructuring, and relaxation therapies Usual care, wait-list control, healthy eating and nutrition, sleep education and hygiene only, no treatment Total sample: 369	2	actigraphy		Non-significant change was identified between control and treatment groups for TST.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Cognitive Behavioural Interventions vs. Active Controls; 2 SR+MAs, 1 SR						
van Straten, 2009[93] **CBT** MA	Moderate	Self-help CBT: stimulus control, sleep restriction, cognitive therapy, sleep hygiene, relaxation, in-bed exercises: NR In-person CBT: NR	3	sleep diary	Cohen's *d* (95% CI): –0.05 (–0.40 to 0.31) I^2: 50.9%	
Seyffert, 2016[47] **CBT** MA	Low	Internet-based CBT: sleep education, stimulus control, sleep restriction, relaxation, sleep hygiene, cognitive techniques: NR In-person CBT: NR	2	sleep diary	Mean difference (95% CI): 0.73 (–311.8 to 313.3) I^2: 75%	
Wang, 2005[85] **CBT** SR	Moderate	CBT: stimulus control, sleep restriction, sleep hygiene education Relaxation therapy Total sample: 46	1	sleep log PSG	Change in outcome: CBT: 352.1 min to 372.4 mins; relaxation: 352.1 min to 337.9 mins	
Behavioural Interventions vs. Inactive Controls; 1 SR+MA, 2 SRs						
Brasure, 2015[29] MA	High	Sleep restriction: 68 Wait-list control, no treatment, or sleep hygiene/sleep education: 73	2	subjective report	Mean difference (95% CI): –17.57 (–102.36 to 67.21) I^2: 93%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
McCurry, 2007[79] SR	Critically Low	Sleep restriction (nap sleep restriction therapy, sleep compression, sleep compression guidance, and sleep hygiene) Placebo, waiting list Total sample : 55	1	actigraphy		Sleep restriction **more effective** than either nap restriction or control on actigraphic TST.
Miller, 2014[81] SR	High	Sleep restriction therapy: 98 Wait-list control; sleep hygiene instructions: 94	4	sleep diary actigraphy	Change in outcome effect size (SD): Intervention (pre-post) 17.06 min (0.30; 0.31); Control (pre-post) 6.13 min (0.01; 0.40)	Secondary pre-to-post measures of sleep diary variables were also compared at post-treatment to baseline levels. This revealed a small non-significant increase in TST (ES = 0.3).
Brasure, 2015[29] MA	High	Relaxation Therapy: 39 Passive control: 38	2	subjective report	Mean difference (95% CI): 10.23 (–19.64 to 40.11) I^2: 29%	
Mindfulness vs. Inactive Controls; 1 SR+MA						
Gong, 2016[34] MA	Low	Mindfulness-based stress reduction, mindfulness meditation, mindfulness-based therapy for insomnia Wait-list control, sleep hygiene education, self-monitoring condition Total sample: 58	2	sleep diary	Standardized mean difference (95% CI): 0.28 (–0.24 to 0.80) I^2: 0%	
Combination Therapy vs. Inactive Controls; 1 SR+MA, 1 SR						
Buscemi, 2005[30] MA	High	Triazolam; temazepam and CBT: 27 Placebo: 25	2	sleep diary	Mean difference (95% CI): 23.2 (–2.3 to 48.8) I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Chiesa, 2009[88] Systematic Review	Low	Pharmacotherapy (general) and mindfulness-based cognitive therapy; mindfulness-based stress reduction: 30 No comparator (pre- / post- intervention)	2	NR	NR	One trial showed an average increase of 1 hour TST; 1 trial showed **significant improvement** in measures of sleep quantity that persisted at 6 and 12 months.

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CBT = cognitive behavioural therapy; CI = confidence interval; EMG = electromyography; ES = effect size; MA = meta-analysis; min = minutes; NNT = number needed to treat; No. = number; NR = not reported; NS = not significant; PSG = polysomnography; SD = standard deviation; SOL = sleep onset latency; SR = systematic review; SR+MA = systematic review plus meta-analysis; TST = total sleep time; vs. = versus.

Table 79: Detailed Results for Wake After Sleep Onset

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Benzodiazepine Drugs vs. Inactive Controls; 1 SR+MA						
Buscemi, 2005[30] MA	High	Temazepam: 38 Placebo: 39	2	sleep diary, PSG	Mean difference (95% CI): **–23.66 (–36.57 to –10.76)** I^2: 0%	
		Triazolam: 30 Placebo: 27	2	sleep diary, PSG	Mean difference (95% CI): **–39.96 (–64.47 to –15.45)** I^2: 0%	
Non-Benzodiazepine Drugs vs. Inactive Controls; 2 SR+MAs, 3 SRs						
Buscemi, 2005[30] MA	High	Zolpidem: 345 Placebo: 345	7	sleep diary, PSG	Mean difference (95% CI): –8.46(–20.17 to 3.26) I^2: 64.1%	
Sateia, 2017[45] MA	Critically Low	Zolpidem: 55 Placebo: 57	2	PSG	Mean difference (95% CI): **–25.46 (–32.99 to –17.94)** I^2: 0%	
		Zolpidem: 384 Placebo: 400	6	subjective measure	Mean difference (95% CI): **–13.57 (–19.84 to –7.30)** I^2: 92%	
Mayers, 2005[78] SR	Critically Low	Zolpidem Placebo Total sample: 306	1	NR		**Significant improvement** in WASO compared with placebo **(*P* = 0.04).**
Mendelson, 2005[80] SR	Critically Low	Zolpidem Placebo Total sample: 306	1	self-reported		Relative to placebo, patients reported **significant improvement** in WASO with trazodone and zolpidem during week 1 **(*P* < 0.02).**
Swainston Harrison, 2005[91] SR	Critically Low	Zolpidem: 16 Placebo: 69	2	NR	Change in outcome (*P* value): **–35 mins vs. +116 mins (*P* < 0.05)** +6 mins vs. –8 mins (*P* = NS)	NR

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Non-Benzodiazepine Drugs vs. Other Pharmacological Interventions; 1 SR						
Swainston Harrison, 2005[91] SR	Critically Low	Zolpidem Triazolam Total sample: 102	3	NR	Change in outcome (*P* value): **–35** vs. **+116 mins (*P* < 0.05)**; **–38** vs. **+17 mins (*P* < 0.01)**; +6 mins vs. +19 mins (*P* = NS)	NR
Suvorexant vs. Inactive Controls; 2 SR+MAs, 1 SRs						
Kishi, 2015[39] MA	Moderate	Suvorexant: 955 Placebo: 960	3	sleep diary	Mean difference (95% CI): **–7.75 (–10.87 to –4.62)** I^2: 0%	
		Suvorexant: 317 Placebo: 542	2	PSG	Mean difference (95% CI): **–25.32 (–31.52 to –19.39)** I^2: 0%	
Kuriyama, 2017[41] MA	Moderate	Suvorexant: NR Placebo: NR	3	sleep diary	Mean difference (95% CI): **–7.51 (–12.46 to –2.56)** I^2: 0%	
		Suvorexant: NR Placebo: NR	3	PSG	Mean difference (95% CI): **–24.19 (–33.81 to –14.58)** I^2: 69.7%	
Citrome, 2014[69] SR	Critically Low	Suvorexant (15 mg, 20 mg): 425 Placebo: 660	2	PSG	Change in outcome least squares mean difference (*P* value): **–4.7 min (*P* < 0.001)** Proportion of respondents with > 15% improvement: 75.8% vs. 69.4%; NNT 16 (95% CI, 9 to 102)	
		Suvorexant (15 mg, 20 mg): 343 Placebo: 585	2	PSG	Change in outcome: least squares mean difference (*P* value): **–23.1 min (*P* < 0.001)**	

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
		Suvorexant (30 mg, 40 mg): 683 Placebo: 660	2	sleep diary	Change in outcome least squares mean difference (*P* value): **–7.8 min (*P* < 0.001)** Proportion of respondents with > 15% improvement: 77.5% vs. 69.4%; NNT 13 (95% CI, 8 to 30)	
		Suvorexant (30 mg, 40 mg): 590 Placebo: 585	2	PSG	Change in outcome: least squares mean difference (*P* value): **–25.9 min (*P* < 0.001)**	
Antidepressant Drugs vs. Inactive Controls; 2 SR+MAs, 5 SRs						
Sateia, 2017[45] MA	Critically Low	Doxepin (3 mg): 282 Placebo: 276	4	PSG	Mean difference (95% CI): **–22.17 (–29.62 to –14.72)** I^2: 23%	
		Doxepin (6 mg): 209 Placebo: 206	3	PSG	Mean difference (95% CI): **–23.4 (–30.34 to –16.46)** I^2: 0%	
		Doxepin (6 mg): 204 Placebo: 197	2	Subjective measure	Mean difference (95% CI): **–14.39 (–24.86 to –3.93)** I^2: 0%	
Yuan, 2010[59] MA	Low	Doxepin (1 mg): 140 Placebo: 139	2	NR	Mean difference (95% CI): –3.57 (–7.46 to 0.32) I^2: NR	
		Doxepin (25 mg): 30 Placebo: 30	2	NR	Mean difference (95% CI): **–10.23 (–14.82 to –5.64)** I^2: NR	
		Doxepin (3 mg): 140 Placebo: 139	2	NR	Mean difference (95% CI): **–5.71 (–9.39 to –2.02)** I^2: NR	
		Doxepin (6 mg): 141 Placebo: 139	2	NR	Mean difference (95% CI): **–7.36 (–10.69 to –4.03)** I^2: NR	

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Vande Griend, 2012[83] SR	Critically Low	Doxepin: NR Placebo: NR	7	PSG questionnaire (Likert-type scale)		Doxepin reduced WASO by 5 min to 20 min across the trials; 6 out of 7 trials found a **significant difference** compared with placebo **(*P* < 0.05).**
Yeung, 2015[87] SR	Moderate	Doxepin: NR Placebo: NR	NR	self-report		Adults < 65 years: mixed results for 3 mg and 6 mg doxepin over 1 to 2 nights, 3 mg and 6 mg doxepin showed positive results at 4 weeks. Adults > 65 years: positive results for 3 mg doxepin over 1 to 2 nights, negative results for 6 mg doxepin over 1 to 2 nights and at 4 weeks.
		Doxepin: NR Placebo: NR	NR	PSG		Adults < 65 years: multiple trials with positive results for *3* mg and 6 mg doxepin over 1 to 2 nights, results were maintained at 4 weeks. Adults > 65 years: positive results for *3* mg doxepin over 1 to 2 nights and at 4 weeks; positive results for 6 mg doxepin over 1 to 2 nights, no data at 4 weeks.
Kolla, 2011[77] SR	Critically Low	Trazodone Placebo Total sample: 16	1	PSG		Improved WASO was observed in trazodone participants compared with placebo.

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Mayers, 2005[78] SR	Critically Low	Trazodone Placebo Total sample: 306	1	NR		**Significant improvement** in WASO compared with placebo **(*P* = 0.04).**
Mendelson, 2005[80] Systematic review	Critically Low	Trazodone Placebo; unspecified control Total sample: 306	1	self-reported		Relative to placebo, patients reported **significant improvement** during week 1 **(*P* < 0.02)**; during week 2, the trazodone group did not differ significantly from the placebo group.
		Trazodone: 15 No comparator (pre- / post-intervention)	2	PSG		Mixed result: 1 trial found **significant improvement (*P* < 0.05)**; 1 trial found no significant change from baseline.
Vande Griend, 2012[83] SR	Critically Low	Trazodone: NR Placebo: NR	2	PSG		Mixed result: 1 trial found a **significant difference** compared with placebo **(*P* < 0.05)**; 1 trial found no difference between groups.
Antidepressant Drugs vs. Other Pharmacological Interventions; 2 SRs						
Mayers, 2005[78] SR	Critically Low	Trazodone Zolpidem Total sample: 306	1	NR		No significant differences found between zolpidem and trazodone.
Vande Griend, 2012[83] SR	Critically Low	Trazodone Zolpidem Total sample: 306	1	daily questionnaire		No significant differences found between zolpidem and trazodone.

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Melatonin vs. Inactive Controls; 3 SR+MAs, 2 SRs						
Buscemi, 2005[30] MA	High	Melatonin: 68 Placebo: 68	5	sleep diary, PSG	Mean difference (95% CI): –9.65 (–33.57 to 14.26) I^2: 89.8%	
Buscemi, 2004[31] MA	High	Melatonin: NR Placebo: NR	5	NR	Mean difference (95% CI): –1.4 (–21.8 to 19) I^2: 84%	
		Melatonin: NR Placebo: NR	3	NR	Mean difference (95% CI): –6.3 (–16.6 to 3.9) I^2: 35.3%	
Zhang, 2016[60] MA	Critically Low	Melatonin: 75 Placebo: 69	2	PSG actigraphy	Mean difference (95% CI): 10.93 (–6.07 to 27.92) I^2: 0%	
Chase, 1997[67] SR	Critically Low	Melatonin Placebo Total sample: 12	1	wrist actigraphy	Change in outcome (*P* value): **49 min vs. 73 min (*P* < 0.001)**	
Vural, 2014[84] SR	Critically Low	Melatonin Control Total sample: 12	1	NR		**Significant decrease** in wake after sleep onset in melatonin group.
Antihistamine Drugs vs. Inactive Controls; 1 SR						
Vande Griend, 2012[83] SR	Critically Low	Diphenhydramine Placebo Total sample: 17	1	questionnaire (unspecified)	Change in outcome (*P* value): no significant difference between groups (*P* = NS)	Overall, the outcomes analyzed from all four trials provided mixed results, with the majority not being statistically different than placebo (*P* > 0.05).

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Cognitive Behavioural Interventions vs. Inactive Controls; 17 SR+MAs, 6 SRs						
Brasure, 2015[29] **CBT** MA	High	CBT-I: 412 (general adult population) Sham treatment/ placebo, wait-list control, no treatment, or sleep hygiene/sleep education): 420	11	subjective report	Mean difference (95% CI): **–22.33 (–37.44 to –7.21)** I^2: 89%	
		CBT-I: 124 (older adults) Placebo, wait-list control, no treatment, or sleep hygiene/sleep education: 96	4	subjective report	Mean difference (95% CI): **–26.96 (–35.73 to –18.19)** I^2: 0%	
		CBT-I: 61 (adults with chronic pain) Passive control (placebo or sham treatment or wait-list): 61	3	subjective report	Mean difference (95% CI): **–38.18 (–65.57 to –10.78)** I^2: 0.82%	
Cheng, 2012[32] **CBT** MA	Low	CBT: sleep hygiene, stimulus control, relaxation training, sleep restriction, cognitive restructuring: NR Wait-list control: NR	4	sleep diary	Standardized mean difference (95% CI): –0.18 (–0.43 to 0.06) I^2: 55%	
Ho, 2016[35] **CBT** MA	Low	CBT: image rehearsal therapy; exposure, re-scripting and relaxation therapy; mind-body bridging; behavioural sleep intervention: NR Wait-list control, sleep hygiene: NR	4	sleep diary	Standardized mean difference (95% CI): **–1.02 (–1.32 to –0.66)** I^2: 0%	

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Irwin, 2006[37] **CBT** MA	Critically Low	CBT: relaxation, biofeedback, hypnosis, sleep compression/restriction, paradoxical intention: NR Control: NR	15	self-report	Cohen's *d* (95% CI): **–0.64 (–0.82 to –0.47)** Q-statistic: 21.65	
Johnson, 2016[38] **CBT** MA	Moderate	CBT-I: with both cognitive and behavioural components: 423 Wait-list control, treatment as usual, sleep education, behavioural placebo, mindfulness-based stress reduction: 297	8	sleep diary	Cohen's *d* (95% CI): **0.29 (0.10 to 0.48)** I^2: 30.1%	
Koffel, 2015[40] **CBT** MA	Critically Low	Group CBT-I: stimulus control, sleep restriction, and addressing dysfunctional beliefs about sleep: NR Wait-list, treatment as usual, placebo: NR	6	sleep diary	Mean effect size (95% CI): **0.65 (0.26 to 1.04)** I^2: NR	
Montgomery, 2003[44] **CBT** MA	High	CBT: sleep hygiene, stimulus control, muscle relaxation, sleep restriction, cognitive therapy, education, imagery training: 95 Wait-list control, placebo: 64	4	Sleep Diary	Mean difference (95% CI): **–21.84 (–37.30 to –6.38)** I^2: 55%	
		CBT: sleep hygiene, stimulus control, muscle relaxation, sleep restriction, cognitive therapy, education, imagery training: 30 Wait-list control, placebo: 29	2	PSG	Mean difference (95% CI): **–24.36 (–41.14 to –7.57)** I^2: 0%	

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Navarro-Bravo, 2015[56] **CBT** MA	Moderate	CBT: sleep restriction, stimulus control, sleep education/hygiene: NR Placebo: wait-list control, stress management and wellness training, treatment as usual, sleep hygiene/education: NR	7	sleep diary PSG actigraphy sleep evaluation (4-item questionnaire)	Cohen's *d* (95% CI): **–0.68 (–1.11 to –0.26)** Chi square: 34.43; 0.000	
Seyffert, 2016[47] **CBT** MA	Low	Internet-based CBT: sleep education, stimulus control, sleep restriction, relaxation, sleep hygiene, cognitive techniques: NR Wait-list control, Internet control, TAU: NR	6	Sleep diary	Mean difference (95% CI): **–20.44 (–34.87 to –6.01)** I^2: 69.3%	
van Straten, 2007[51] **CBT** MA	Moderate	CBT: relaxation, sleep restriction, stimulus control, paradoxical intention, identifying and challenging dysfunctional thoughts: NR Wait-list control, no treatment, placebo, psychoeducation: NR	71	sleep diary	Hedges' *g* (95% CI): **0.63 (0.53 to 0.73)** I^2: 60%	
van Straten, 2009[93] **CBT** MA	Moderate	CBT: self-help: stimulus control; sleep restriction; cognitive therapy; sleep hygiene; relaxation; in-bed exercises: NR Waiting list: NR	6	sleep diary	Cohen's *d* (95% CI): **0.3 (0.13 to 0.48)** I^2: 63.9%	

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Ye, 2016[54] **CBT** MA	Moderate	CBT: sleep hygiene education, cognitive restructuring, stimulus control, sleep restriction, relaxation therapy, hierarchy development, imagery training, scheduled pseudo desensitization, breathing control: 828 Wait-list control, treatment as usual, Internet + email, Internet + telephone, telephone, Internet-based control: 827	11	sleep diary	Mean difference (95% CI): **–22.31 (–31.11 to –13.50)** I^2: 76%	
Brooks, 2014[66] **CBT** SR	Low	CBT-I: NR Control NR: NR	1	daily sleep diary; PSQI; actigraphy		WASO improved in treatment group based on self-reported data and effect remained for 6 months post-treatment; not corroborated by actigraphy.
Dickerson, 2014[73] **CBT** SR	High	CBT(unspecified) Usual treatment, wait-list crossover, wait-list control, control, usual treatment Total sample: 150	1	Actigraphy	Change in outcome: CBT vs. placebo **–0.50 (–0.89 to –0.1)**	CBT showed a moderate effect in decreasing insomnia symptoms compared with control.
		CBT (unspecified): 12 No comparator (pre- / post-intervention)	1	sleep diary	Change in outcome: Pre/post scores –1.18 (–2.45 to 0.62)	

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Venables, 2014[90] **CBT** SR	Critically Low	group CBT: 660 No comparison	8	NR		Eight of 8 studies demonstrated improvement in WASO (*P* values not reported); results demonstrate that group-delivered CBT sessions may be slightly more effective than individual sessions.
		Professionally administered CBT: 615 No comparison	8	actigraphy sleep diary		Eight of 8 studies in professionally administered CBT reported an increase in WASO (*P* values not reported).
Wang, 2005[85] **CBT** SR	Moderate	CBT: stimulus control, sleep restriction, cognitive therapy, sleep hygiene education, sleep scheduling control, Quasi-desensitization, self-monitoring control, sleep hygiene recommendations, waiting-list control Total sample: 162	3	PSG sleep log		**Significant improvement** in WASO for CBT compared with placebo **(*P* < 0.05)**; CBT group averaged a 52% reduction in WASO from study entry to 3-month follow-up time point; 60% of CBT group and none of control group achieved the criterion for clinically significant WASO improvement.
Buscemi, 2005[30] **CBT+ Behavioural** MA	High	CBT + relaxation technique: relaxation training, cognitive control, stimulus control, group relaxation, aggressive muscle relaxation, cognitive distraction: 23 Placebo: 26	2	NR	Mean difference (95% CI): –7.6 (–26.3 to 11.1) I^2: 0%	

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
		Multi-component CBT: paradoxical intention, sleep compression, stimulus control:128 Placebo: 120	8	sleep diary	Mean difference (95% CI): **–18.17 (–30.37 to –5.98)** I^2: 52.9%	
Ho, 2015[36] **Multi-CBT** MA	Low	Multi-component CBT: stimulus control, sleep restriction, sleep hygiene, relaxation and/or cognitive therapy: NR Waiting-list control, routine care or no treatment: NR	6	sleep diary	Hedges' *g* (95% CI): **–0.74 (–1.3 to –0.2)** I^2: 93%	
Okajima, 2011[57] **Multi-CBT** MA	Critically Low	Multi-component CBT: sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, relaxation, paradoxical intention: NR Wait-list control, placebo, sleep hygiene education, control (unspecified), treatment as usual: NR	6	sleep diary	Cohen's *d* (95% CI): **0.34 (0.15 to 0.52)** I^2: NR	
Trauer, 2015[50] **Multi-CBT** MA	Moderate	Multi-component CBT: cognitive therapy, stimulus control, sleep restriction, relaxation, sleep hygiene: NR Wait-list control, treatment as usual, sleep hygiene, sham, placebo: NR	14	Sleep diary	Mean difference (95% CI): –26 (–36.52 to 15.48) I^2: 47.2%	

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Zachariae, 2016[55] **Multi-CBT** MA	Moderate	Multi-component CBT: stimulus control, sleep hygiene, cognitive therapy, sleep restriction, relaxation techniques: NR Wait-list control, treatment as usual: NR	7	NR	Hedges' *g* (95% CI): **0.45 (0.25 to 0.66)** I^2: 48.5%	
Howell, 2014[75] **Multi-CBT** SR	Moderate	Multi-component CBT: sleep hygiene, sleep restriction, stimulus control, cognitive restructuring, and relaxation therapies Usual care, wait-list control, healthy eating and nutrition, sleep education and hygiene only, no treatment Total sample: 207	2	actigraphy sleep diary		Two of 2 studies found **significant improvement** in WASO for undergoing CBT.
McCurry, 2007[79] **Multi-CBT** SR	Critically Low	Multi-component CBT: sleep hygiene, relaxation, sleep compression, cognitive behavioural therapy, stimulus control Delayed treatment, wait-list control, placebo; stress management: Total sample: 154	3	sleep logs		CBT **significantly improved** WASO compared with stress management and wait-list control.

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
		Multi-component CBT: sleep restriction, education, stimulus control: 4 No comparator (pre- / post-intervention)	1	Sleep logs sleep assessment device	Effect size (*P* value): 1.12 (NR)	Large effect size supports the effectiveness of CBT to improve WASO (*P* values not reported).
Cognitive Behavioural Interventions vs. Active Controls; 2 SR+MAs, 2 SRs						
van Straten, 2009[93] **CBT** MA	Moderate	Self-help CBT: stimulus control, sleep restriction, cognitive therapy, sleep hygiene, relaxation, in-bed exercises: NR In-person CBT: NR	3	sleep diary	Cohen's *d* (95% CI): –0.03 (–0.32 to 0.38) I^2: 44.5%	
Wang, 2005[85] **CBT** SR	Moderate	CBT: stimulus control, sleep restriction, sleep hygiene education Relaxation therapy Total sample: 46	1	PSG sleep log	Change in outcome: CBT: 50.8 mins to 30.1 min relaxation: 50.8 min to 50.6 min	**Significant improvement** in WASO for CBT compared with relaxation therapy; CBT recipients reported a 54% reduction whereas relaxation group reported 16% **(*P* < 0.01).**
McCurry, 2007[79] **CBT** SR	Critically Low	CBT (unspecified) CBT (unspecified) + Temazepam Total sample: 78	1	sleep logs		CBT and CBT + temazepam groups both showed **significant improvement** compared with placebo.

Author, Year Synthesis type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Buscemi, 2005[30] **CBT+ Behavioural** MA	High	CBT + relaxation: relaxation training, stimulus control, aggressive muscle relaxation, cognitive distraction: 23 CBT: cognitive therapy, sleep restriction, stimulus control, sleep hygiene: 24	2	NR	Mean difference (95% CI): 5.1 (–12.0 to 22.2) I^2: 0%	
Behavioural Interventions vs. Inactive Controls; 2 SR+MAs, 1 SRs						
Miller, 2014[81] SR	High	Sleep restriction therapy: 82 Wait-list control; sleep hygiene instructions: 78	3	sleep diary actigraphy	Change in outcome, effect size (SD): Intervention (pre-post): –42.17 mins, 1.36 (0.42) control: (pre-post) –11.30 mins, 0.01 (0.55)	Reductions for wake after sleep onset were found in 3 studies; the weighted effect size in the intervention was large (1.36).
Buscemi, 2005[30] MA	High	Relaxation Training (autogenic, breathing process, EMG feedback); Relaxation exercises (group, hypnotic, progressive): 60 Placebo: 57	3	sleep diary	Mean difference (95% CI): –1.61 (–14.05 to 10.82) I^2: 20%	
Brasure, 2015[29] MA	High	Multi-component behavioural interventions or brief behavioural therapy: 70 Information control or placebo: 76	3	subjective report	Mean difference (95% CI): **–14.9 (–22.66 to –7.14)** I^2: 0%	

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CBT = cognitive behavioural therapy; CBT-I = cognitive behavioural therapy for insomnia; CI = confidence interval; EMG = electromyography; MA = meta-analysis; mins = minutes; NNT = number needed to treat; No. = number; NR = not reported; NS = not significant; PSG = polysomnography; SOL = sleep onset latency; SR = systematic review; SR+MA = systematic review plus meta-analysis; vs. = versus; WASO = wake after sleep onset.

Table 80: Detailed Results for Sleep Quality

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Benzodiazepine Drugs vs. Inactive Controls; 1 SR+MA						
Sateia, 2017[45] MA	Critically Low	Temazepam: 39 Placebo: 39	2	subjective measure	Mean difference (95% CI): 0.25 (–0.20 to 0.70) I^2: 0%	
Non-Benzodiazepines vs. Inactive Controls; 2 SR+MAs, 2 SRs						
Brasure, 2015[29] MA	High	Zolpidem: 289 Placebo: 268	3	participants reporting improvement	Mean difference (95% CI): **1.4 (1.20 to 1.65)** I^2: 14%	
Sateia, 2017[45] MA	Critically Low	Zolpidem: 314 Placebo: 324	6	subjective measure	Standardized mean difference (95% CI): **0.64 (0.03 to 1.26)** I^2: 92%	
Mayers, 2005[78] SR	Critically Low	Zolpidem Placebo Total sample: 306	1	NR		**Significant improvement** on sleep quality compared with placebo **(*P* = 0.0003).**
Mendelson, 2005[80] SR	Critically Low	Zolpidem Placebo Total sample: 306	1	self-reported		Relative to placebo, patients reported **significant improvement** in (sleep quality) with zolpidem during week 1 **(*P* < 0.02).**
Suvorexant vs. Inactive Controls; 1 SR+MAs						
Kishi, 2015[39] MA	Moderate	Suvorexant: 955 Placebo: 960	2	Sleep diary; 4-point scale	Mean difference (95% CI): **–0.17 (–0.25 to –0.09)** I^2: 0%	
Antidepressant Drugs vs. Inactive Controls; 1 SR+MA, 3 SRs						
Sateia, 2017[45] MA	Critically Low	Doxepin (3 mg): 148 Placebo: 143	2	subjective measure	Standardized mean difference (95% CI): **0.57 (0.26 to 0.88)** I^2: 43%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
		Doxepin (6 mg): 204 Placebo: 200	2	subjective measure	Standardized mean difference (95% CI): **0.28 (0.06 to 0.49)** I^2: 15%	
Mayers, 2005[78] SR	Critically Low	Doxepin Placebo Total sample: 57	2	NR		Doxepin **significantly improved** sleep quality relative to placebo **(*P* < 0.001).**
Kolla, 2011[77] SR	Critically Low	Trazodone placebo Total sample: 173	1	PSQI		Sleep quality **improved significantly** in trazodone group during active treatment phase.
Mayers, 2005[78] SR	Critically Low	Trazodone Placebo Total sample: 323	2	NR; PSQI		Sleep quality **significantly improved** compared with placebo in one trial **(*P* = 0.003)**, and almost reached significance in the other (*P* = 0.06) but **significantly higher proportion** of patients in this trial showed **improvement** on sleep quality compared with placebo **(P = 0.004).**

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Mendelson, 2005[80] SR	Critically Low	Trazodone Placebo; unspecified control Total sample: 767	5	self-reported (1); PSQI (1); LSEQ (3)		Relative to placebo, patients reported **significant improvement** during week 1 **(*P* < 0.02)**; during week 2, the trazodone group did not differ significantly from the placebo group Three trials reported **significant improvements** throughout the 6-week treatment period for "quality of sleep." **(*P* < 0.001)**; PSQI improvements were similar for the placebo and trazodone groups.
		Trazodone: 9 No comparator (pre- / post- intervention)	1	VAS		In the subjective ratings, sleep quality **improved significantly** during weeks 1 and 2 **(*P* < 0.001)** but not during week 3.
Antidepressant Drugs vs. Other Pharmacological Interventions; 1 SR						
Mayers, 2005[78] SR	Critically Low	Trazodone Zolpidem Total sample: 306	1	NR		No significant differences found between zolpidem and trazodone.
Antipsychotic Drugs vs. Inactive Controls; 4 SRs						
Anderson, 2014[63] SR	Critically Low	Quetiapine: 84 No comparator (pre- / post-intervention)	3	PSQI; SSQ		**Significant improvements** on PSQI global scores **(*P* < 0.001)**; 75% improvement in global score for SSQ (*P* value not reported).
		Quetiapine Placebo; no therapy Total sample: 78	3	PSQI; actigraphy		**Significant improvement** in PSQI scores from baseline and compared with placebo **(*P* < 0.001).**

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Coe, 2014[70] SR	Critically Low	Quetiapine: 18 No comparison	1	PSQI; sleep diary		Subjective parameters such as PSQI and sleep diaries also showed **significant improvement** from baseline to weeks 2 and 6.
Kolla, 2011[77] SR	Critically Low	Quetiapine: 28 No comparator (pre- / post-intervention)	1	HAM-D sleep question subset		Middle and late insomnia was **significantly reduced** at 2 weeks, no other sleep data presented.
Wine, 2009[86] SR	Critically Low	Quetiapine: 18 No comparator (pre-/post-intervention)	1	PSQI		PSQI decreased total scores with use of quetiapine vs baseline.
Melatonin vs. Inactive Controls; 5 SR+MAs, 5 SRs						
Buscemi, 2004[31] MA	High	Melatonin: NR Placebo: NR	2	NR	Standardized mean difference (95% CI): 0.5 (–0.1 to 1.1) I^2: 0%	
Ferracioli-Oda, 2013[33] MA	Critically Low	Melatonin: NR Placebo: NR	14	PSG actigraphy sleep scales questionnaires sleep logs	Mean change (95% CI): **0.22 (0.13 to 0.32)** I^2: 0%	
McCleery, 2016[43] MA	High	Melatonin: 111 Lactose placebo: 53	2	carer-rated sleep quality	Standardized mean difference (95% CI): 0.04 (–0.29 to 0.38) I^2: 46%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Lee, NA[58] MA	Critically Low	Melatonin: 675 Placebo: 672	10	LSEQ – Quality of Sleep; PSQI Component 1; Northside Hospital Sleep Medicine Institute Test; Daily Sleep Questionnaire	Standardized mean difference (95% CI): 0.16 (–0.06 to 0.39) I^2: 58%	
Sateia, 2017[45] MA	Critically Low	Melatonin: 233 Placebo: 228	3	subjective measure	Standardized mean difference (95% CI): 0.21 (–0.36 to 0.77) I^2: 83%	
Bellon, 2006[64] SR	Critically Low	Melatonin: NR Placebo: NR	11	subjective PSG actigraphy		Adult patients: 4 studies showed **significant improvement**; 2 studies showed no change. Elderly patients: 2 studies no change Medically ill patients: 1 study **significant improvement.** Dementia or Alzheimer patients: 2 studies, no change.
Chase, 1997[67] SR	Critically Low	Melatonin Placebo Total sample: 10	1	daily sleep questionnaire		No statistical difference between groups noted, except patients in melatonin group had **significantly improved** perceived quality of sleep **(*P* < 0.03).**

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Costello, 2014[71] SR	Moderate	Melatonin Placebo Total sample: 54	3	sleep diary; subjective sleep quality questionnaire; daily sleep questionnaire; Stanford Sleepiness Scale; VAS		Melatonin did not affect sleep quality in patients with primary insomnia; melatonin **significantly improved** sleep quality compared with placebo, indicating that controlled-release melatonin may effectively facilitate discontinuation of benzodiazepine therapy while maintaining good sleep quality; melatonin 5 mg resulted in an improvement in overall subjective sleep quality **(*P* = 0.03)** compared with 1 mg and placebo.
Culpepper, 2015[72] SR	Critically Low	Melatonin Placebo Total sample: 48	2	sleep questionnaire: VAS; 38-item Northside Hospital Sleep Medicine Institute test	Change in outcome (*P* value): **1.78 vs. 3.44 (*P* < 0.05)**	One study: No significant difference between groups (melatonin vs placebo); One study: **Significantly improved** sleep quality.
		Melatonin Placebo Total sample: 344	2	PSG, sleep diary (2)	Change in outcome (*P* value): **26% vs. 15% (*P* < 0.05)**	One study: no significant difference between groups; One study: **Higher rate** of sleep quality in patients while on melatonin vs. placebo.
Vural, 2014[84] SR	Critically Low	Melatonin Control Total sample: 27	1	NR		**Significant increase** in sleep quality in melatonin group.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Antihistamine Drugs vs. Inactive Controls; 1 SRs						
Culpepper, 2015[72] SR	Critically Low	Diphenhydramine Placebo Total Sample: 20	1	sleep diary	Change in outcome (*P* value): No difference in subjective scores 3.0 vs. 2.9 (*P* = NS)	No significant treatment difference for sleep quality.
Cognitive Behavioural Interventions vs. Inactive Controls; 14 SR+MAs, 4 SRs						
Brasure, 2015[29] **CBT** MA	High	CBT-I: 296 Sham treatment/ placebo, wait-list control, no treatment, or sleep hygiene/sleep education): 284	6	PSQI	Mean difference (95% CI): **–2.1 (–2.87 to –1.34)** I^2: 37%	
Ho, 2016[35] **CBT** MA	Low	CBT: image rehearsal therapy, exposure, re-scripting and relaxation therapy, mind-body bridging, behavioural sleep intervention: NR Wait-list control, sleep hygiene: NR	6	PSQI	Standardized mean difference (95% CI): **–0.87 (–1.18 to –0.56)** I^2: 33%	
Irwin, 2006[37] **CBT** MA	Critically Low	CBT: relaxation, biofeedback, hypnosis, sleep compression/ restriction, paradoxical intention: NR control: NR	7	self-report	Cohen's *d* (95% CI): **0.76 (0.48 to 1.03)** Q-statistic: 7.92	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Koffel, 2015[40] **CBT** MA	Critically Low	Group CBT-I - stimulus control, sleep restriction, and addressing dysfunctional beliefs about sleep: NR Wait-list, treatment as usual, placebo: NR	5	sleep diary, sleep quality measures	Mean effect size (95% CI): 0.4 (–0.14 to 0.93) I^2: NR	
Navarro-Bravo, 2015[56] **CBT** MA	Moderate	CBT: sleep restriction, stimulus control, sleep education/hygiene: NR Placebo, wait-list control, stress management and wellness training, treatment as usual, sleep hygiene/education: NR	5	PSQI	Cohen's *d* (95% CI): **–0.59 (–0.59 to –0.85)** Chi square: 6.85; 0.144	
Tang, 2015[49] **CBT** MA	Moderate	CBT-I: psychoeducation, sleep hygiene, stimulus control, sleep restriction, cognitive therapy, and relaxation: 510 Wait-list, treatment as usual: 455	11	PSQI; ISI	Standardized mean difference (95% CI): **0.78 (0.42 to 1.13)** I^2: 84%	
van Straten, 2007[51] **CBT** MA	Low	CBT: relaxation, sleep restriction, stimulus control, paradoxical Intention, identifying and challenging dysfunctional thoughts: NR Wait-list control, no treatment, placebo, psychoeducation: NR	19	PSQI	Hedges' *g* (95% CI): **0.65 (0.51 to 0.79)** I^2: 39%	
			40	sleep diary	Hedges' *g* (95% CI): **0.4 (0.24 to 0.56)** I^2: 74%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
van Straten, 2009[93] **CBT** MA	Moderate	CBT: self-help: stimulus control, sleep restriction, cognitive therapy, sleep hygiene, relaxation, in-bed exercises: NR Waiting list: NR	7	sleep diary	Cohen's *d* (95% CI): **0.21 (0.06 to 0.35)** I^2: 52.3%	
Cheng, 2012[32] **CBT** MA	Low	Sleep hygiene, stimulus control, relaxation training, sleep restriction, cognitive restructuring: NR Wait-list control: NR	4	PSQI	Standardized mean difference (95% CI): **0.41 (0.16 to 0.65)** I^2: 45%	
Bogdanov, 2017[65] **CBT** SR	Low	CBT (unspecified) Control (unspecified) Total sample: 3	1	PSQI		No clinically meaningful improvement in either group.
Venables, 2014[90] **CBT** SR	Critically Low	Professionally administered CBT: 215 No comparator (pre- / post-intervention)	2	PSQI	Change in outcome (mean change (%)): 7.3 (37.6)	Two of 2 studies found a reduction in PSQI scores (*P* values not reported); neither of the scores decreased to below 5.0, above which is a diagnostic score for insomnia.
Buscemi, 2005[30] **CBT+ Behavioural** MA	High	CBT + relaxation - relaxation training, cognitive control, stimulus control, group relaxation, aggressive muscle relaxation, cognitive distraction: 23 placebo: 26	2	NR	Mean difference (95% CI): 0.69 (–0.34 to 1.73) I^2: 65.4%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Yang, 2014[53] **CBT+ Behavioural** MA	Moderate	CBT + relaxation - CBT, sleep hygiene, relaxation CD: 93 Sleep hygiene education, treatment as usual: 91	3	global PSQI	Standardized mean difference (95% CI): **0.85 (0.37 to 1.34)** I^2: 56%	
		CBT + relaxation - CBT, sleep hygiene, relaxation CD: 56 Sleep hygiene education, treatment as usual: 56	2	subjective sleep quality in PSQI	Standardized mean difference (95% CI): 0.44 (–0.28 to 1.17) I^2: 64%	
Ho, 2015[36] **Multi-CBT** MA	Low	Multi-component CBT: stimulus control, sleep restriction, sleep hygiene, relaxation and/or cognitive therapy: NR Waiting-list control, routine care or no treatment: NR	4	sleep diary	Hedges' *g* (95% CI): **0.43 (0.2 to 0.6)** I^2: 0%	
Okajima, 2011[57] **Multi-CBT** MA	Critically Low	Multi-component CBT: sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, relaxation, paradoxical intention: NR Wait-list control, placebo, sleep hygiene education, control(unspecified), treatment as usual: NR	2	PSQI	Cohen's *d* (95% CI): **0.77 (0.48 to 0.97)** I^2: NR	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Zachariae, 2016[55] Multi-CBT MA	Moderate	Multi-component CBT: stimulus control, sleep hygiene, cognitive therapy, sleep restriction, relaxation techniques: NR Wait-list control, treatment as usual: NR	8	NR	Hedges' *g* (95% CI): **0.49 (0.30 to 0.68)** I^2: 34.5%	
Howell, 2014[75] Multi-CBT SR	Moderate	Multi-component CBT: sleep hygiene, sleep restriction, stimulus control, cognitive restructuring, and relaxation therapies Usual care, wait-list control, healthy eating and nutrition, sleep education and hygiene only, no treatment Total sample: 233	2	actigraphy sleep diary		**Significant improvement** in all studies post CBT intervention identified for sleep quality (*P* values not reported).
McCurry, 2007[79] Multi-CBT SR	Critically Low	Multi-component CBT: sleep hygiene, relaxation, sleep compression, cognitive behavioural therapy, stimulus control Delayed treatment, wait-list control, placebo;, stress management: Total sample: 210	4	sleep logs PSQI		**Significant improvement** in sleep quality ratings compared with control.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Cognitive Behavioural Interventions vs. Active Controls; 2 SR+MAs						
van Straten, 2009[93] **CBT** MA	Moderate	Self-help CBT: stimulus control, sleep restriction, cognitive therapy, sleep hygiene, relaxation, in-bed exercises: NR In-person CBT: NR	2	sleep diary	Cohen's *d* (95% CI): –0.5 (–0.90 to 0.02) I^2: 0%	
Buscemi, 2005[30] **CBT+ Behavioural** MA	High	CBT + relaxation: relaxation training, stimulus control, aggressive muscle relaxation, cognitive distraction: 23 CBT: cognitive therapy, sleep restriction, stimulus control, sleep hygiene: 24	2	NR	Mean difference (95% CI): 0.2 (–0.38 to 0.77) I^2: 0%	
Behavioural Interventions vs. Inactive Controls; 1 SRs with meta-analysis, 5 SRs						
Hwang, 2016[61] MA	Critically Low	Behavioural therapy, Brief behavioural treatment: NR Control (unspecified): NR	5	PSQI	Standardized mean difference (95% CI): **1.90 (0.04 to 2.94)** I^2: 96.27%	
Bogdanov, 2017[65] SR	Low	Problem-solving therapy sleep education only Total sample: 356	1	PSQI		**Significant improvement** compared with control at 6-month but not 12-month follow-up **(*P* = 0.003, 6 months; *P* = 0.88, 12 months).**
Miller, 2014[81] SR	High	Sleep restriction therapy: 44 Wait-list control, sleep hygiene instructions: 50	1	sleep diary	Change in outcome (effect size; SD): intervention (pre-post) 2.77 to 2.90 (0.3; NA); control (pre-post): 2.57 to 2.58 (0.03; NA)	Sleep quality ratings were only reported in one study and were found to increase (ES = 0.3).

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Brooks, 2014[66] SR	Low	Progressive relaxation training: 37 Control: NR	1	sleep diary		Treatment group had **significant difference** in sleep quality pre- and post-treatment.
Hellström, 2011[74] SR	Moderate	Mental imagery Usual care Total sample: 36	1	VSH-sleep scale		Effects of relaxation on sleep quality were small and did not reach significance.
Tamrat, 2013[89] SR	Low	Relaxation techniques, audiotape guided imagery, relaxation tapes Usual care Solitary activity, baseline Total sample: 211	3	self-rating (poor, fair, good); RCSQ		In summary, there is low strength of evidence that studies of relaxation techniques improve sleep quality.
Behavioural Interventions vs. Active Controls; 1 SR+MAs						
Seda, 2015[46] MA	Low	IRT: NR CBT (stimulus control and sleep restriction therapy) + IRT: NR	8	PSQI	Cohen's *d* (95% CI): IRT post-treatment: 0.50 (0.16 to 0.84) IRT+CBT post-treatment: 1.32 (0.68 to 1.96) Q-statistic (*P* value): 4.75 (*P* = 0.03)	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Mindfulness vs. Inactive Controls; 1 SR+MAs, 1 SRs						
Gong, 2016[34] MA	Low	Mindfulness-based stress reduction, mindfulness meditation, mindfulness-based therapy for insomnia Wait-list control, sleep hygiene education, self-monitoring condition Total sample: 83	2	sleep diary	standardized mean difference (95% CI): **0.68 (0.24 to 1.13)** I^2: 0%	
		Mindfulness-based stress reduction, mindfulness meditation, mindfulness-based therapy for insomnia Wait-list control, sleep hygiene education, self-monitoring condition Total sample: 109	2	PSQI	standardized mean difference (95% CI): –1.09 (–1.50 to 0.69) I^2: 0%	
Venables, 2014[90] SR	Critically Low	Mindfulness-based stress reduction, mind-body bridging, mindfulness meditation: 63 No comparator (pre- / post- intervention)	1	PSQI	Proportion of respondents: (pre-intervention) 91% score > 5 51% score > 10 (post-intervention) 79% score > 5 27% score > 10	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Combination Therapy vs. Inactive Controls; 1 SR						
Chiesa, 2009[88] SR	Low	Pharmacotherapy (general) and mindfulness-based cognitive therapy, mindfulness-based stress reduction: 14 No comparator (pre- / post- intervention)	1	NR	NR	Measures of sleep quality **improved significantly** post-treatment, improvements were maintained at 6 and 12 months; levels of mindfulness were shown to correlate with quality of sleep.

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CBT = cognitive behavioural therapy; CD = compact disc; CI = confidence interval; HAM-D = Hamilton Rating Scale for Depression; IRT = imagery rehearsal therapy; LSEQ = Leeds Sleep Evaluation Questionnaire; MA = meta-analysis; No. = number; NR = not reported; NS = not significant; PSG = polysomnography; PSQI = Pittsburgh Sleep Quality Index; RCSQ = Richards Campbell Sleep Questionnaire; SOL = sleep onset latency; SR = systematic review; SR+MA = systematic review plus meta-analysis; SSQ = Spiegel Sleep Questionnaire; VAS = Visual Analogue Scale; vs. = versus; VSH = Verran and Snyder-Halpern Sleep Scale.

Table 81: Detailed Results for Sleep Satisfaction

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Antipsychotic Drugs vs. Inactive Controls; 1 SRs						
Anderson, 2014[63] SR	Critically Low	Quetiapine Placebo; no therapy Total sample: 25	1	VAS		Non-significant improvement based on VAS (*P* = 0.505).
Melatonin vs. Inactive Controls; 1 SR						
Vural, 2014[84] SR	Critically Low	Melatonin Control Total sample: 112	1	% nights scored good; % good mood		**Significant increase** in % nights scored good and significant increase in % good mood in melatonin group.
Cognitive Behavioural Interventions vs. Inactive Controls; 1 SR						
Wang, 2005[85] **CBT** SR	Moderate	CBT: stimulus control; sleep restriction; cognitive therapy; sleep hygiene education; sleep scheduling Control: quasi-desensitization; self-monitoring control; sleep hygiene recommendations; waiting-list control Total sample: 81	2	DBAS evaluation; BAS scale		CBT provided greater improvements in DBAS scores than did placebo, CBT endorsed less dysfunctional beliefs and attitudes about sleep than the placebo group; **significantly greater improvement** in BAS scores.
Behavioural Interventions vs. Inactive Controls; 1 SR						
McCurry, 2007[79] SR	Critically Low	Sleep restriction: nap sleep restriction therapy; sleep compression; sleep compression guidance and sleep hygiene Placebo: waiting list Total sample: 125	1	NR		Sleep compression guidance in combination with sleep education delivered via a standardized video resulted in greater post-test sleep satisfaction scores compared with placebo.

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; BAS = beliefs and attitudes about sleep; CBT = cognitive behavioural therapy; DBAS = Dysfunctional Attitudes and Beliefs About Sleep; ES = effect size; No. = number; NR = not reported; SR = systematic review; VAS = visual analogue scale; vs. = versus.

Table 82: Detailed Results for Sleep Efficiency

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Non-Benzodiazepine Drugs vs. Inactive Controls; 1 SR+MA, 1 SR						
Sateia, 2017[45] MA	Critically Low	Zolpidem: 111 Placebo: 115	4	PSG	Mean difference (95% CI): **6.12 (4.39 to 7.85)** I^2: 35%	
Swainston Harrison, 2005[91] SR	Critically Low	Zolpidem Placebo Total sample: 69	1	NR	Change in outcome (*P* value): –3 mins vs. +5 mins (*P* = NS)	NR
Non-Benzodiazepine Drugs vs. Other Pharmacological Interventions; 1 SR						
Swainston Harrison, 2005[91] SR	Critically Low	Zolpidem Triazolam Total sample: 86	2	NR	Change in outcome (*P* value): **+10 mins vs. –6 mins (*P* < 0.01)** –3 mins vs. –15 mins (*P* = NS)	NR
Antidepressant Drugs to Inactive Controls; 2 SR+MAs, 4 SRs						
Sateia, 2017[45] MA	Critically Low	Doxepin (3 mg): 214 Placebo: 209	3	PSG	Mean difference (95% CI): **6.78 (4.50 to 9.07)** I^2: 17%	
		Doxepin (6 mg): 141 Placebo: 139	2	PSG	Mean difference (95% CI): **7.06 (5.12 to 9.01)** I^2: 0%	
Yuan, 2010[59] MA	Low	Doxepin (1 mg): 140 Placebo: 139	2	NR	Mean difference (95% CI): **3.59 (1.55 to 5.63)** I^2: NR	
		Doxepin (25 mg): 30 Placebo: 30	2	NR	Mean difference (95% CI): **12.58 (7.60 to 17.56)** I^2: NR	
		Doxepin (3 mg): 140 Placebo: 139	2	NR	Mean difference (95% CI): **5.82 (3.75 to 7.90)** I^2: NR	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
		Doxepin (6 mg): 141 Placebo: 139	2	NR	Mean difference (95% CI): **7.07 (5.12 to 9.01)** I^2: NR	
Mayers, 2005[78] SR	Critically Low	Doxepin Placebo Total sample: 47	1	NR		Doxepin **significantly increased** SE compared with placebo **(*P* < 0.05).**
Vande Griend, 2012[83] SR	Critically Low	Doxepin: NR Placebo: NR	6	PSG questionnaire (7-point Likert-type scale)		Doxepin increased SE by 6% to 10% across the trials; **significant differences** were found compared with placebo **(*P* < 0.05).**
Yeung, 2015[87] SR	Moderate	Doxepin Placebo Total sample:	1	PSG		SE **significantly improved** compared with placebo after 28 nights (*P* value not reported).
Mendelson, 2005[80] SR	Critically Low	Trazodone placebo; unspecified control Total sample: 56	3	PSG		Mixed result: 2 trials found **significant improvements** in SE compared with placebo **(*P* < 0.05)**; 1 trial found no significant change compared with placebo.
		Trazodone: 20 No comparator (pre- / post-intervention)	3	PSG		Mixed result: 1 trial found **significant improvements** in SE compared with baseline **(*P* < 0.05)**; 2 trials found no significant change from baseline.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Vande Griend, 2012[83] SR	Critically Low	Trazodone: NR Placebo: NR	2	sleep diaries; PSG		Mixed result: 1 study found **significant difference** between groups (***P* < 0.05**, PSG data only); 1 study found no difference between group (PSG and sleep diary data).
Antipsychotic Drugs vs. Inactive Controls; 3 SRs						
Anderson, 2014[63] SR	Critically Low	Quetiapine: 18 No comparator (pre- / post-intervention)	1	PSG	Change in outcome (*P* value): **89.9 ± 8.2 (*P* < 0.05)**	NR
		Quetiapine Placebo; no therapy Total sample: 27	1	PSG or actigraphy	Change in outcome (*P* value): **82.7 ± 9.1 vs. 77.0 ± 7.9 (*P* < 0.05)**	NR
Coe, 2014[70] SR	Critically Low	Quetiapine: 18 No comparator (pre- / post-intervention)	1	Objective measure		SE **significantly improved** from baseline compared with week 6 **(*P* = 0.02).**
Wine, 2009[86] SR	Critically Low	Quetiapine: 18 No comparator (pre- / post-intervention)	1	NR	Change in outcome (*P* value): **83% ± 14% to 90% ± 8% (*P* < 0.05)**	**Significant increase** in SE with quetiapine use compared with baseline.
Melatonin vs. Inactive Controls; 5 SR+MAs, 3 SRs						
Buscemi, 2004[31] MA	High	Melatonin:117 Placebo: 117	9	NR	Mean difference (95% CI): 1.45 (–0.66 to 3.56) I^2: 62.8%	
McCleery, 2016[43] MA	High	Melatonin: 104 Placebo: 47	1	actigraphy	Mean difference (95% CI): –0.01 (–0.04 to 0.03) I^2: 0%	
Xu, 2015[52] MA	Moderate	Melatonin: 232 Placebo; light therapy: 214	6	actigraphy	Mean difference (95% CI): 1.78 (–0.13 to 3.70) I^2: 25%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Lee, NA[58] MA	Critically Low	Melatonin: 123 Placebo: 125	8	sleep diary PSG actigraphy	Mean difference (95% CI): **2.74 (0.41 to 5.88)** I^2: 54%	
Zhang, 2016[60] MA	Critically Low	Melatonin: 75 Placebo: 69	2	PSG actigraphy	Mean difference (95% CI): –0.01 (–0.04 to 0.02) I^2: 0%	
Bellon, 2006[64] SR	Critically Low	Melatonin: NR Placebo: NR	12	subjective PSG actigraphy		Adult patients: No change across all studies. Elderly patients: 2 studies no change; 2 studies **significant improvement.** Schizophrenia patients: 1 study **significant improvement.** Dementia or Alzheimer: studies, no change.
Chase, 1997[67] SR	Critically Low	Melatonin Placebo Total sample: 35	2	wrist actigraphy	Proportion of respondents (*P* value): **83% vs. 75% (*P* < 0.001)**	Increase in SE; a **significant difference** in SE was noted in the elderly without sleep disorders and compared with those with insomnia **(*P* < 0.0001).**
Culpepper, 2015[72] SR	Critically Low	Melatonin Placebo Total sample: 40	1	Actigraphy		No significant difference between groups.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Antihistamines vs. Inactive Controls; 1 SR						
Vande Griend, 2012[83] SR	Critically Low	Diphenhydramine Placebo Total Sample: 204	1	sleep diaries PSG		Overall, the outcomes analyzed from all 4 trials provided mixed results, with the majority not being statistically different than placebo ($P > 0.05$). Sleep diary data showed **significant improvement ($P < 0.05$)**. PSG data showed no difference compared with placebo.
Cognitive Behavioural Interventions vs. Inactive Controls; 16 SR+MAs, 8 SRs						
Cheng, 2012[32] **CBT** MA	Low	CBT: sleep hygiene, stimulus control, relaxation training, sleep restriction, cognitive restructuring: NR Wait-list control: NR	4	sleep diary	Standardized mean difference (95% CI): **0.4 (0.15 to 0.64)** I^2: 63%	
Ho, 2016[35] **CBT** MA	Low	CBT: image rehearsal therapy, exposure, re-scripting and relaxation therapy, mind-body bridging, behavioural sleep intervention: NR wait-list control; sleep hygiene: NR	5	sleep diary	Standardized mean difference (95% CI): **1.15 (0.75 to 1.56)** I^2: 37%	
Irwin, 2006[37] **CBT** MA	Critically Low	CBT: relaxation, biofeedback, hypnosis, sleep compression/restriction, paradoxical intention: NR control: NR	8	self-report	Cohen's *d* (95% CI): **0.52 (0.28 to 0.75)** Q-statistic: 47.85	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Johnson, 2016[38] CBT MA	Moderate	CBT-I with both cognitive and behavioural components: 423 Wait-list control, treatment as usual, sleep education, behavioural placebo, mindfulness-based stress reduction: 297	8	sleep diary	Cohen's *d* (95% CI): **0.33 (0.11 to 0.54)** I^2: 41.1%	
Koffel, 2015[40] CBT MA	Critically Low	Group CBT-I: stimulus control, sleep restriction, and addressing dysfunctional beliefs about sleep: NR Wait-list, treatment as usual, placebo: NR	6	sleep diary	Mean effect size (95% CI): **0.84 (0.38 to 1.31)** I^2: NR	
Montgomery, 2003[44] CBT MA	High	CBT: CBT (unspecified), sleep hygiene, stimulus control, muscle relaxation, sleep restriction, cognitive therapy, education, imagery training: 86 wait-list control, placebo: 57	3	sleep diary	Mean difference (95% CI): –7.49 (–15.45 to 0.47) I^2: 77%	
		CBT: cognitive behavioural therapy (unspecified); sleep hygiene; stimulus control; muscle relaxation; sleep restriction; cognitive therapy; education; imagery training: 30 Wait-list control, placebo: 29	2	PSG	Mean difference (95% CI): **–6.25 (–10.18 to –2.31)** I^2: 0%	
Navarro-Bravo, 2015[56] CBT MA	Moderate	CBT: sleep restriction, stimulus control, sleep education/hygiene: NR Placebo, wait-list control, stress management and wellness training, treatment as usual, sleep hygiene/education: NR	8	sleep diary PSG actigraphy sleep evaluation (4-item questionnaire)	Cohen's *d* (95% CI): **0.78 (0.34 to 1.21)** Chi square: 47.56; 0.000	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Seyffert, 2016[47] Multi-CBT MA	Low	Internet-based CBT: sleep education, stimulus control, sleep restriction, relaxation, sleep hygiene, cognitive techniques: NR Wait-list control, Internet control, treatment as usual: NR	9	Sleep diary	Mean difference (95% CI): **7.22 (5.13 to 9.32)** I^2: 39.5%	
van Straten, 2007[51] CBT **MA**	Low	CBT: relaxation, sleep restriction, stimulus control, paradoxical intention, identifying and challenging dysfunctional thoughts: NR Wait-list control, no treatment, placebo, psychoeducation: NR	79	sleep diary	Hedges' *g* (95% CI): **0.71 (0.61 to 0.82)** I^2: 70%	
van Straten, 2009[93] CBT MA	Moderate	CBT: self-help: stimulus control, sleep restriction, cognitive therapy, sleep hygiene, relaxation, in-bed exercises: NR Waiting list: NR	7	sleep diary	Cohen's *d* (95% CI): **0.26 (0.11 to 0.40)** I^2: 65.5%	
Ye, 2016[54] CBT MA	Moderate	CBT: sleep hygiene education, cognitive restructuring, stimulus control, sleep restriction, relaxation therapy, hierarchy development, imagery training, scheduled pseudo desensitization, breathing control: 1,006 Wait-list control, treatment as usual, Internet + email, Internet + telephone, telephone, Internet-based control: 1,003	15	sleep diary	Mean difference (95% CI): **9.58 (7.30 to 11.85)** I^2: 76%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Bogdanov, 2017[65] CBT SR	Low	CBT (unspecified) Control (unspecified) Total sample: 11	1	sleep diary		**Significant improvement** in SE compared with control **(*P* = 0.01).**
Brooks, 2014[66] CBT SR	Low	CBT-I: 7 No comparator (pre- / post-intervention)	1	daily sleep diary		Improvement in SE (*P* values not reported).
		CBT-I (unspecified): NR Control (unspecified): NR	2	daily sleep diary PSQI actigraphy		Self-reported SE improved in treatment group; maintained for 6 months post-treatment; not corroborated by actigraphy.
Dickerson, 2014[73] CBT SR	High	CBT (unspecified): 12 No comparator (pre- / post-intervention)	1	sleep diary	Change in outcome: pre-/post- scores **1.49 (0.88 to 2.79)**	SE improved compared with baseline at week 4 and week 8.
Ishak, 2012[76] CBT SR	Low	CBT (unspecified) placebo, no treatment, usual care Total sample: 209	1	SF-36; CIS-20; GHQ; PANAS; FACT-G		**Significant improvements** in SE at both 3- and 6-month follow-up **(*P* < 0.01).**
Wang, 2005[85] CBT SR	Moderate	CBT: stimulus control, sleep restriction, cognitive therapy, sleep hygiene education, sleep scheduling Control: quasi-desensitization, self-monitoring control, sleep hygiene recommendations, waiting-list control Total sample: 128	4	sleep diary/log PSG structured interview		Four of 4 studies found improvement in SE compared with control; only 2 of 4 were **statistically significant.**

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Taylor, 2014[82] **CBT** SR	Critically Low	CBT: stimulus control, sleep restriction, relaxation therapy, cognitive therapy, image rehearsal therapy, medication withdrawal: NR Wait-list, usual care, sleep hygiene, placebo control: NR	13	sleep diaries	Mean effect size (95% CI; *P* value): **0.758** **(0.557 to 0.958; *P* < 0.01)**	CBT-I results in **significant improvement** in SE in patients with comorbid psychiatric disorders, medium to large effects were homogeneous across studies.
Venables, 2014[90] **CBT** SR	Critically Low	Group CBT: 660 No comparator (pre- / post-intervention)	8	NR		Eight of 8 studies obtained improvements in SQ; results demonstrate that group-delivered CBT sessions may be slightly more effective than individual sessions.
		Professionally administered CBT: 615 No comparator (pre- / post-intervention)	8	actigraphy sleep diary		Eight of 8 studies found a **significant improvement** in SE (*P* values not reported).
Yang, 2014[53] **CBT+ Behavioural** MA	Moderate	CBT + relaxation: CBT, sleep hygiene, relaxation CD: 56 Sleep hygiene education; treatment as usual: 56	2	habitual SE in PSQI	Standardized mean difference (95% CI): –0.43 (–1.68 to 0.83) I^2: 86%	
Ho, 2015[36] **Multi-CBT** MA	Low	Multi-component CBT: stimulus control, sleep restriction, sleep hygiene, relaxation and/or cognitive therapy: NR Waiting-list control; routine care or no treatment: NR	7	sleep diary	Hedges' *g* (95% CI): **0.79 (0.2 to 1.4)** I^2: 92%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Okajima, 2011[57] **Multi-CBT** MA	Critically Low	Multi-component CBT: sleep hygiene education; sleep restriction; stimulus control; cognitive therapy; relaxation; paradoxical intention: NR Wait-list control, placebo; sleep hygiene education; control(unspecified); treatment as usual: NR	8	sleep diary	Cohen's *d* (95% CI): **0.43 (0.25 to 0.59)** I^2: NR	
			2	PSG actigraphy	Cohen's *d* (95% CI): **0.78 (0.27 to 1.17)** I^2: NR	
Trauer, 2015[50] **Multi-CBT** MA	Moderate	Multi-component CBT: cognitive therapy, stimulus control, sleep restriction, relaxation, sleep hygiene: NR Wait-list control, treatment as usual, sleep hygiene, sham, placebo: NR	17	sleep diary	Mean difference (95% CI): **9.91 (8.09 to 11.73)** I^2: 47.1%	
Zachariae, 2016[55] **Multi-CBT** MA	Moderate	Multi-component CBT: stimulus control, sleep hygiene, cognitive therapy, sleep restriction, relaxation techniques: NR Wait-list control, treatment as usual: NR	10	NR	Hedges' *g* (95% CI): **0.58 (0.36 to 0.81)** I^2: 68.4%	
Howell, 2014[75] **Multi-CBT** SR	Moderate	Multi-component CBT: sleep hygiene, sleep restriction, stimulus control, cognitive restructuring, and relaxation therapies Usual care, wait-list control, healthy eating and nutrition, sleep education and hygiene only, no treatment Total sample: 209	1	SF-36		SE **increased** in all studies post CBT intervention **(*P* < 0.01).**

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
McCurry, 2007[79] Multi-CBT SR	Critically Low	Multi-component CBT: sleep hygiene, relaxation, sleep compression, cognitive behavioural therapy, stimulus control Delayed treatment, wait-list control, placebo; stress management: Total sample: 154	3	sleep logs		CBT group had **significant improvement** in SE compared with stress management.
Cognitive Behavioural Interventions vs. Active Controls; 2 SR+MAs, 2 SRs						
van Straten, 2009[93] CBT MA	Moderate	Self-help CBT: stimulus control; sleep restriction; cognitive therapy; sleep hygiene; relaxation; in-bed exercises: NR In-person CBT: NR	3	sleep diary	Cohen's *d* (95% CI): –0.29 (–0.65 to 0.06) I^2: 22.4%	
Seyffert, 2016[47] CBT MA	Low	Internet-based CBT: sleep education, stimulus control, sleep restriction, relaxation, sleep hygiene, cognitive techniques: NR In-person CBT: NR	2	sleep diary	Mean difference (95% CI): –1.21 (–49.0 to 46.6) I^2: 59.7%	
Wang, 2005[85] CBT SR	Moderate	CBT: stimulus control; sleep restriction; sleep hygiene education CBT + relaxation therapy Total sample: 46	1	PSG sleep log	Change in outcome: CBT: 77.8% to 85.5%; relaxation: 77.8% to 78.1%	NR
McCurry, 2007[79] CBT SR	Critically Low	CBT + Temazepam CBT Total sample: 78	1	PSG sleep logs		The combination of CBT + temazepam was **significantly more effective** than placebo.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Behavioural Interventions vs. Inactive Controls; 2 SRs						
McCurry, 2007[79] SR	Critically Low	Sleep restriction (nap sleep restriction therapy; sleep compression; sleep compression guidance and sleep hygiene) Placebo, waiting list Total sample: 129	2	sleep logs		Sleep restriction therapy was found to be **significantly more beneficial** than a sleep hygiene/placebo control.
Miller, 2014[81] SR	High	Sleep restriction therapy: 82 Wait-list control; sleep hygiene instructions: 78	3	sleep diary actigraphy	Change in outcome (effect size; SD): intervention (pre-/post-): 16.28% (1.50; 0.35); Control (pre-/post-): 4.59% (0.04; 0.23)	SE increased in 3 studies; the effect size for SE the intervention was large.
Mindfulness vs. Inactive Controls; 1 SR+MAs, 1 SRs						
Gong, 2016[34] MA	Low	Mindfulness-based stress reduction; mindfulness meditation; mindfulness-based therapy for insomnia Wait-list control; sleep hygiene education; self-monitoring condition Total sample: 58	2	sleep diary	Standardized mean difference (95% CI): 0.85 (–0.31 to 1.40) I^2: 0%	
Venables, 2014[90] SR	Critically Low	Mindfulness-based stress reduction; mind-body bridging; mindfulness meditation: 205 No comparator (pre- / post- intervention)	3	NR		Two trials showed **significant improvement** in SE; 1 trial showed no significant improvement.

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CBT = cognitive behavioural therapy; CD = compact disc; CI = confidence interval; MA = meta-analysis; mins = minutes; No. = number; NR = not reported; NS = not significant; PSG = polysomnography; SD = standard deviation; SE = sleep efficiency; SQ = sleep quality; SR = systematic review; SR+MA = systematic review plus meta-analysis; VAS = visual analogue scale; vs. = versus.

Table 83: Detailed Results for Insomnia Severity Index

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Suvorexant vs. Inactive Controls; 2 SR+MAs, 1 SR						
Kishi, 2015[39] MA	Moderate	Suvorexant: 947 Placebo: 952	3	ISI	Mean difference (95% CI): **–1.35 (–1.78 to –0.93)** I^2: 0%	
Kuriyama, 2017[41] MA	Moderate	Suvorexant: NR Placebo: NR	3	ISI	Mean difference (95% CI): **–1.42 (–1.85 to –0.98)** I^2: 0%	
Citrome, 2014[69] SR	Critically Low	Suvorexant (15 mg, 20 mg): 411 Placebo: 638	2	ISI	Proportion of respondents with > 6-point improvement: 55.5% vs. 42.2%; NNT 8 (95% CI, 6 to 14)	
		Suvorexant (30 mg, 40 mg): 656 Placebo: 638	2	ISI	Proportion of respondents with > 6-point improvement: 54.9% vs. 42.2%; NNT 8 (95% CI, 6 to 14)	
Antidepressant Drugs vs. Inactive Controls; 1 SR+MA						
Brasure, 2015[29] MA	High	Doxepin: 289 Placebo: 205	2	ISI	Mean change (95% CI): **–1.74 (–2.59 to –0.88)** I^2: 0%	
Antipsychotic Drugs vs. Inactive Controls; 1 SR						
Anderson, 2014[63] SR	Critically Low	Quetiapine: 6 No comparator (pre- / post-intervention)	1	ISI		In 5 of 6 patients, the ISI score moved from moderate insomnia to absence of insomnia at week 1 and was maintained.
Antihistamines to Inactive Controls; 1 SR						
Culpepper, 2015[72] SR	Critically Low	Diphenhydramine Placebo Total sample: 184	1	ISI	Change in outcome (*P* = value): **9.39 vs. 11.63 (*P* < 0.01)**	**Significantly lower** ISI with diphenhydramine after 2 weeks.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Cognitive Behavioural Interventions vs. Inactive Controls; 9 SR+MAs, 6 SRs						
Brasure, 2015[29] **CBT** MA	High	CBT-I: 172 Sham treatment/ placebo, wait-list control, no treatment, or sleep hygiene/sleep education): 173	5	ISI	Mean difference (95% CI): **–5.15 (–7.13 to –3.16)** I^2: 67%	
		CBT-I: 68 Passive control (placebo or sham treatment or wait-list): 63	4	ISI	Mean difference (95% CI): **–7.1 (–12.87 to –1.32)** I^2: 89%	
Cheng, 2012[32] **CBT** MA	Low	CBT: sleep hygiene, stimulus control, relaxation training, sleep restriction, cognitive restructuring: NR Wait-list control: NR	2	ISI	Standardized mean difference (95% CI): **–0.86 (–1.18 to –0.53)** I^2: 0%	
Ho, 2016[35] **CBT** MA	Low	CBT: image rehearsal therapy; exposure, re-scripting and relaxation therapy; mind-body bridging; behavioural sleep intervention: NR Wait-list control, sleep hygiene: NR	5	ISI	Standardized mean difference (95% CI): **–1.15 (–1.81 to –0.49)** I^2: 77%	
Johnson, 2016[38] **CBT** MA	Moderate	CBT-I with both cognitive and behavioural components: NR Wait-list control, treatment as usual, sleep education, behavioural placebo, mindfulness-based stress reduction: NR	4	ISI	Cohen's *d* (95% CI): **0.547 (0.37 to 0.73)** I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Navarro-Bravo, 2015[56] **CBT** MA	Moderate	CBT: sleep restriction, stimulus control, sleep education/hygiene: NR Placebo; wait-list control, stress management and wellness training, treatment as usual, sleep hygiene/education: NR	4	ISI	Cohen's *d* (95% CI): **–0.7 (–1.1 to –0.22)** Chi square: 11.54; 0.009	
Seyffert, 2016[47] **CBT** MA	Low	CBT: sleep education, stimulus control, sleep restriction, relaxation, sleep hygiene, cognitive techniques: NR Wait-list control, Internet control, treatment as usual: NR	4	sleep diary	Mean difference (95% CI): **–3.74 (–7.10 to –0.39)** I^2: 90%	
van Straten, 2007[51] **CBT** MA	Low	CBT: relaxation, sleep restriction, stimulus control, paradoxical intention, identifying and challenging dysfunctional thoughts: NR Wait-list control, no treatment, placebo, psychoeducation: NR	38	ISI	Hedges' *g* (95% CI): **0.98 (0.82 to 1.15)** I^2: 74%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Ye, 2016[54] **CBT** MA	Moderate	CBT: sleep hygiene education, cognitive restructuring, stimulus control, sleep restriction, relaxation therapy, hierarchy development, imagery training, scheduled pseudo desensitization, breathing control: 828 Wait-list control, treatment as usual, Internet + email, Internet + telephone, Internet-based control: 827	11	sleep diary (ISI)	Mean difference (95% CI): **–5.88 (–7.46 to –4.29)** I^2: NR	
Bogdanov, 2017[65] **CBT** SR	Low	CBT (unspecified) Control (unspecified): NR	2	ISI		**Significant improvement** compared with control **(*P* < 0.01)**; no clinically meaningful improvement.
Dickerson, 2014[73] **CBT** SR	High	CBT (unspecified) Usual treatment, wait-list crossover, wait-list control, control, usual treatment Total sample: 72	1	NR	Change in outcome: CBT vs. placebo –0.37 (0.10 to 0.84)	NR
		CBT: 10 Pre-/post-intervention; no comparator	1	ISI	Change in outcome: pre-/post- scores 2.67 (1.37 to 3.73)	Treatment **significantly improved** ISI scores.
Ishak, 2012[76] **CBT** SR	Low	CBT Placebo, no treatment, unspecified, usual care Total sample: 209	1	ISI		Intervention group had reduced insomnia scores at 12-month follow-up when compared with placebo **(*P* < 0.01).**

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Venables, 2014[90] CBT SR	Critically Low	Group CBT: 660 No comparison	8	ISI	Change in outcome: Average decrease (%): **53.1; 39.9; 63.9 (*P* < 0.05)**	Three of 8 studies had a **significant decrease** in ISI scores.
		Professionally administered CBT: 132 No comparison	5	ISI	Change in outcome: average decrease (%): 58.2; 53.1; 63.9; 27.4; 39.9 (*P* = NR)	Five of 5 studies found a reduction in ISI scores.
		Self-help CBT: 328 No comparison	4	ISI	Change in outcome: average decrease (%): 45.2; 44.5; 52; 56.2 (*P* = NR)	Four of 4 studies found a non-significant decrease in ISI scores.
Zachariae, 2016[55] Multi-CBT MA	Moderate	Multi-component CBT: stimulus control, sleep hygiene, cognitive therapy, sleep restriction, relaxation techniques: NR Wait-list control; treatment as usual: NR	8	ISI	Hedges' *g* (95% CI): **1.09 (0.74 to 1.45)** I^2: 82.8%	
Howell, 2014[75] Multi-CBT SR	Moderate	Multi-component CBT: sleep hygiene, sleep restriction, stimulus control, cognitive restructuring, and relaxation therapies Usual care, wait-list control, healthy eating and nutrition, sleep education and hygiene only, no treatment: Total sample: 180	4	ISI		Overall **significant improvement** in ISI after CBT intervention.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Cognitive Behavioural Interventions to Active Controls; 1 SR+MA						
Seyffert, 2016[47] **CBT** MA	Low	Self-help CBT: sleep education, stimulus control, sleep restriction, relaxation, sleep hygiene, cognitive techniques: NR In-person CBT: NR	2	sleep diary	Mean difference (95% CI): 1.07 (–6.23 to 8.38) I^2: 0%	

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CBT = cognitive behavioural therapy; CBT-I = cognitive behavioural therapy for insomnia; CI = confidence interval; ISI = Insomnia Severity Index; MA = meta-analysis; mins = minutes; NNT = number needed to treat; No. = number; NNT = number needed to treat; NR = not reported; NS = not significant; SOL = sleep onset latency; SR = systematic review; SR+MA = systematic review plus meta-analysis; TST = total sleep time; vs. = versus.

Table 84: Detailed Results for Fatigue Severity

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Cognitive Behavioural Interventions vs. Inactive Controls; 3 SR+MA, 2 SRs						
Ballesio, 2017[62] **CBT** MA	High	CBT-I Group: 302 Sleep hygiene, wait-list control, pharmacological, placebo, psychological: 226	6	FSI, Multi-Dimensional FSI, Flinders Fatigue Scale, MFI, Krupp Fatigue Scale	Cohen's *d* [95% CI]: 0.35 [–0.16 to 0.86] I^2: 76.5%	
		CBT-I Individual: 238 Placebo, sleep hygiene, wait-list control, psychological, CBT-I self-help: 160	7	MFI, FSS, Chronic Respiratory Disease Questionnaire-Fatigue Scale, PFS	Cohen's *d* [95% CI]: **0.45 [0.07 to 0.83]** I^2: 76.5%	
		CBT-I self-help: 665 Sleep hygiene, wait-list control, pharmacological: 433	7	FSS, MFI, daytime fatigue scale, MFSI-SF	Cohen's *d* [95% CI]: 0.36 [–0.15 to 0.88] I^2: 76.5%	
Tang, 2015[49] **CBT** MA	Moderate	CBT-I: psychoeducation, sleep hygiene, stimulus control, sleep restriction, cognitive therapy, and relaxation: 380 Wait-list, treatment as usual, sleep hygiene advice, healthy eating control, nutrition control: 341	6	MFI, FSI, PFS, GFS, MFSI-SF	Standardized mean difference [95% CI]: **0.38 [0.08 to 0.69]** I^2: 71%	
Dickerson, 2014[73] **CBT** SR	High	CBT (unspecified): 12 No comparator (pre- / post-intervention)	1	NR	Change in outcome: pre-/post- scores (95% CI) **–0.82 (–1.87 to –0.16)**	Fatigue improved by week 8
Yang, 2014[53] **CBT+ Behavioural** MA	Moderate	CBT + relaxation: CBT, sleep hygiene, relaxation CD: 50 Sleep hygiene education; treatment as usual: 48	2	subjective fatigue questionnaire	Standardized mean difference (95% CI): 0.77 (0.36 to 1.18) I^2: 0%	

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Howell, 2014[75] **Multi-CBT** SR	Moderate	Multi-component CBT: sleep hygiene, sleep restriction, stimulus control, cognitive restructuring, and relaxation therapies Usual care, wait-list control, healthy eating and nutrition, sleep education and hygiene only, no treatment Total sample: 178	3	sleep diary		Fatigue had **significant improvement** in all studies post CBT intervention.
Behavioural Interventions vs. Inactive Controls; 1 SR+MA						
Ballesio, 2017[62] MA	High	BT Group: 24 Placebo: 50	2	FSS	Cohen's *d* (95% CI): 0.09 (–0.61 to 0.79) I^2: 76.5%	

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; BT = behavioural therapy; CBT = cognitive behavioural therapy; CBT-I = cognitive behavioural therapy for insomnia; CD = compact disc; CI = confidence interval; FSI = Fatigue Symptom Inventory; FSS = Fatigue Severity Scale; GFS = General Fatigue Scale; MA = meta-analysis; MFI = Multi-Dimensional Fatigue Inventory; MFSI-SF = Multi-Dimensional Fatigue Symptom Inventory-Short Form; No. = number; NR = not reported; PFS = Piper Fatigue Scale; SR = systematic review; SR+MA = systematic review plus meta-analysis; vs. = versus.

Table 85: Detailed Results for Health-Related Quality of Life

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Non-Benzodiazepine Drugs vs. Inactive Controls; 1 SR						
Ishak, 2012[76] SR	Low	Zopiclone Placebo Total sample: 1,006	2	23-item questionnaire developed by sleep experts; QOLI		Contradicting evidence between both studies. No differences found in QoL between subjects treated with zopiclone and placebo.
Non-Benzodiazepine Drugs vs. Other Pharmacological Interventions; 1 SR						
Ishak, 2012[76] SR	Low	Zolpidem (5 nights/week) or Zolpidem (nightly) Total sample: 789	1	SF-36		Both groups demonstrated **improvement** with treatment (***P* = 0.005**). The continuous group demonstrated greater increase in mean SF-36 than the discontinuous group.
Melatonin vs. Inactive Controls; 1 SR						
Vural, 2014[84] SR	Critically Low	Melatonin Control Total sample: 42	1	NR		**Significant increase** in quality of life in melatonin group.
Cognitive Behavioural Interventions vs. Inactive Controls; 4 SRs						
Brooks, 2014[66] **CBT** SR	Low	CBT-I: 7 No comparator (pre- / post-intervention)	1	daily sleep diaries, ISI		Improvements in quality of life measure (*P* values not reported).
Dickerson, 2014[73] **CBT** SR	High	CBT (unspecified) usual treatment; wait-list crossover; wait-list control; control; usual treatment Total sample: 72	1	FACT-B	Change in outcome: CBT vs placebo 0.37 [–0.11 to 0.83]	
		CBT (unspecified): 10 No comparator (pre- / post-intervention)	1	Global QoL	Change in outcome: –1.09 [–1.98 to –.011]	Increase in global and cognitive dimensions of QoL at 8-week follow-up.

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Ishak, 2012[76] **CBT** SR	Low	CBT (unspecified) Placebo; no treatment; unspecified; usual care Total sample: 706	4	SF-36; CIS-20; GHQ; PANAS; FACT-G	Change in outcome (pre-post ES): physical HRQoL 0.739; 0.739; mental HRQoL 0.739; 0.082	**Significant improvement** in physical, emotional, and mental health QoL was found in all studies.
Howell, 2014[75] **Multi-CBT** SR	Moderate	Multi-component CBT - sleep hygiene, sleep restriction, stimulus control, cognitive restructuring, and relaxation therapies Usual care, wait-list control, healthy eating and nutrition, sleep education and hygiene only, no treatment Total sample: 81	1	NR		**Significant improvement** since baseline after CBT intervention (*P* values not reported).
Cognitive Behavioural Interventions vs. Active Controls; 1 SR						
Ishak, 2012[76] **CBT** SR	Low	CBT (individual): psychoeducation, sleep hygiene, stimulus control, sleep restriction, relaxation exercises, cognitive restructuring CBT (group): psychoeducation, sleep hygiene, stimulus control, sleep restriction, relaxation exercises, cognitive restructuring Total sample: 58	1	SF-36 SIP		Both groups demonstrated **significant improvement** in QoL compared with baseline **(*P* = 0.025).**

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CBT = cognitive behavioural therapy; CI = confidence interval; CIS-20 = Checklist Individual Strength 20; ES = effect size; FACT-B = Functional Assessment of Cancer Therapy – Breast Cancer; FACT-G = Functional Assessment of Cancer Therapy – General; GHQ = General Health Questionnaire; HRQoL = health-related quality of life; MA = meta-analysis; No. = number; NR = not reported; PANAS = Positive and Negative Affect Schedule; QoL = quality of life; QOLI = Quality of Life Inventory; SF-36 = Short Form (36) Health Survey; SIP = Sickness Impact Profile; SR = systematic review; SR+MA = systematic review plus meta-analysis; vs. = versus.

Table 86: Detailed Results for Hangover / Morning Sedation

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Non-Benzodiazepine Drugs vs. Other Pharmacological Interventions; 1 SR						
Cimolai, 2007[68] SR	Critically Low	Zopiclone Flurazepam Placebo Total sample: 24	1	NR		After 3 weeks of treatment, zopiclone has no effect on early-morning performance and free of residual sedative activity
Suvorexant vs. Inactive Controls; 2 SR+MAs						
Kishi, 2015[39] MA	Moderate	Suvorexant: 1,784 Placebo: 1,025	3	NR	Risk ratio [95% CI]: **3.34 [1.08 to 10.32]** I^2: 0%	
Kuriyama, 2017[41] MA	Moderate	Suvorexant: 2,027 Placebo: 1,274	3	"excessive daytime sleepiness"	Relative risk [95% CI]: **3.05 [1.10 to 8.48]** I^2: 0%	
Antipsychotic Drugs vs. Inactive Controls; 1 SR						
Anderson, 2014[63] SR	Critically Low	Quetiapine Placebo; no therapy	2	NR		Daytime sedation was **significantly more common** in the quetiapine group (compared with placebo, *P* value not reported)

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CI = confidence interval; MA = meta-analysis; No. = number; NR = not reported; SR = systematic review; SR+MA = systematic review plus meta-analysis; vs. = versus.

Table 87: Detailed Results for Accidental Injuries

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Suvorexant vs. Inactive Controls; 2 SR+MA						
Kishi, 2015[39] MA	Moderate	Suvorexant: 1,784 Placebo: 1,025	3	"motor vehicle accidents/violations"	Risk ratio [95% CI]: **1.16 [0.52 to 2.60]** I^2: 14%	
Kuriyama, 2017[41] MA	Moderate	Suvorexant: 1,784 Placebo: 1,025	3	"falls"	Relative risk [95% CI]: **0.84 [0.44 to 1.62]** I^2: 0%	
		Suvorexant: 1,784 Placebo: 1,025	3	"motor vehicle accident/violation"	Relative risk [95% CI]: **1.16 [0.39 to 3.40]** I^2: 50.2%	

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CI = confidence interval; MA = meta-analysis; No. = number; SR = systematic review; SR+MA = systematic review plus meta-analysis; vs. = versus.

Table 88: Detailed Results for Addiction, Dependence, or Diversion

Author, Year Synthesis Type	AMSTAR Rating	Intervention: Sample Size	No. of Studies	Measurement Method	Pooled Estimates	Narrative Results (From SR Without MA)
Non-Benzodiazepine Drugs vs. Inactive Controls; 1 SR						
Cimolai, 2007[68] SR	Critically Low	Zopiclone No comparator (pre- / post-intervention) Total sample: 119	3	NR		One study found no carryover effect after 3 weeks of treatment. A second study found that, after 7 to 8 weeks of treatment, sleep variables returned to pre-treatment baseline after withdrawal, and 1 out of 11 patients had marked rebound insomnia and daytime anxiety for the first week off. The third study found withdrawal effects after 3 months of treatment, despite tapering dose.
Non-Benzodiazepine Drugs vs. Other Pharmacological Interventions; 1 SR						
Cimolai, 2007[68] SR	Critically Low	Zopiclone Triazolam Total sample: 48	1	NR		Worse psychomotor deterioration after triazolam than zopiclone, 3 out of 24 zopiclone patients felt agitated early after withdrawal.
		Zopiclone Zolpidem Total sample: 248	1	NR		After 2 weeks of treatment, 15.4% of zopiclone group had rebound insomnia.
		Zopiclone Temazepam Placebo Total sample: 35	2	NR		No psychomotor performance deterioration after 2 weeks of treatment; no rebound insomnia or anxiety after 3 weeks of treatment.
Suvorexant vs. Inactive Controls; 2 SRs with MA						
Kishi, 2015[39] MA	Moderate	Suvorexant: 1,784 Placebo: 1,025	3	"events suggesting drug abuse potential"	Risk ratio [95% CI]: **1.05 [0.67 to 1.65]** I^2: 0%	
Kuriyama, 2017[41] MA	Moderate	Suvorexant: 1,784 Placebo: 1,025	3	"potential drug abuse"	Relative risk [95% CI]: **1.05 [0.66 to 1.65]** I^2: 0%	

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CI = confidence interval; MA = meta-analysis; mins = minutes; No. = number; NR = not reported; SR = systematic review; SR+MA = systematic review plus meta-analysis; vs. = versus.

Appendix 10: Tables of Primary Studies by Treatment Comparison for Outcomes With More Than One Included Systematic Review or Systematic Review with Meta-Analysis

10.1 Overlap of Primary Studies Across Included Systematic Reviews That Compared Benzodiazepine Drugs to Inactive Controls

Table 89: Sleep Onset Latency

Primary Studies (n = 48)	Systematic Reviews			Times Cited
	Buscemi, 2005[a] n = 18	Sateia, 2017[a] n = 2	Soldatos, 1999[a] n = 28[b]	
Fillingim, 1982 *Flurazepam* *Temazepam*	+			1
Hartmann, 1983 *Flurazepam*	+			1
Mello de Paula, 1984 *Flurazepam*	+			1
Mitler, 1984 *Flurazepam* *Triazolam*	+		+	1
Campbell, 1987 *Flurazepam*	+			1
Mamelak, 1987 *Flurazepam*	+			1
Mamelak, 1989 *Flurazepam*	+			1
Scharf, 1990 *Flurazepam* *Triazolam*	+		+	1
Cohn, 1991 *Flurazepam* *Triazolam*	+			1

Primary Studies (n = 48)	Systematic Reviews			Times Cited
	Buscemi, 2005[a] n = 18	Sateia, 2017[a] n = 2	Soldatos, 1999[a] n = 28[b]	
Fleming, 1995 *Flurazepam*	+			1
Beary, 1984 *Temazepam*	+			1
Leppik, 1997 *Temazepam* *Triazolam*	+			1
Tuk, 1997 *Temazepam*	+			1
Bowen, 1978 *Triazolam*	+			1
Steens, 1993 *Triazolam*	+			1
Walsh, 1998 *Triazolam*	+			1
Drake(1), 2000 *Triazolam*	+			1
Drake(2), 2000 *Triazolam*	+			1
Glass, 2008 *Temazepam*		+		1
Wu, 2006 *Temazepam*		+		1
Roth, 1974 *Triazolam*			+	–
Vogel, 1975 *Triazolam*			+	–
Kales 1976 *Triazolam*			+	–
Roth, 1976 *Triazolam*			+	–

Primary Studies (n = 48)	Systematic Reviews			Times Cited
	Buscemi, 2005[a] n = 18	Sateia, 2017[a] n = 2	Soldatos, 1999[a] n = 28[b]	
Roth, 1977 *Triazolam*			+	–
Okuma and Honda, 1978 *Triazolam*			+	–
Nicholson and Stone, 1980 *Triazolam*			+	–
Ogura, 1980 *Triazolam*			+	–
Pegram, 1980 *Triazolam*			+	–
Nicholson, 1982 *Triazolam*			+	–
Spinweber and Johnson, 1982 *Triazolam*			+	–
Stepanski, 1982 *Triazolam*			+	–
Adam, 1984 *Triazolam*			+	–
Mamelak, 1984 *Triazolam*			+	–
Cluydts, 1986 *Triazolam*			+	–
Kales, 1986 *Triazolam*			+	–
Merlotti, 1988 *Triazolam*			+	–
Tiberge, 1988 *Triazolam*			+	–
Mamelak, 1990 *Triazolam*			+	–
Mouret, 1990 *Triazolam*			+	–

Primary Studies (n = 48)	Systematic Reviews			Times Cited
	Buscemi, 2005[a] n = 18	Sateia, 2017[a] n = 2	Soldatos, 1999[a] n = 28[b]	
Borberly and Achermann, 1991 *Triazolam*			+	–
Kales, 1991 *Triazolam*			+	–
Bergougnan, 1992 *Triazolam*			+	–
Roehrs, 1992 *Triazolam*			+	–
Kanno, 1993 *Triazolam*			+	–
Monti, 1994 *Triazolam*			+	–
Saletu, 1994 *Triazolam*			+	–
Ware, 1997 *Triazolam*			+	–

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] The authors of the Soldatos, 1999 paper did not clearly report which studies were included in the analyses for each outcome. The primary studies in this review are not included in times cited count.

Table 90: Total Sleep Time

Primary Studies (n = 33)	Systematic Reviews				Times Cited
	Sateia, 2017[a] n = 2	Soldatos, 1999[a] n = 12[b]	Kolla, 2011 n = 1	Swainston Harrison, 2005 n = 1	
Glass, 2008 *Temazepam*	+				1
Wu, 2006 *Temazepam*	+				1
Roth, 1974 *Triazolam*		+			–
Vogel, 1975		+			–

Primary Studies (n = 33)	Systematic Reviews				Times Cited
	Sateia, 2017[a] n = 2	Soldatos, 1999[a] n = 12[b]	Kolla, 2011 n = 1	Swainston Harrison, 2005 n = 1	
Triazolam					
Kales 1976 *Triazolam*		+			–
Roth, 1976 *Triazolam*		+			–
Roth, 1977 *Triazolam*		+			–
Okuma and Honda, 1978 *Triazolam*		+			–
Nicholson and Stone, 1980 *Triazolam*		+			–
Ogura, 1980 *Triazolam*		+			–
Pegram, 1980 *Triazolam*		+			–
Nicholson, 1982 *Triazolam*		+			–
Spinweber and Johnson, 1982 *Triazolam*		+			–
Stepanski, 1982 *Triazolam*		+			–
Adam, 1984 *Triazolam*		+			–
Mamelak, 1984 *Triazolam*		+			–
Mitler, 1984 *Triazolam*		+			–
Cluydts, 1986 *Triazolam*		+			–
Kales, 1986 *Triazolam*		+			–
Merlotti, 1988		+			–

Primary Studies (n = 33)	Systematic Reviews				Times Cited
	Sateia, 2017[a] n = 2	Soldatos, 1999[a] n = 12[b]	Kolla, 2011 n = 1	Swainston Harrison, 2005 n = 1	
Triazolam					
Tiberge, 1988 *Triazolam*		+			–
Mamelak, 1990 *Triazolam*		+			–
Mouret, 1990 *Triazolam*		+			–
Scharf, 1990 *Triazolam*		+			–
Borberly and Achermann, 1991 *Triazolam*		+			–
Kales, 1991 *Triazolam*		+			–
Bergougnan, 1992 *Triazolam*		+			–
Roehrs, 1992 *Triazolam*		+			–
Kanno, 1993 *Triazolam*		+			–
Monti, 1994 *Triazolam*		+		+	1
Saletu, 1994 *Triazolam*		+			–
Ware, 1997 *Triazolam*		+			–
Fabre, 1997 *Triazolam*			+		1

+ = Primary study included in systematic review.
[a] Systematic review with meta-analysis.
[b] The authors of the Soldatos, 1999 paper did not clearly report which studies were included in the analyses for each outcome. The primary studies in this review are not included in times cited count.

10.2 Overlap of Primary Studies Across Included Systematic Reviews That Compared Non-Benzodiazepines to Inactive Controls

Table 91: Sleep Onset Latency

Primary Studies (n = 60)	Systematic Reviews							Times Cited
	Brasure, 2015[a] n = 6	Buscemi, 2005[a] n = 22	Sateia, 2017[a] n = 11	Soldatos, 1999[a] n = 43[b]	Mayers, 2005 n = 1	Mendelson, 2005 n = 1	Swainston Harrison, 2005 n = 1	
Fry, 2000 *Zolpidem*	+	+						2
Jacobs, 2004 *Zolpidem*	+		+					2
Randall, 2012 *Zolpidem*	+		+					2
Scharf, 1994 *Zolpidem*	+	+	+	+				3
Perlis, 2004 *Zolpidem*	+		+					2
Walsh, 2002 *Zolpidem*	+	+						2
Hermann, 1993 *Zolpidem*		+	+					2
Steens, 1993 *Zolpidem*		+						1
Fleming, 1995 *Zolpidem*		+						1
Monti, 1996 *Zolpidem*		+						1
Lahmeyer, 1997 *Zolpidem*		+						1
Leppik, 1997 *Zolpidem*		+						1
Dujardin, 1998 *Zolpidem*		+						1

Primary Studies (n = 60)	Systematic Reviews							Times Cited
	Brasure, 2015[a] n = 6	Buscemi, 2005[a] n = 22	Sateia, 2017[a] n = 11	Soldatos, 1999[a] n = 43[b]	Mayers, 2005 n = 1	Mendelson, 2005 n = 1	Swainston Harrison, 2005 n = 1	
Walsh, 1998 *Zolpidem*		+	+		+	+		4
Asnis, 1999 *Zolpidem*		+						1
Declerck, 1999 *Zolpidem*		+						1
Elie, 1999 *Zolpidem*		+	+					2
Monti, 2000 *Zolpidem*		+						1
Walsh, 2000 *Zolpidem*		+						1
Allain, 2001 *Zolpidem*		+						1
Chaudoir, 1983 *Zopiclone*		+						1
Monchesky, 1986 *Zopiclone*		+						1
Campbell, 1987 *Zopiclone*		+						1
Mamelak, 1987 *Zopiclone*		+						1
Lamphere, 1989 *Zopiclone*		+		+				1
Uchimura, 2012 *Zolpidem*			+					1
Ware, 1997 *Zolpidem*			+	+			+	2
Dorsey, 2004 *Zolpidem*			+					1
Erman, 2008			+					1

Primary Studies (n = 60)	Systematic Reviews							Times Cited
	Brasure, 2015[a] n = 6	Buscemi, 2005[a] n = 22	Sateia, 2017[a] n = 11	Soldatos, 1999[a] n = 43[b]	Mayers, 2005 n = 1	Mendelson, 2005 n = 1	Swainston Harrison, 2005 n = 1	
Zolpidem								
Nicholson and Pascoe, 1986 *Zolpidem*				+				–
Hermann, 1988 *Zolpidem*				+				–
Koshorec, 1988 *Zolpidem*				+				–
Oswald and Adam, 1988 *Zolpidem*				+				–
Merlotti, 1989 *Zolpidem*				+				–
Monti, 1989 *Zolpidem*				+				–
Vogel, 1989 *Zolpidem*				+				–
Brunner, 1991 *Zolpidem*				+				–
De Roeck and Cluydts, 1991 *Zolpidem*				+				–
Kryger, 1991 *Zolpidem*				+				–
Scharf, 1991a *Zolpidem*				+				–
Scharf, 1991 b *Zolpidem*				+				–
Scharf, 1991 c *Zolpidem*				+				–
Benoit, 1992 *Zolpidem*				+				–

Primary Studies (n = 60)	Systematic Reviews							Times Cited
	Brasure, 2015[a] n = 6	Buscemi, 2005[a] n = 22	Sateia, 2017[a] n = 11	Soldatos, 1999[a] n = 43[b]	Mayers, 2005 n = 1	Mendelson, 2005 n = 1	Swainston Harrison, 2005 n = 1	
Bergougnan, 1992 *Zolpidem*				+				–
Declerck, 1992 *Zolpidem*				+				–
Nobuhara, 1992 *Zolpidem*				+				–
Herrmann, 1993 *Zolpidem*				+				–
Kanno, 1993b *Zolpidem*				+				–
Besset, 1995 *Zolpidem*				+				–
Godtlibsen and Dreyfus, 1980 *Zopiclone*				+				–
Mamelak, 1982 *Zopiclone*				+				–
Nicholson and Stone, 1982 *Zopiclone*				+				–
Petre-Quadens ,1982 *Zopiclone*				+				–
Nicholson and Stone, 1987 *Zopiclone*				+				–
Fleming, 1988 *Zopiclone*				+				–
Tiberge, 1988 *Zopiclone*				+				–
Billiard, 1989 *Zopiclone*				+				–
Mouret, 1990 *Zopiclone*				+				–

Primary Studies (n = 60)	Systematic Reviews							Times Cited
	Brasure, 2015[a] n = 6	Buscemi, 2005[a] n = 22	Sateia, 2017[a] n = 11	Soldatos, 1999[a] n = 43[b]	Mayers, 2005 n = 1	Mendelson, 2005 n = 1	Swainston Harrison, 2005 n = 1	
Jobert, 1993 *Zopiclone*				+				–
Kim, 1993 *Zopiclone*				+				–

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] The authors of the Soldatos, 1999 paper did not clearly report which studies were included in the analyses for each outcome. The primary studies in this review are not included in times cited count.

Table 92:Total Sleep Time

Primary Studies (n = 41)	Systematic Reviews					Times Cited
	Brasure, 2015[a] n = 3	Sateia, 2017[a] n = 8	Soldatos, 1999[a] n = 36[b]	Mayers, 2005 n = 1	Swainston Harrison, 2005 n = 1	
Jacobs, 2004 *Zolpidem*	+	+				2
Randall, 2012 *Zolpidem*	+	+				2
Scharf, 1994 *Zolpidem*	+	+	+			2
Hermann, 1993 *Zolpidem*		+	+			1
Elie, 1999 *Zolpidem*		+				1
Erman, 2008 *Zolpidem*		+				1
Perlis, 2004 *Zolpidem*		+				1
Walsh, 1998 *Zolpidem*		+		+		2

Primary Studies (n = 41)	Systematic Reviews					Times Cited
	Brasure, 2015[a] n = 3	Sateia, 2017[a] n = 8	Soldatos, 1999[a] n = 36[b]	Mayers, 2005 n = 1	Swainston Harrison, 2005 n = 1	
Nicholson and Pascoe, 1986 *Zolpidem*			+			–
Hermann, 1988 *Zolpidem*			+			–
Koshorec, 1988 *Zolpidem*			+			–
Oswald and Adam, 1988 *Zolpidem*			+			–
Merlotti, 1989 *Zolpidem*			+			–
Monti, 1989 *Zolpidem*			+			–
Vogel, 1989 *Zolpidem*			+			–
Brunner, 1991 *Zolpidem*			+			–
De Roeck and Cluydts, 1991 *Zolpidem*			+			–
Kryger, 1991 *Zolpidem*			+			–
Scharf, 1991a *Zolpidem*			+			–
Scharf, 1991 b *Zolpidem*			+			–
Scharf, 1991 c *Zolpidem*			+			–
Benoit, 1992 *Zolpidem*			+			–
Bergougnan, 1992 *Zolpidem*			+			–

Primary Studies (n = 41)	Systematic Reviews					Times Cited
	Brasure, 2015[a] n = 3	Sateia, 2017[a] n = 8	Soldatos, 1999[a] n = 36[b]	Mayers, 2005 n = 1	Swainston Harrison, 2005 n = 1	
Declerck, 1992 *Zolpidem*			+			–
Nobuhara, 1992 *Zolpidem*			+			–
Kanno, 1993b *Zolpidem*			+			–
Besset, 1995 *Zolpidem*			+			–
Ware, 1997 *Zolpidem*			+			–
Godtlibsen and Dreyfus, 1980 *Zopiclone*			+			–
Mamelak et al., 1982 *Zopiclone*			+			–
Nicholson and Stone, 1982 *Zopiclone*			+			–
Petre-Quadens ,1982 *Zopiclone*			+			–
Nicholson and Stone, 1987 *Zopiclone*			+			–
Fleming, 1988 *Zopiclone*			+			–
Tiberge, 1988 *Zopiclone*			+			–
Billiard, 1989 *Zopiclone*			+			–
Lamphere, 1989 *Zopiclone*			+			–
Mouret, 1990 *Zopiclone*			+			–

Primary Studies (n = 41)	Systematic Reviews					Times Cited
	Brasure, 2015[a] n = 3	Sateia, 2017[a] n = 8	Soldatos, 1999[a] n = 36[b]	Mayers, 2005 n = 1	Swainston Harrison, 2005 n = 1	
Jobert, 1993 *Zopiclone*			+			–
Kim, 1993 *Zopiclone*			+			–
Monti, 1994 *Zolpidem*					+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] The authors of the Soldatos, 1999 paper did not clearly report which studies were included in the analyses for each outcome. The primary studies in this review are not included in times cited count.

Table 93: Wake After Sleep Onset

Primary Studies (n = 15)	Systematic Reviews					Times Cited
	Buscemi, 2005[a] n = 7	Sateia, 2017[a] n = 7	Mayers, 2005 n = 1	Mendelson, 2005 n = 1	Swainston Harrison, 2005 n = 2	
Steens, 1993 *Zolpidem*	+					1
Monti, 1996 *Zolpidem*	+					1
Walsh, 1998 *Zolpidem*	+	+	+	+		4
Asnis, 1999 *Zolpidem*	+					1
Declerck, 1999 *Zolpidem*	+					1
Monti, 2000 *Zolpidem*	+					1
Allain, 2001 *Zolpidem*	+					1
Hermann, 1993 *Zolpidem*		+				1

Primary Studies (n = 15)	Systematic Reviews					Times Cited
	Buscemi, 2005[a] n = 7	Sateia, 2017[a] n = 7	Mayers, 2005 n = 1	Mendelson, 2005 n = 1	Swainston Harrison, 2005 n = 2	
Randall, 2012 *Zolpidem*		+				1
Dorsey, 2004 *Zolpidem*		+				1
Erman, 2008 *Zolpidem*		+				1
Perlis, 2004 *Zolpidem*		+				1
Scharf, 1994 *Zolpidem*		+				1
Monti, 1994 *Zolpidem*					+	1
Ware, 1997 *Zolpidem*					+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

Table 94: Sleep Quality

Primary Studies (n = 9)	Systematic Reviews				Times Cited
	Brasure, 2015[a] n = 3	Sateia, 2017[a] n = 6	Mayers, 2005 n = 1	Mendelson, 2005 n = 1	
Elie, 1999 *Zolpidem*	+				1
Fry, 2000 *Zolpidem*	+				1
Lahmeyer, 1997 *Zolpidem*	+				1
Erman, 2008 *Zolpidem*		+			1
Randall, 2012 *Zolpidem*		+			1
Scharf, 1994 *Zolpidem*		+			1
Staner, 2005 *Zolpidem*		+			1
Uchimura, 2012 *Zolpidem*		+			1
Walsh, 1998 *Zolpidem*		+	+	+	3

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

Table 95: Sleep Efficiency

Primary Studies (n = 4)	Systematic Reviews		Times Cited
	Sateia, 2017[a] n = 4	Swainston Harrison, 2005 n = 1	
Hermann, 1993 *Zolpidem*	+		1
Randall, 2012 *Zolpidem*	+		1
Scharf, 1994 *Zolpidem*	+		1
Ware, 1997 *Zolpidem*	+	+	2

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

10.3 Overlap of Primary Studies Across Included Systematic Reviews That Compared Suvorexant to Inactive Controls

Table 96: Sleep Onset Latency

Primary Studies (n = 3)	Systematic Reviews				Times Cited
	Kishi, 2015[a] n = 3	Kuriyama, 2017[a] n = 3[c]	Brasure, 2015[a] n = 2	Citrome, 2014[a] n = 3	
Michelson, 2014	+	**			1
Herring, 2012		**			–
Herring, 2014[b] Suvorexant; 15 mg and 20 mg Suvorexant; 30 mg and 40 mg	+	**	+	+	3

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] This publication includes two trials.

[c] Only able to ascertain that these three trials were the only ones included in the SR+MA, unable to determine which outcome analyses they contributed to, thus they are not counted in the final column.

Table 97: Total Sleep Time

Primary Studies (n = 3)	Systematic Reviews				Times Cited
	Kishi, 2015[a] n = 2	Kuriyama, 2017[a] n = 3[c]	Brasure, 2015[a] n = 2	Citrome, 2014[a] n = 3	
Michelson, 2014	+	**			1
Herring, 2012		**			–
Herring, 2014[b] Suvorexant; 15 mg and 20 mg Suvorexant; 30 mg and 40 mg	+	**	+	+	3

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis

[b] This publication includes two trials.

[c] Only able to ascertain that these three trials were the only ones included in the SR+MA, unable to determine which outcome analyses they contributed to, thus they are not counted in the final column.

Table 98: Wake After Sleep Onset

Primary Studies (n = 3)	Systematic Reviews			Times Cited
	Kishi, 2015[a] n = 2	Kuriyama, 2017[a] n = 3[c]	Citrome, 2014[a] n = 3	
Michelson, 2014	+	**		1
Herring, 2012		**		–
Herring, 2014[b] Suvorexant; 15 mg and 20 mg Suvorexant; 30 mg and 40 mg	+	**	+	2

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis

[b] This publication includes two trials.

[c] Only able to ascertain that these three trials were the only ones included in the SR+MA, unable to determine which outcome analyses they contributed to, thus they are not counted in the final column.

Table 99: Insomnia Severtiy Indes

Primary Studies (n = 3)	Systematic Reviews			Times Cited
	Kishi, 2015[a] n = 2	Kuriyama, 2017[a] n = 3[c]	Citrome, 2014[a] n = 3	
Michelson, 2014	+	**		1
Herring, 2012		**		–
Herring, 2014[b] Suvorexant; 15 mg and 20 mg Suvorexant; 30 mg and 40 mg	+	**	+	2

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] This publication includes two trials.

c Only able to ascertain that these three trials were the only ones included in the SR+MA, unable to determine which outcome analyses they contributed to, thus they are not counted in the final column.

Table 100: Hangover/Morning Sedation

Primary Studies	Systematic Reviews		Times Cited
	Kishi, 2015[a] n = 2	Kuriyama, 2017[a] n = 3	
Michelson, 2014	+	**[c]	1
Herring, 2012		**[c]	–
Herring, 2014[b] Suvorexant; 15 mg and 20 mg Suvorexant; 30 mg and 40 mg	+	**[c]	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis

[b] This publication includes two trials.

[c] Only able to ascertain that these three trials were the only ones included in the SR+MA, unable to determine which outcome analyses they contributed to, thus they are not counted in the final column.

Table 101: Accidental Injuries (Falls, Fractures, Traffic Injuries)

Primary Studies	Systematic Reviews		Times Cited
	Kishi, 2015[a] n = 2	Kuriyama, 2017[a] n = 3[c]	
Michelson, 2014	+	**	1
Herring, 2012		**	–
Herring, 2014[b] Suvorexant; 15 mg and 20 mg Suvorexant; 30 mg and 40 mg	+	**	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis

[b] This publication includes two trials.

[c] Only able to ascertain that these three trials were the only ones included in the SR+MA, unable to determine which outcome analyses they contributed to, thus they are not counted in the final column.

Table 102: Addiction, Dependence, Diversion

Primary Studies	Systematic Reviews		Times Cited
	Kishi, 2015[a] n = 2	Kuriyama, 2017[a] n = 3[c]	
Michelson, 2014	+	**	1
Herring, 2012		**	–
Herring, 2014[b] Suvorexant; 15 mg and 20 mg Suvorexant; 30 mg and 40 mg	+	**	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis

[b] This publication includes two trials.

[c] Only able to ascertain that these three trials were the only ones included in the SR+MA, unable to determine which outcome analyses they contributed to, thus they are not counted in the final column.

10.4 Overlap of Primary Studies Across Included Systematic Reviews That Compared Antidepressant Drugs to Inactive Controls

Table 103:Sleep Onset Latency

Primary Studies (n = 21)	Systematic Reviews							Times Cited
	Buscemi, 2005[a] n = 5	Sateia, 2017[a] n = 4	Yuan, 2010[a] n = 4	Mayers, 2005 n = 3	Vande Griend, 2012 n = 9	Yeung, 2015 n = NR[b]	Mendelson, 2005 n = 8	
Hajak, 1996 *Doxepin 25 mg*	+			+				2
Hajak, 2001 *Doxepin 25 mg*	+		+					2
Rodenbeck, 2003 *Doxepin 25 mg*	+		+					2
Walsh, 1998 *Trazodone*	+			+	+		+	4
Haffmans, 1999 *Trazodone*	+						+	2
Krystal, 2010 *Doxepin 1 mg and 3 mg*		+			+			2
Krystal, 2011 *Doxepin 3 mg and 6 mg*		+			+			2
Roth, 2007 *Doxepin 1 mg, 3 mg, and 6 mg*		+	+		+			3
Scharf, 2008 *Doxepin 1 mg, 3 mg, and 6 mg*		+	+		+			3
Nierenberg, 1994 *Trazodone*				+				1
Roth, 2010 *Doxepin 6 mg*					+			1
Lankford, 2011 *Doxepin 6 mg*					+			1

Primary Studies (n = 21)	Systematic Reviews							Times Cited
	Buscemi, 2005[a] n = 5	Sateia, 2017[a] n = 4	Yuan, 2010[a] n = 4	Mayers, 2005 n = 3	Vande Griend, 2012 n = 9	Yeung, 2015 n = NR[b]	Mendelson, 2005 n = 8	
Le Bon, 2003 *Trazodone*					+			1
Roth, 2011 *Trazodone*					+			1
Goldberg, 1974 *Doxepin 50 mg to 300 mg*						+		1
Saletu-Zyhlarz, 2001 *Trazodone*							+	1
Montgomery, 1983 *Trazodone*							+	1
Mouret, 1988 *Trazodone*							+	1
Parrino, 1994 *Trazodone*							+	1
Scharf and Sachais, 1990 *Trazodone*							+	1
Van Bemmel, 1992 *Trazodone*							+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] Grey cells: unable to determine the primary studies associated with this outcome.

Table 104: Total Sleep Time

Primary Studies (n = 24)	Systematic Reviews								Times Cited
	Brasure, 2015[a] n = 2	Liu, 2017[a] n = 6	Sateia, 2017[a] n = 5	Yuan, 2010[a] n = 4	Mayers, 2005 n = 4	Vande Griend, 2012 n = 7	Yeung, 2015 n = NR[b]	Mendelson, 2005 n = 9	
Krystal, 2010 *Doxepin 1 mg and 3 mg*	+	+	+			+			4
Lankford, 2011 epub/2012 *Doxepin 6 mg*	+		+			+			3
Hajak, 1996 *Doxepin 25 mg*		+			+				2
Hajak, 2000 *Doxepin*		+							1
Krystal, 2011 *Doxepin 3 mg and 6 mg*		+	+			+			3
Roth, 2007 *Doxepin 1 mg, 3 mg, and 6 mg*		+	+	+		+			4
Scharf, 2008 *Doxepin 1 mg, 3 mg, and 6 mg*		+	+	+		+			4
Hajak, 2001 *Doxepin 25 mg and 25 mg to 50 mg*				+		+			2
Rodenbeck, 2003 *Doxepin 25 mg*				+					1
Walsh, 1998 *Trazodone*					+				1
Nierenberg, 1994 *Trazodone*					+				1
Mashiko, 1999 *Trazodone*					+				1

Primary Studies (n = 24)	Systematic Reviews								Times Cited
	Brasure, 2015[a] n = 2	Liu, 2017[a] n = 6	Sateia, 2017[a] n = 5	Yuan, 2010[a] n = 4	Mayers, 2005 n = 4	Vande Griend, 2012 n = 7	Yeung, 2015 n = NR[b]	Mendelson, 2005 n = 9	
Roth, 2010 *Doxepin 6 mg*						+			1
Le Bon, 2003 *Trazodone*						+			1
Stein, 2011 *Trazodone*						+			1
Haffmans and Vos, 1999 *Trazodone*								+	1
Saletu-Zyhlarz, 2001 *Trazodone*								+	1
Saletu-Zyhlarz, 2002 *Trazodone*								+	1
Kaynak, 2004 *Trazodone*								+	1
Montgomery, 1983 *Trazodone*								+	1
Mouret, 1988 *Trazodone*								+	1
Parrino, 1994 *Trazodone*								+	1
Scharf and Sachais, 1990 *Trazodone*								+	1
Van Bemmel, 1992 *Trazodone*								+	1

+ = Primary study included in systematic review.
[a] Systematic review with meta-analysis.
[b] Unable to determine the primary studies associated with this outcome.

Table 105: Wake After Sleep Onset

Primary Studies (n = 13)	Systematic Reviews							Times Cited
	Sateia, 2017[a] n = 5	Yuan, 2010[a] n = 4	Vande Griend, 2012 n = 9	Yeung, 2015 n = NR[b]	Kolla, 2011 n = 1	Mayers, 2005 n = 1	Mendelson, 2005 n = 3	
Krystal, 2010 *Doxepin 1 mg and 3 mg*	+		+					2
Krystal, 2011 *Doxepin 3 mg and 6 mg*	+		+					2
Roth, 2007 *Doxepin 1 mg, 3 mg, and 6 mg*	+	+	+					3
Scharf, 2008 *Doxepin 1 mg, 3 mg, and 6 mg*	+	+	+					3
Lankford, 2011 epub/2012 *Doxepin 6 mg*	+		+					2
Hajak, 2001 *Doxepin 25 mg, 25 mg to 50 mg*		+	+					2
Rodenbeck, 2003 *Doxepin 25 mg*		+						1
Roth, 2010 *Doxepin 6 mg*			+					1
Walsh, 1998 *Trazodone*						+	+	2
Le Bon, 2003 *Trazodone*			+		+			2
Roth, 2011 *Trazodone*			+					1
Parrino, 1994 *Trazodone*							+	1
Scharf, 1990 *Trazodone*							+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] Unable to determine the primary studies associated with this outcome.

Table 106: Sleep Quality

Primary Studies (n = 13)	Systematic Reviews				Times Cited
	Sateia, 2017[a] n = 3	Mayers, 2005 n = 4	Kolla, 2011 n = 1	Mendelson, 2005 n = 6	
Krystal, 2010 *Doxepin 3 mg*	+				1
Scharf, 2008 *Doxepin 3 mg and 6 mg*	+				1
Lankford, 2012 *Doxepin 6 mg*	+				1
Hajak, 2001 *Doxepin 20 mg to 50 mg*		+			1
Hajak, 1996 *Doxepin 25 mg*		+			1
Walsh, 1998 *Trazodone*		+		+	2
Nierenberg, 1994 *Trazodone*		+			1
Friedmann, 2008 *Trazodone*			+		1
Blacker, 1988 *Trazodone*				+	1
Davey, 1988 *Trazodone*				+	1
Moon, 1998 *Trazodone*				+	1
Kaynak, 2004 *Trazodone*				+	1
Montgomery, 1983 *Trazodone*				+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

Table 107: Sleep Efficiency

Primary Studies (n = 15)	Systematic Reviews						Times Cited
	Sateia, 2017[a] n = 3	Yuan, 2010[a] n = 4	Mayers, 2005 n = 1	Vande Griend, 2012 n = 8	Yeung, 2015 n = 1	Mendelson, 2005 n = 6	
Krystal, 2010 *Doxepin 1 mg and 3 mg*	+			+			2
Roth, 2007 *Doxepin 1 mg, 3 mg, and 6 mg*	+	+		+			3
Scharf, 2008 *Doxepin 1 mg, 3 mg, and 6 mg*	+	+		+			3
Hajak, 2001 *Doxepin 25 mg and 25 mg to 50 mg*		+	+	+	+		4
Rodenbeck, 2003 *Doxepin 25 mg*		+					1
Roth, 2010 *Doxepin 6 mg*				+			1
Krystal, 2011 *Doxepin 3 mg and 6 mg*				+			1
Le Bon, 2003 *Trazodone*				+			1
Stein, 2011 *Trazodone*				+			1
Saletu-Zyhlarz, 2001 *Trazodone*						+	1
Saletu-Zyhlarz, 2002 *Trazodone*						+	1
Kaynak, 2004 *Trazodone*						+	1
Parrino, 1994 *Trazodone*						+	1
Van Bemmel, 1992 *Trazodone*						+	1
Scharf and Sachais, 1990 *Trazodone*						+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

10.5 Overlap of Primary Studies Across Included Systematic Reviews That Compared Antidepressant Drugs to Active Controls

Table 108: Sleep Onset Latency

Primary Studies (n = 1)	Systematic Reviews			Times Cited
	Mayers, 2005 n =1	Mendelson, 2005 n =1	Vande Griend, 2012 n =1	
Walsh, 1998 *Trazodone and Zolpidem*	+	+	+	3

+ = Primary study included in systematic review.

Table 109:Total Sleep Time

Primary Studies (n = 1)	Systematic Reviews		Times Cited
	Mayers, 2005 n =1	Vande Griend, 2012 n =1	
Walsh, 1998 *Trazodone and Zolpidem*	+	+	2

+ = Primary study included in systematic review.

Table 110: Wake After Sleep Onset

Primary Studies (n = 1)	Systematic Reviews		Times Cited
	Mayers, 2005 n =1	Vande Griend, 2012 n =1	
Walsh, 1998 *Trazodone and Zolpidem*	+	+	2

+ = Primary study included in systematic review.

10.6 Overlap of Primary Studies Across Included Systematic Reviews That Compared Antipsychotic Drugs to Inactive Controls

Table 111: Sleep Onset Latency

Primary Studies (n = 5)	Systematic Reviews			Times Cited
	Anderson, 2014 n = 5	Coe, 2014 n = 1	Wine, 2009 n = 2	
Wiegand, 2008	+		+	2
Tassniyom, 2010	+	+		2
Terán, 2008	+			1
Todder, 2006	+			1
Juri, 2005	+		+	2

+ = Primary study included in systematic review.

Table 112: Total Sleep Time

Primary Studies (n = 4)	Systematic Reviews			Times Cited
	Anderson, 2014 n = 3	Coe, 2014 n = 2	Wine, 2009 n = 2	
Wiegand, 2008	+	+	+	3
Tassniyom, 2010	+	+		2
Todder, 2006	+			1
Robert, 2005			+	1

+ = Primary study included in systematic review.

Table 113: Sleep Quality

Primary Studies (n = 6)	Systematic Reviews				Times Cited
	Anderson, 2014 n = 6	Coe, 2014 n = 1	Kolla, 2011 n = 1	Wine, 2009 n = 1	
Wiegand, 2008	+	+			2
Endicott, 2008	+				1
Juri, 2005	+				1
Terán, 2008	+				1
Todder, 2006	+				1
Baune, 2007	+				1
Martinotti, 2008			+		1
Robert, 2005				+	1

+ = Primary study included in systematic review.

Table 114: Sleep Efficiency

Primary Studies (n = 2)	Systematic Reviews			Times Cited
	Anderson, 2014 n = 2	Coe, 2014 n = 1	Wine, 2009 n = 1	
Wiegand, 2008	+	+	+	3
Todder, 2006	+			1

+ = Primary study included in systematic review.

10.7 Overlap of Primary Studies Across Included Systematic Reviews That Compared Melatonin to Inactive Controls

Table 115: Sleep Onset Latency

Primary Studies (n = 24)	Systematic Reviews							Times Cited
	Buscemi, 2005[a] n = 8	Buscemi, 2004[a] n = 12	Ferracioli-Oda, 2013[a] n = 8	Lee, NA[a] n = 15	Bellon, 2006 n = 13	Culpepper, 2015 n = 3	Vural, 2014 n = 1	
Almeida, 2003				+	+	+		3
Andrade, 2001		+						1
Baskett, 2003		+		+		+		3
Dahlitz, 1991		+			+			2
Dawson, 1998	+	+	+	+				4
Ellis, 1996	+	+			+			3
Garfunkel, 1995	+	+						2
Garfunkel, 1997	+			+				2
Nagtegaal, 1995			+					1
Nagtegaal, 1998					+			1
Haimov, 1995	+	+	+	+				4
He, 2005				+				1
Hughes, 1998				+			+	2
James, 1990	+	+	+	+	+			5
Kayumov, 2001		+	+		+			3
Kunz, 2010			+					1
Luthringer, 2009			+	+				2
Montes, 2003	+	+						2
Smits, 2001				+				1
Smits, 2003		+		+				2
Van Geijlswijk, 2011				+				1
Wade, 2011				+				1
Wade, 2017				+				1
Zhdanova, 2001	+	+	+	+				4

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

Table 116: Total Sleep Time

Primary Studies (n = 31)	Systematic Reviews										Times Cited
	Buscemi, 2004[a] n = 11[b]	Ferracioli-Oda, 2013[a] n = 10	McCleery, 2016[a] n = 2	Xu, 2015[a] n = 8	Lee, NA[a] n = 11	Zhang, 2016[a] n = 4	Bellon, 2006 n = 15	Chase, 1997 n = 2	Costello, 2014 n = 1	Culpepper, 2015 n = 2	
Almeida, 2003							+			+	2
Asaya, 2003				+		+					2
Baskett, 2003					+					+	2
Dawson, 1998		+			+						2
Dowling, 2008			+	+		+					3
Eckerberg, 2012					+						1
Ellis, 1995					+						1
Ellis, 1996		+					+				2
Gehman, 2009				+		+					2
Nagtegaal, 1998							+				1
He, 2005					+						1
Hughes, 1998					+						1
James, 1989		+									1
James, 1990					+		+				2
Kayumov, 2001		+					+				2
Kunz, 2010		+									1
Luthringer, 2009		+			+						2
MacFarlane, 1991							+				1
Medeiros, 2007						+					1
Montes, 2002		+									1
Mundey, 2005		+									1
Riemersma, 2008a and 2008b				+							1
Serfaty, 2002				+		+					2
Singer, 2003			+								1

Primary Studies (n = 31)	Systematic Reviews										Times Cited
	Buscemi, 2004[a] n = 11[b]	Ferracioli-Oda, 2013[a] n = 10	McCleery, 2016[a] n = 2	Xu, 2015[a] n = 8	Lee, NA[a] n = 11	Zhang, 2016[a] n = 4	Bellon, 2006 n = 15	Chase, 1997 n = 2	Costello, 2014 n = 1	Culpepper, 2015 n = 2	
Singer, 2003a and 2003b				+		+					2
Smiths, 2001					+						1
Smiths, 2003					+						1
Wade, 2011					+						1
Zhdanova, 2001		+			+						2
Dahlitz, 1991		+					+	+			3
Garfunkel, 1995					+			+	+		3

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] Grey cells: unable to determine the primary studies associated with this outcome.

Table 117: Wake After Sleep Onset

Primary Studies (n = 13)	Systematic Reviews					Times Cited
	Buscemi, 2005[a] n = 5	Buscemi, 2004[a] n = 8[b]	Zhang, 2016[a] n = 2	Chase, 1997 n = 1	Vural, 2014 n = 1	
Andrade, 2001		+				1
Dawson, 1998					+	1
Dowling, 2005			+			1
Ellis, 1996	+					1
Garfunkel, 1995	+			+		2
Garfunkel, 1997	+					1
Gehrman, 2009			+			1
Haimov, 1995		+				1
James, 1990	+	+				2
Montes, 2003	+	+				2
Singer, 2003			+			1

Primary Studies (n = 13)	Systematic Reviews					Times Cited
	Buscemi, 2005[a] n = 5	Buscemi, 2004[a] n = 8[b]	Zhang, 2016[a] n = 2	Chase, 1997 n = 1	Vural, 2014 n = 1	
Wade, 2014			+			1
Zhdanova, 2001		+				1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] Grey cells: unable to determine some of the primary studies associated with this outcome.

Table 118: Sleep Quality

Primary Studies (n = 25)	Systematic Reviews										Times Cited
	Buscemi, 2004[a] n = 2	Ferracioli-Oda, 2013[a] n = 14	McCleery, 2016[a] n = 2	Lee, NA[a] n = 10	Sateia, 2017[a] n = 3	Bellon, 2006 n = 11	Chase, 1997 n = 1	Costello, 2014 n = 3	Culpepper, 2015 n = 4	Vural, 2014 n = 1	
Almeida, 2003				+		+			+		3
Arendt, 1986a and 1986b							+				1
Baskett, 2003				+							1
Dawson, 1998		+									1
Ellis, 1995				+							1
Ellis, 1996		+				+					2
Garfunkel, 47								+			1
Garzon, 2009		+		+					+		3
Gooneratne, 2012										+	1
Nagtegaal, 1998						+					1
Haimov, 1995		+									1
Hughes, 1998				+							2
James, 1990	+	+		+		+	+	+			6
James, 48								+			1
Kayumo, 2001						+					1

Primary Studies (n = 25)	Systematic Reviews										Times Cited
	Buscemi, 2004[a] n = 2	Ferracioli-Oda, 2013[a] n = 14	McCleery, 2016[a] n = 2	Lee, NA[a] n = 10	Sateia, 2017[a] n = 3	Bellon, 2006 n = 11	Chase, 1997 n = 1	Costello, 2014 n = 3	Culpepper, 2015 n = 4	Vural, 2014 n = 1	
Kayumov, 2001		+									1
Kunz, 2010		+									1
Lemoine, 2007		+		+	+				+		4
Luthringer, 2009		+		+	+						3
Montes, 2003	+	+									2
Mundey, 2005		+									1
Singer, 2003			+								1
Wade, 2007		+	+	+	+				+		5
Wade, 2011		+		+							2
Zhadnova, 2001		+									1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

Table 119: Sleep Efficiency

Primary Studies (n = 20)	Systematic Reviews								Times Cited
	Buscemi, 2004[a] n = 9	McCleery, 2016[a] n = 1	Xu, 2015[a] n = 6	Lee, NA [a] n = 8	Zhang, 2016[a] n = 2	Bellon, 2006 n = 12	Chase, 1997 n = 2	Culpepper, 2015 n = 1	
Almeida, 2003						+			1
Baskett, 2003	+			+				+	3
Dawson, 1998	+			+					2
Ellis, 1994	+								1
Ellis, 1996						+			1
Garfunkel, 1995	+			+			+		3
Gehrman, 2009			+						1
Nagtegaal, 1998						+			1
Haimov, 1995	+			+			+		3
He, 2005				+					1

Primary Studies (n = 20)	Systematic Reviews								Times Cited
	Buscemi, 2004[a] n = 9	McCleery, 2016[a] n = 1	Xu, 2015[a] n = 6	Lee, NA [a] n = 8	Zhang, 2016[a] n = 2	Bellon, 2006 n = 12	Chase, 1997 n = 2	Culpepper, 2015 n = 1	
Hughes, 1998				+					1
James, 1990	+			+					2
Kayumov,2001						+			1
Kayumov, 2001	+					+			1
Medeiros, 2007					+				2
Montes, 2003	+								1
Riemersma, 2008a and 2008b			+						1
Serfaty, 2003			+						1
Singer, 2003		+	+						2
Zhdanova, 2001	+			+					2

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

10.8 Overlap of Primary Studies Across Included Systematic Reviews That Compared Diphenhydramine to Inactive Controls

Table 120: Sleep Onset Latency

Primary Studies (n = 5)	Systematic Reviews			Times Cited
	Sateia, 2017[a] n = 2	Culpepper, 2015 n = 3	Vande Griend, 2012 n = 4	
Glass, 2008	+	+	+	3
Morin, 2005	+	+	+	3
Katayose, 2012		+		1
Rickels, 1983			+	1
Meuleman, 1987			+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

Table 121: Total Sleep Time

Primary Studies (n = 4)	Systematic Reviews			Times Cited
	Sateia, 2017[a] n = 2	Culpepper, 2015 n = 2	Vande Griend, 2012 n = 4	
Glass, 2008	+	+	+	3
Morin, 2005	+	+	+	3
Rickels, 1983			+	1
Meuleman, 1987			+	1

+ = Primary study included in systematic review.
[a] Systematic review with meta-analysis.

10.9 Overlap of Primary Studies Across Included Systematic Reviews That Compared Cognitive Behavioural Interventions to Inactive Controls

Table 122: Sleep Onset Latency

Primary Studies n = 89	Systematic Reviews																							Times Cited
	Brasure, 2015[a] n = 21	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 7	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Yang, 2014[a] n = 1	Buscemi, 2005[a] n = 13[c]	Ho, 2015[a] n = 8[c]	Johnson, 2016[a] n = 7	Trauer, 2015[a] n = 16	Montgomery, 2003[a] n = 3	Irwin, 2006[a] n = 20	van Straten, 2009[a] n = 8[c]	Seyffert, 2016[a] n = 7	Okajima, 2011[a] n = 9[c]	Zachariae, 2016[a] n = 10	Howell, 2014 n = 3	McCurry, 2007 n = 1	Brooks, 2014 n = 1	Ishak, 2012 n = 1	Dickerson, 2014 n = 1	Venables, 2014 n = 8	
Altena, 2008												+												1
Arnedt, 2013	+																							1
Ascher, 1979									+															1
Berger, 2009																							+	1
Blom, 2015a							+																	1
Blom, 2015b							+																	1

Primary Studies n = 89	Systematic Reviews																						Times Cited
	Brasure, 2015[a] n = 21	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 7	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Yang, 2014[a] n = 1	Buscemi, 2005[a] n = 13[c]	Ho, 2015[a] n = 8[c]	Johnson, 2016[a] n = 7	Trauer, 2015[a] n = 16	Montgomery, 2003[a] n = 3	Irwin, 2006[a] n = 20	van Straten, 2009[a] n = 8[c]	Seyffert, 2016[a] n = 7	Okajima, 2011[a] n = 9[c]	Zachariae, 2016[a] n = 10	Howell, 2014 n = 3	McCurry, 2007 n = 1	Brooks, 2014 n = 1	Ishak, 2012 n = 1	Dickerson, 2014 n = 1	Venables, 2014 n = 8	
Bothelius, 2013	+											+													2
Buysse, 2011												+													1
Carr-Kaffashan, 1979														+											1
Chen, 2008								+																	1
Chen, 2011					+																				1
Currie, 2000				+	+																				2
Currie, 2014																					+				1
Dirksen, 2008																								+	1
Dixon, 2006																						+			1
Edinger and Sampson, 2003												+													1
Edinger, 2003	+								+					+											3
Edinger, 2007												+													1
Edinger, 2009	+											+													2
Epstein and Dirksen, 2007				+	+						+													+	4
Epstein, 2012					+																				1
Espie, 1989									+					+											2
Espie, 2001												+		+											3
Espie, 2006																							+	+	2

Primary Studies n = 89	Systematic Reviews																						Times Cited
	Brasure, 2015[a] n = 21	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 7	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Yang, 2014[a] n = 1	Buscemi, 2005[a] n = 13[c]	Ho, 2015[a] n = 8[c]	Johnson, 2016[a] n = 7	Trauer, 2015[a] n = 16	Montgomery, 2003[a] n = 3	Irwin, 2006[a] n = 20	van Straten, 2009[a] n = 8[c]	Seyffert, 2016[a] n = 7	Okajima, 2011[a] n = 9[c]	Zachariae, 2016[a] n = 10	Howell, 2014 n = 3	McCurry, 2007 n = 1	Brooks, 2014 n = 1	Ishak, 2012 n = 1	Dickerson, 2014 n = 1	Venables, 2014 n = 8	
Espie, 2007	+			+	+							+												4
Espie, 2008a											+								+				+	+	4
Espie, 2008b																								+	1
Espie, 2012	+						+									+		+							4
Fiorentino, 2008																							+		1
Garland, 2014											+														1
Harvey, 2003									+																1
Ho, 2014							+									+		+							3
Holqvist, 2014							+																		1
Irwin, 2014	+																								1
Jacobs, 2004	+											+													2
Jernelov, 2012	+																								1
Jungquist, 2010	+																								1
Kaldo, 2015							+																		1
Lacks, 1983b									+					+											2
Lancee, 2012							+									+		+							3
Lancee, 2013a							+																		1
Lancee, 2013b							+																		1
Lancee, 2015							+																		1

Primary Studies n = 89	Systematic Reviews																						Times Cited
	Brasure, 2015[a] n = 21	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 7	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Yang, 2014[a] n = 1	Buscemi, 2005[a] n = 13[c]	Ho, 2015[a] n = 8[c]	Johnson, 2016[a] n = 7	Trauer, 2015[a] n = 16	Montgomery, 2003[a] n = 3	Irwin, 2006[a] n = 20	van Straten, 2009[a] n = 8[c]	Seyffert, 2016[a] n = 7	Okajima, 2011[a] n = 9[c]	Zachariae, 2016[a] n = 10	Howell, 2014 n = 3	McCurry, 2007 n = 1	Brooks, 2014 n = 1	Ishak, 2012 n = 1	Dickerson, 2014 n = 1	Venables, 2014 n = 8	
Lichstein, 2001									+				+	+										3
Lick, 1977														+										1
Lovato, 2014												+												1
Mack, 2013			+																					1
Margolies, 2013			+																					1
Matthews, 2010																						+		1
Matthews, 2014											+													1
McCrae, 2007												+												1
Mimeault, 1999	+																							1
Morawetz, 1989														+										1
Morin, 1988													+	+										2
Morin, 1993	+			+								+	+	+										5
Nicassio, 1974														+										1
Nicassio, 1982														+										1
Pallesen, 2003														+										1
Pillai, 2015																		+						1

Primary Studies n = 89	Systematic Reviews																						Times Cited
	Brasure, 2015[a] n = 21	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 7	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Yang, 2014[a] n = 1	Buscemi, 2005[a] n = 13[c]	Ho, 2015[a] n = 8[c]	Johnson, 2016[a] n = 7	Trauer, 2015[a] n = 16	Montgomery, 2003[a] n = 3	Irwin, 2006[a] n = 20	van Straten, 2009[a] n = 8[c]	Seyffert, 2016[a] n = 7	Okajima, 2011[a] n = 9[c]	Zachariae, 2016[a] n = 10	Howell, 2014 n = 3	McCurry, 2007 n = 1	Brooks, 2014 n = 1	Ishak, 2012 n = 1	Dickerson, 2014 n = 1	Venables, 2014 n = 8	
Puder, 1983														+										1
Quesnel, 2003																						+	+	2
Raymond, 2010																							+	1
Riedel, 1995														+										1
Ritterband, 2009	+	+					+									+		+						5
Ritterband, 2012		+					+				+							+	+					5
Rybarczyk, 2002				+										+										2
Rybarczyk, 2005	+				+															+				3
Sanavio, 1990									+															1
Savard, 2005					+						+								+				+	4
Savard, 2014[b]											+													1
Smith, 2015	+																							1
Soeffing, 2008												+												1
Stanton, 1989									+					+										2
Strom, 2004	+	+					+									+		+						5
Suzuki, 2008																		+						1
Talbot, 2014			+																					1
Tang, 2012	+																							1

Primary Studies n = 89	Systematic Reviews																							Times Cited
	Brasure, 2015[a] n = 21	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 7	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Yang, 2014[a] n = 1	Buscemi, 2005[a] n = 13[c]	Ho, 2015[a] n = 8[c]	Johnson, 2016[a] n = 7	Trauer, 2015[a] n = 16	Montgomery, 2003[a] n = 3	Irwin, 2006[a] n = 20	van Straten, 2009[a] n = 8[c]	Seyffert, 2016[a] n = 7	Okajima, 2011[a] n = 9[c]	Zachariae, 2016[a] n = 10	Howell, 2014 n = 3	McCurry, 2007 n = 1	Brooks, 2014 n = 1	Ishak, 2012 n = 1	Dickerson, 2014 n = 1	Venables, 2014 n = 8	
Taylor, 2014												+												1
Thiart, 2015																								
Turner, 1979														+										1
Turner, 1982														+										1
Ulmer, 2011			+																					1
Van Straten, 2009	+																							1
Van Straten, 2014	+						+									+		+						4
Vincent, 2009	+	+					+									+		+						5
Vitiello, 2009				+																				1
Waters, 2003									+			+												2
Woolfolk, 1983														+										1
Wu, 2006	+											+												2

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] This study involves two trials: in-person CBT-I vs. control and video-based CBT-I vs. control.

[c] Grey cells: unable to determine some or all of the primary studies associated with this outcome.

Table 123: Total Sleep Time

Primary Studies n = 72	Systematic Reviews																			Times Cited
	Brasure, 2015[a] n = 15	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 8	van Straten, 2007[a] n = 10[b]	Ye, 2016[a] n = 15	Dickerson, 2014 n = 2	Venables, 2014 n = 8	Ho, 2015[a] n = 8[b]	Irwin, 2006[a] n = 15	Montgomery, 2003[a] n = 4	Okajima, 2011[a] n = 9[b]	Seyffert, 2016[a] n = 8	Trauer, 2015[a] n = 16	van Straten, 2009[a] n = 8[b]	Zachariae, 2016[a] n = 10	Howell, 2014 n = 2	Wang, 2005 n = 2	
Arnedt, 2013	+																			1
Barsevick, 2010																		+		1
Berger, 2009									+											1
Blom, 2015a							+													1
Blom, 2015b							+													1
Bothelius, 2013															+					1
Buysse, 2011															+					1
Chen, 2001					+															1
Currie, 2000				+	+															2
Davidson, 2001								+												1
Dirksen, 2008									+											1
Edinger and Sampson, 2003															+					1
Edinger, 2001	+										+				+				+	4
Edinger, 2003	+										+									2
Edinger, 2007															+					1
Edinger, 2009	+														+					2
Epstein and Dirksen, 2007				+	+				+											3
Epstein, 2012					+															1
Espie, 2001											+									1

Primary Studies n = 72	Systematic Reviews																			Times Cited
	Brasure, 2015[a] n = 15	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 8	van Straten, 2007[a] n = 10[b]	Ye, 2016[a] n = 15	Dickerson, 2014 n = 2	Venables, 2014 n = 8	Ho, 2015[a] n = 8[b]	Irwin, 2006[a] n = 15	Montgomery, 2003[a] n = 4	Okajima, 2011[a] n = 9[b]	Seyffert, 2016[a] n = 8	Trauer, 2015[a] n = 16	van Straten, 2009[a] n = 8[b]	Zachariae, 2016[a] n = 10	Howell, 2014 n = 2	Wang, 2005 n = 2	
Espie, 2003											+									1
Espie, 2006									+											1
Espie, 2007	+			+	+										+					4
Espie, 2008a								+	+											2
Espie, 2008b									+											1
Espie, 2012	+						+							+			+			4
Fiorentino, 2008									+											1
Ho, 2014							+							+			+			3
Holmqvist, 2014							+													1
Jacobs, 2004	+														+					2
Jernelov, 2012	+																			1
Kaldo, 2015							+							+						2
Lancee, 2012							+							+			+			3
Lancee, 2013a							+													1
Lancee, 2013b							+													1
Lancee, 2015							+													1
Lichstein, 2001											+	+								2
Lick, 1977											+									1
Lovato, 2014															+					1
Mack, 2013			+																	1
Margolies, 2013			+																	1
Matthews, 2010									+											1

Primary Studies n = 72	Systematic Reviews																			Times Cited
	Brasure, 2015[a] n = 15	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 8	van Straten, 2007[a] n = 10[b]	Ye, 2016[a] n = 15	Dickerson, 2014 n = 2	Venables, 2014 n = 8	Ho, 2015[a] n = 8[b]	Irwin, 2006[a] n = 15	Montgomery, 2003[a] n = 4	Okajima, 2011[a] n = 9[b]	Seyffert, 2016[a] n = 8	Trauer, 2015[a] n = 16	van Straten, 2009[a] n = 8[b]	Zachariae, 2016[a] n = 10	Howell, 2014 n = 2	Wang, 2005 n = 2	
McCrae, 2007															+					1
Mimeault, 1999	+																		+	2
Morawetz, 1989											+									1
Morin, 1988											+	+								2
Morin, 1993				+							+	+			+					4
Morin, 1999					+						+	+			+					4
Pallesen, 2003											+									1
Pillai, 2015																	+			1
Quesnel, 2003									+											1
Raymond, 2010									+											1
Riedel, 1995											+									1
Ritterband, 2009	+	+					+							+			+			5
Ritterband, 2012		+					+										+			3
Rybarczyk, 2002				+							+									2
Rybarczyk, 2005					+															1
Savard, 2005					+				+									+		3
Savard, 2013									+											1
Sivertsen, 2006															+					1
Soeffing, 2008															+					1
Strom, 2004	+	+					+							+			+			5
Suzuki, 2008																	+			1
Talbot, 2014			+																	1

Primary Studies n = 72	Systematic Reviews																			Times Cited
	Brasure, 2015[a] n = 15	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 8	van Straten, 2007[a] n = 10[b]	Ye, 2016[a] n = 15	Dickerson, 2014 n = 2	Venables, 2014 n = 8	Ho, 2015[a] n = 8[b]	Irwin, 2006[a] n = 15	Montgomery, 2003[a] n = 4	Okajima, 2011[a] n = 9[b]	Seyffert, 2016[a] n = 8	Trauer, 2015[a] n = 16	van Straten, 2009[a] n = 8[b]	Zachariae, 2016[a] n = 10	Howell, 2014 n = 2	Wang, 2005 n = 2	
Taylor, 2014															+					1
Turner, 1979											+									1
Turner, 1982											+									1
Ulmer, 2011			+																	1
Van Straten, 2009	+																			1
Van Straten, 2014	+						+							+			+			4
Vincent, 2009	+	+					+							+			+			5
Vitiello, 2009				+																1
Wu, 2006	+														+					2

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] Grey cells: unable to determine some or all of the primary studies associated with this outcome.

Table 124: Wake After Sleep Onset

Primary Studies n = 70	Systematic Reviews																						Times Cited
	Brasure, 2015[a] n = 11	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 7	van Straten, 2007[ab] n = 10[1]	Ye, 2016[a] n = 11	Brooks, 2014 n = 1	Dickerson, 2014 n = 1	Venables, 2014 n = 8	Wang, 2005 n = 3	Buscemi, 2005[a] n =10[b]	Ho, 2015[a] n = 6[b]	Irwin, 2006[a] n = 15	Johnson, 2016[a] n = 7	Okajima, 2011[a] n = 6[b]	Trauer, 2015[a] n = 14	Montgomery, 2003[a] n = 4	Seyffert, 2016[a] n = 6	van Straten, 2009[a] n = 6[b]	Zachariae, 2016[a] n = 7	Howell, 2014 n = 2	McCurry, 2007 n = 1	
Arnedt, 2013	+																						1
Berger, 2009										+													1
Bothelius, 2013	+																+						2
Buysse, 2011																	+						1
Currie, 2000				+	+																		2
Currie, 2004								+															1
Davies, 1986												+						+					2
Dirksen, 2008										+													1
Edinger and Sampson, 2003											+						+						2
Edinger, 2001											+	+		+			+						4
Edinger, 2003	+											+		+									3
Edinger, 2007																	+						1
Edinger, 2009	+																+						2
Epstein and Dirksen, 2007				+	+					+					+								4
Espie, 2001											+			+									2
Espie, 2006										+													1
Espie, 2007	+			+	+												+						4
Espie, 2008a									+	+					+							+	4
Espie, 2008b										+													1
Espie, 2012	+						+												+		+		4

Primary Studies n = 70	Systematic Reviews																							Times Cited
	Brasure, 2015[a] n = 11	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 7	van Straten, 2007[ab] n = 10[1]	Ye, 2016[a] n = 11	Brooks, 2014 n = 1	Dickerson, 2014 n = 1	Venables, 2014 n = 8	Wang, 2005 n = 3	Buscemi, 2005[a] n =10[b]	Ho, 2015[a] n = 6[b]	Irwin, 2006[a] n = 15	Johnson, 2016[a] n = 7	Okajima, 2011[a] n = 6[b]	Trauer, 2015[a] n = 14	Montgomery, 2003[a] n = 4	Seyffert, 2016[a] n = 6	van Straten, 2009[a] n = 6[b]	Zachariae, 2016[a] n = 7	Howell, 2014 n = 2	McCurry, 2007 n = 1	
Esptein, 2012					+																			1
Fiorentino, 2008										+														1
Garland, 2014															+									1
Ho, 2014							+												+		+			3
Hoelscher and Edinger, 1988																							+	1
Holmqvist, 2014							+																	1
Irwin, 2014	+																							1
Jernelov, 2012	+																							1
Jungquist, 2010	+																							1
Lacks, 1983												+		+										2
Lancee, 2012							+												+		+			3
Lancee, 2013a							+																	1
Lancee, 2013b							+																	1
Lancee, 2015							+																	1
Lichstein, 2001												+		+				+						3
Lick, 1977														+										1
Lovato, 2014																	+							1
Mack, 2013			+																					1
Margolies, 2013			+																					1
Matthews, 2010										+														1
Matthews, 2014															+									1
McCrae, 2007																	+							1

Primary Studies n = 70	Systematic Reviews																						Times Cited
	Brasure, 2015[a] n = 11	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 7	van Straten, 2007[ab] n = 10[1]	Ye, 2016[a] n = 11	Brooks, 2014 n = 1	Dickerson, 2014 n = 1	Venables, 2014 n = 8	Wang, 2005 n = 3	Buscemi, 2005[a] n =10[b]	Ho, 2015[a] n = 6[b]	Irwin, 2006[a] n = 15	Johnson, 2016[a] n = 7	Okajima, 2011[a] n = 6[b]	Trauer, 2015[a] n = 14	Montgomery, 2003[a] n = 4	Seyffert, 2016[a] n = 6	van Straten, 2009[a] n = 6[b]	Zachariae, 2016[a] n = 7	Howell, 2014 n = 2	McCurry, 2007 n = 1	
Mimeault, 1999	+																						1
Morawetz, 1989														+									1
Morin, 1988														+									1
Morin, 1993	+			+										+			+	+					6
Morin, 1999	+				+							+		+			+	+					6
Pallesen, 2003														+									1
Quesnel, 2003										+													1
Raymond, 2010										+													1
Riedel, 1995														+									1
Ritterband, 2009	+	+					+												+		+		5
Ritterband, 2012		+					+								+						+		4
Rybarczyk, 2002				+										+								+	3
Rybarczyk, 2005	+				+																	+	3
Sanavio, 1990												+											1
Savard, 2005					+					+					+							+	4
Savard, 2014[1]															+								1
Smith, 2015	+																						1
Soeffing, 2008																	+						1
Strom, 2004	+	+					+												+		+		5
Talbot, 2014			+																				1
Tang, 2012	+																						1
Taylor, 2014																	+						1

Primary Studies n = 70	Systematic Reviews																						Times Cited
	Brasure, 2015[a] n = 11	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 4	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 7	van Straten, 2007[ab] n = 10[1]	Ye, 2016[a] n = 11	Brooks, 2014 n = 1	Dickerson, 2014 n = 1	Venables, 2014 n = 8	Wang, 2005 n = 3	Buscemi, 2005[a] n =10[b]	Ho, 2015[a] n = 6[b]	Irwin, 2006[a] n = 15	Johnson, 2016[a] n = 7	Okajima, 2011[a] n = 6[b]	Trauer, 2015[a] n = 14	Montgomery, 2003[a] n = 4	Seyffert, 2016[a] n = 6	van Straten, 2009[a] n = 6[b]	Zachariae, 2016[a] n = 7	Howell, 2014 n = 2	McCurry, 2007 n = 1	
Turner, 1979														+									1
Turner, 1982														+									1
Ulmer, 2011			+																				1
Vincent, 2009	+	+					+												+		+		5
Vitiello, 2009				+																			1
Waters, 2003												+					+						2

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] Grey cells: unable to determine some or all of the primary studies associated with this outcome.

Table 125: Sleep Quality

Primary Studies n = 47	Systematic Reviews																		Times Cited
	Brasure, 2015[a] n = 6	Ho, 2016[a] n = 6	Koffel, 2015[a] n = 5	Navarro-Bravo, 2015[a] n = 5	van Straten, 2007[a] n = 10[b]	Cheng, 2012[a] n = 4	Bogdanov, 2017 n = 1	Venables, 2014 n = 2	Buscemi, 2005[a] n = 2[b]	Yang, 2014[a] n = 3	Ho, 2015[a] n = 4[b]	Irwin, 2006[a] n = 7	Okajima, 2011[a] n = 2[b]	Tang, 2015[a] n = 11	van Straten, 2009[a] n = 7[b]	Zachariae, 2016[a] n = 8	Howell, 2014 n = 2	McCurry, 2007 n = 4	
Arnedt, 2013	+																		1
Barsevick, 2010														+					1
Berger, 2009								+						+			+		3
Bjorvatn, 2011	+																		1
Chen, 2008										+									1
Chen, 2011				+						+									2
Currie, 2000			+	+										+					3
Davis, 2007		+																	1
Davis, 2011,		+																	1
Edinger, 2001												+							1
Edinger, 2003												+							1
Edinger, 2005														+					1
Edinger, 2009	+																		1
Epstein and Dirksen, 2007			+																1
Espie, 2007	+		+	+															3
Espie, 2008														+					1
Espie, 2012																+			1
Fiorentino, 2008								+											1
Fiorentino, 2009																	+		1

Primary Studies n = 47	Systematic Reviews																		Times Cited
	Brasure, 2015[a] n = 6	Ho, 2016[a] n = 6	Koffel, 2015[a] n = 5	Navarro-Bravo, 2015[a] n = 5	van Straten, 2007[a] n = 10[b]	Cheng, 2012[a] n = 4	Bogdanov, 2017 n = 1	Venables, 2014 n = 2	Buscemi, 2005[a] n = 2[b]	Yang, 2014[a] n = 3	Ho, 2015[a] n = 4[b]	Irwin, 2006[a] n = 7	Okajima, 2011[a] n = 2[b]	Tang, 2015[a] n = 11	van Straten, 2009[a] n = 7[b]	Zachariae, 2016[a] n = 8	Howell, 2014 n = 2	McCurry, 2007 n = 4	
Garland, 2014														+					1
Ho, 2014																+			1
Jungquist, 2010														+					1
Krakow, 2001		+																	1
Lichstein, 2000																		+	1
Lichstein, 2001												+							1
Lick, 1977												+							1
Lu, 2016							+												1
Mack, 2013		+																	1
Margolies, 2013		+																	1
Martinez, 2014														+					1
McCurry, 1998																		+	1
Mimeault, 1999	+																		1
Miro, 2011			+	+										+					3
Rambod, 2013										+									1
Riedel, 1995												+							1
Ritterband, 2009						+										+			2
Ritterband, 2012						+								+		+			3
Rybarcyzk, 2002			+															+	2
Rybarcyzk, 2005				+														+	2
Savard, 2005														+					1

Primary Studies n = 47	Systematic Reviews																		Times Cited
	Brasure, 2015[a] n = 6	Ho, 2016[a] n = 6	Koffel, 2015[a] n = 5	Navarro-Bravo, 2015[a] n = 5	van Straten, 2007[a] n = 10[b]	Cheng, 2012[a] n = 4	Bogdanov, 2017 n = 1	Venables, 2014 n = 2	Buscemi, 2005[a] n = 2[b]	Yang, 2014[a] n = 3	Ho, 2015[a] n = 4[b]	Irwin, 2006[a] n = 7	Okajima, 2011[a] n = 2[b]	Tang, 2015[a] n = 11	van Straten, 2009[a] n = 7[b]	Zachariae, 2016[a] n = 8	Howell, 2014 n = 2	McCurry, 2007 n = 4	
Strom, 2004						+										+			2
Suzuki, 2008																+			1
Turner, 1979												+							1
Turner, 1982												+							1
Ulmer, 2011		+																	1
Van Straten, 2014	+															+			2
Vincent, 2009						+										+			2

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] Grey cells: unable to determine some or all of the primary studies associated with this outcome.

Table 126: Sleep Efficiency

Primary Studies n = 83	Systematic Reviews																								Times Cited
	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 5	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 8	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Bogdanov, 2017 n = 1	Brooks, 2014 n = 3	Dickerson, 2014 n = 1	Ishak, 2012 n = 1	Wang, 2005 n = 4	Venables, 2014 n = 12	Yang, 2014[a] n = 2	Ho, 2015[a] n = 7[c]	Irwin, 2006[a] n = 8	Johnson, 2016[a] n = 7	Montgomery, 2003[a] n = 3	Okajima, 2011[a] n = 10[c]	Seyffert, 2016[a] n = 9	Trauer, 2015[a] n = 17	van Straten, 2009[a] n = 7[c]	Zachariae, 2016[a] n = 11	Howell, 2014 n = 3	Taylor, 2014 n = 13	McCurry, 2007 n = 3	
Altena, 2008																				+						1
Arnedt, 2007								+																		1
Arnedt, 2011																								+		1
Berger, 2009												+														1
Blom, 2015a						+																				1
Blom, 2015b						+																				1
Bootzin and Stevens, 2005								+																		1
Bothelius, 2013																				+						1
Buysse, 2011																				+						1
Chen, 2008													+													1

Primary Studies n = 83	Systematic Reviews																								Times Cited
	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 5	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 8	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Bogdanov, 2017 n = 1	Brooks, 2014 n = 3	Dickerson, 2014 n = 1	Ishak, 2012 n = 1	Wang, 2005 n = 4	Venables, 2014 n = 12	Yang, 2014[a] n = 2	Ho, 2015[a] n = 7[c]	Irwin, 2006[a] n = 8	Johnson, 2016[a] n = 7	Montgomery, 2003[a] n = 3	Okajima, 2011[a] n = 10[c]	Seyffert, 2016[a] n = 9	Trauer, 2015[a] n = 17	van Straten, 2009[a] n = 7[c]	Zachariae, 2016[a] n = 11	Howell, 2014 n = 3	Taylor, 2014 n = 13	McCurry, 2007 n = 3	
Chen, 2011				+																						1
Currie, 2000			+	+																						2
Currie, 2004								+																+		2
Davidson, 2001									+																	1
Dirksen, 2008												+														1
Dixon, 2006										+																1
Edinger and Sampson, 2003											+									+						2
Edinger, 2001											+				+					+						3
Edinger, 2003															+											1
Edinger, 2007																				+						1
Edinger, 2009																				+						1

Primary Studies n = 83	Systematic Reviews																								Times Cited
	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 5	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 8	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Bogdanov, 2017 n = 1	Brooks, 2014 n = 3	Dickerson, 2014 n = 1	Ishak, 2012 n = 1	Wang, 2005 n = 4	Venables, 2014 n = 12	Yang, 2014[a] n = 2	Ho, 2015[a] n = 7[c]	Irwin, 2006[a] n = 8	Johnson, 2016[a] n = 7	Montgomery, 2003[a] n = 3	Okajima, 2011[a] n = 10[c]	Seyffert, 2016[a] n = 9	Trauer, 2015[a] n = 17	van Straten, 2009[a] n = 7[c]	Zachariae, 2016[a] n = 11	Howell, 2014 n = 3	Taylor, 2014 n = 13	McCurry, 2007 n = 3	
Epstein and Dirksen, 2007			+	+								+				+										4
Epstein, 2012				+																						1
Espie, 2006												+														1
Espie, 2007			+	+																+						3
Espie, 2008a												+				+							+			3
Espie, 2008b												+														1
Espie, 2012						+													+			+				3
Fiorentino, 2008												+														1
Garland, 2014																+										1
Ho, 2014						+													+			+				3
Holmqvist, 2014						+																				1
Jacobs, 2004																				+						1
Kaldo, 2015						+													+							2

Primary Studies n = 83	Systematic Reviews																								Times Cited
	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 5	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 8	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Bogdanov, 2017 n = 1	Brooks, 2014 n = 3	Dickerson, 2014 n = 1	Ishak, 2012 n = 1	Wang, 2005 n = 4	Venables, 2014 n = 12	Yang, 2014[a] n = 2	Ho, 2015[a] n = 7[c]	Irwin, 2006[a] n = 8	Johnson, 2016[a] n = 7	Montgomery, 2003[a] n = 3	Okajima, 2011[a] n = 10[c]	Seyffert, 2016[a] n = 9	Trauer, 2015[a] n = 17	van Straten, 2009[a] n = 7[c]	Zachariae, 2016[a] n = 11	Howell, 2014 n = 3	Taylor, 2014 n = 13	McCurry, 2007 n = 3	
Lancee, 2012						+													+			+				3
Lancee, 2013a						+																				1
Lancee, 2013b						+																				1
Lancee, 2015						+																				1
Lichstein, 1999																								+		1
Lichstein, 2001															+		+									2
Lichstein, 2013																								+		1
Lovato, 2014																				+						1
Mack, 2013		+																								1
Manber, 2008																								+		1
Margolies, 2013		+																						+		2
Matthews, 2010												+														1

Primary Studies n = 83	Systematic Reviews																								Times Cited
	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 5	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 8	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Bogdanov, 2017 n = 1	Brooks, 2014 n = 3	Dickerson, 2014 n = 1	Ishak, 2012 n = 1	Wang, 2005 n = 4	Venables, 2014 n = 12	Yang, 2014[a] n = 2	Ho, 2015[a] n = 7[c]	Irwin, 2006[a] n = 8	Johnson, 2016[a] n = 7	Montgomery, 2003[a] n = 3	Okajima, 2011[a] n = 10[c]	Seyffert, 2016[a] n = 9	Trauer, 2015[a] n = 17	van Straten, 2009[a] n = 7[c]	Zachariae, 2016[a] n = 11	Howell, 2014 n = 3	Taylor, 2014 n = 13	McCurry, 2007 n = 3	
Matthews, 2014																+									1
McCrae, 2007																				+					1
Mimeault and Morin, 1999											+														1
Morin, 1993			+												+		+			+				+	4
Morin, 1999				+											+		+			+					4
Morin, 2004																								+	1
Morin, 2012											+														1
Okajima, 2013																								+	1
Ouellet and Morin, 2007							+																		1
Pallesen, 2003															+										1
Quesnel, 2003												+													1
Quesnel, 2003												+													1
Rambod, 2013													+												1

Primary Studies n = 83	Systematic Reviews																								Times Cited
	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 5	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 8	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Bogdanov, 2017 n = 1	Brooks, 2014 n = 3	Dickerson, 2014 n = 1	Ishak, 2012 n = 1	Wang, 2005 n = 4	Venables, 2014 n = 12	Yang, 2014[a] n = 2	Ho, 2015[a] n = 7[c]	Irwin, 2006[a] n = 8	Johnson, 2016[a] n = 7	Montgomery, 2003[a] n = 3	Okajima, 2011[a] n = 10[c]	Seyffert, 2016[a] n = 9	Trauer, 2015[a] n = 17	van Straten, 2009[a] n = 7[c]	Zachariae, 2016[a] n = 11	Howell, 2014 n = 3	Taylor, 2014 n = 13	McCurry, 2007 n = 3	
Raymond, 2010												+														1
Riedel, 1995															+											1
Ritterband, 2009	+					+													+			+				4
Ritterband, 2012	+					+										+						+	+			5
Rybarczyk, 2002			+												+										+	3
Rybarczyk, 2005				+																					+	1
Savard, 2005				+								+				+							+			4
Savard, 2014[b]																+										1
Sivertsen, 2006																				+						1
Soeffing, 2008																				+				+		2
Strom, 2004	+					+													+			+				4

Primary Studies n = 83	Systematic Reviews																									Times Cited
	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 5	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 8	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Bogdanov, 2017 n = 1	Brooks, 2014 n = 3	Dickerson, 2014 n = 1	Ishak, 2012 n = 1	Wang, 2005 n = 4	Venables, 2014 n = 12	Yang, 2014[a] n = 2	Ho, 2015[a] n = 7[c]	Irwin, 2006[a] n = 8	Johnson, 2016[a] n = 7	Montgomery, 2003[a] n = 3	Okajima, 2011[a] n = 10[c]	Seyffert, 2016[a] n = 9	Trauer, 2015[a] n = 17	van Straten, 2009[a] n = 7[c]	Zachariae, 2016[a] n = 11	Howell, 2014 n = 3	Taylor, 2014 n = 13	McCurry, 2007 n = 3	
Suzuki, 2008																						+				1
Talbot, 2014		+																						+		2
Taylor, 2012																								+		1
Taylor, 2014																				+						1
Thiart, 2015																			+			+				2
Ulmer, 2011		+																						+		2
Ustinov, 2013		+																								1
Van Straten, 2013																						+				1
Van Straten, 2014						+													+							2
Vincent, 2009	+					+													+			+				4
Vitiello, 2009			+																							1

Primary Studies n = 83	Systematic Reviews																							Times Cited
	Cheng, 2012[a] n = 4	Ho, 2016[a] n = 5	Koffel, 2015[a] n = 6	Navarro-Bravo, 2015[a] n = 8	van Straten, 2007[a] n = 10[c]	Ye, 2016[a] n = 15	Bogdanov, 2017 n = 1	Brooks, 2014 n = 3	Dickerson, 2014 n = 1	Ishak, 2012 n = 1	Wang, 2005 n = 4	Venables, 2014 n = 12	Yang, 2014[a] n = 2	Ho, 2015[a] n = 7[c]	Irwin, 2006[a] n = 8	Johnson, 2016[a] n = 7	Montgomery, 2003[a] n = 3	Okajima, 2011[a] n = 10[c]	Seyffert, 2016[a] n = 9	Trauer, 2015[a] n = 17	van Straten, 2009[a] n = 7[c]	Zachariae, 2016[a] n = 11	Howell, 2014 n = 3	Taylor, 2014 n = 13	McCurry, 2007 n = 3	
Wagley, 2013																								+		1
Wu, 2006																				+						1

+ = Primary study included in systematic review.
[a] Systematic review with meta-analysis.
[b] This study involves two trials: in-person CBT-I vs. control and video-based CBT-I vs. control.
[c] Grey cells: unable to determine some or all of the primary studies associated with this outcome.

Table 127: Insomnia Severity Index

Primary Studies n = 46	Systematic Reviews														Times Cited
	Brasure, 2015[a] n = 9	Cheng, 2012[a] n = 2	Ho, 2016[a] n = 5	Navarro-Bravo, 2015[a] n = 4	van Straten, 2007[a] n = 38[b]	Ye, 2016[a] n = 11	Bogdanov, 2017 n = 2	Dickerson, 2014 n = 2	Ishak, 2012 n = 1	Venables, 2014 n = 10	Johnson, 2016[a] n = 4	Seyffert, 2016[a] n = 4	Zachariae, 2016[a] n = 8	Howell, 2014 n = 4	
Arnedt, 2013	+														1
Bothelius, 2013	+														1
Byles, 2003									+						1
Casault, 2011										+					1
Dirksen and Epstein, 2008								+		+					2
Dirksen, 2008										+				+	2
Epstein and Dirksen, 2007				+											1
Epstein, 2012				+											1
Espie, 2012						+							+		2
Fiorentino, 2008										+					1
Fiorentino, 2009														+	1
Garland, 2014											+				2
Ho, 2014						+						+	+		3
Holmqvist, 2014						+									1
Jernelov, 2013	+														1
Jungquist, 2010	+														1
Kaldo, 2015												+			1

Primary Studies n = 46	Systematic Reviews														Times Cited
	Brasure, 2015[a] n = 9	Cheng, 2012[a] n = 2	Ho, 2016[a] n = 5	Navarro-Bravo, 2015[a] n = 4	van Straten, 2007[a] n = 38[b]	Ye, 2016[a] n = 11	Bogdanov, 2017 n = 2	Dickerson, 2014 n = 2	Ishak, 2012 n = 1	Venables, 2014 n = 10	Johnson, 2016[a] n = 4	Seyffert, 2016[a] n = 4	Zachariae, 2016[a] n = 8	Howell, 2014 n = 4	
Lancee 2015						+									1
Lancee, 2012						+							+		2
Lancee, 2013a						+									1
Lancee, 2013b						+									1
Lu, 2016							+								1
Mack, 2013			+												1
Margolies, 2013			+												1
Matthews, 2014											+				2
Ouellet and Morin, 2007							+								1
Pigeon, 2012	+														1
Pillai, 2015													+		1
Quesnel, 2003								+		+					2
Raymond, 2010										+					1
Ritterband, 2009	+	+				+							+		4
Ritterband, 2011														+	1
Ritterband, 2012						+				+			+		3
Rybarczyk, 2005				+											1
Savard, 2005				+						+	+			+	4

Primary Studies n = 46	Systematic Reviews														Times Cited
	Brasure, 2015[a] n = 9	Cheng, 2012[a] n = 2	Ho, 2016[a] n = 5	Navarro-Bravo, 2015[a] n = 4	van Straten, 2007[a] n = 38[b]	Ye, 2016[a] n = 11	Bogdanov, 2017 n = 2	Dickerson, 2014 n = 2	Ishak, 2012 n = 1	Venables, 2014 n = 10	Johnson, 2016[a] n = 4	Seyffert, 2016[a] n = 4	Zachariae, 2016[a] n = 8	Howell, 2014 n = 4	
Savard, 2011										+					1
Savard, 2013										+					1
Savard, 2014											+				2
Smith, 2015	+														1
Strom, 2004						+									1
Talbot, 2014			+												1
Tang, 2012	+														1
Thiart, 2015												+	+		2
Ulmer, 2011			+												1
Ustinov, 2013			+												1
Vincent, 2009	+	+				+						+	+		5

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] Grey cells: unable to determine some or all of the primary studies associated with this outcome.

Table 128: Fatigue Severity

Primary Studies n = 26	Systematic Reviews					Times Cited
	Ballesio, 2017[a,b] n = 20	Dickerson, 2014 n = 1	Yang, 2014[a] n = 2	Tang, 2015[a] n = 6	Howell, 2014 n = 2	
Arendt, 2011	+					–
Barsevick, 2010				+		1
Berger, 2009				+		1
Chen, 2008	+		+			1
Chen, 2011	+		+			1
Davidson, 2001		+				1
Dirksen, 2008	+					–
Espie, 2008	+			+	+	2
Ho, 2014	+					–
Irwin, 2014	+					–
Jernelov, 2012	+					–
Kapella, 2011	+					–
Lichstein, 2001	+					–
Lovato, 2014	+					–
Martinez, 2013	+					–
Martinez, 2014				+		1
Matthews, 2014	+					–
Morgan, 2012	+					–
Pigeon, 2012	+					–
Rios, 2013	+			+		1
Ritterband, 2011					+	1
Ritterband, 2012	+			+		1

Primary Studies n = 26	Systematic Reviews					Times Cited
	Ballesio, 2017[a,b] n = 20	Dickerson, 2014 n = 1	Yang, 2014[a] n = 2	Tang, 2015[a] n = 6	Howell, 2014 n = 2	
Savard, 2005	+					–
Savard, 2014	+					–
Tang, 2012	+					–
Vincent, 2009	+					–

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

[b] The authors of the Ballesio, 2017 paper did not clearly report which studies were included in the analyses. The listed studies are all of the primary studies related to fatigue, but are not included in the times cited count.

Table 129: Health-Related Quality of Life — Measure of Daytime Functioning

Primary Studies n = 7	Systematic Reviews				Times Cited
	Brooks, 2014 n = 1	Dickerson, 2014 n = 2	Ishak, 2012 n = 4	Howell, 2014 n = 1	
Arnedt, 2007	+				1
Byles, 2003			+		1
Dirksen and Epstein, 2008		+		+	2
Dixon, 2006			+		1
Espie, 2008			+		1
Quesnel, 2003		+			1
Van Houdenhove, 2011			+		1

+ = Primary study included in systematic review.

10.10 Overlap of Primary Studies Across Included Systematic Reviews That Compared Cognitive Behavioural Interventions to Active Controls

Table 130: Total Sleep Time

Primary Studies	Systematic Reviews		Times Cited
	van Straten, 2009[a,b] n = 3	Seyffert, 2016[a] n = 2	
Holmqvist, 2014		+	1
Blom, 2015		+	1

+ = Primary study included in systematic review.
[a] Systematic review with meta-analysis.
[b] Grey cells: unable to determine the primary studies associated with this outcome.

Table 131: Sleep Efficiency

Primary Studies n = 4	Systematic Reviews		Times Cited
	van Straten, 2009[a,b] n = 3	Seyffert, 2016[a] n = 2	
Holmqvist, 2014		+	1
Blom, 2015		+	1
Edinger, 2001			–
Morin, 1999			–

+ = Primary study included in systematic review.
[a] Systematic review with meta-analysis.
[b] Grey cells: unable to determine the primary studies associated with this outcome.

10.11 Overlap of Primary Studies Across Systematic Reviews That Compared Behavioural Interventions to Inactive Controls

Table 132: Sleep Onset Latency

Primary Studies (n = 22)	Systematic Reviews				Times Cited
	Brasure, 2015[a] n = 5	Miller, 2014 n = 4	Buscemi, 2005[a] n = 13	Wang, 2005 n = 1	
Buysse, 2011	+				1
McCrae, 2007	+				1
Soeffing, 2008	+				1
Epstein, 2012	+	+			2
Lichstein, 2001	+		+		2
Nicassio, 1974			+		1
Choliz, 1995			+		1
Haynes, 1977			+		1
Hughes, 1978			+		1
Sanavio, 1990			+		1
Shealy, 1979			+		1
Stanton, 1989			+		1
Carr-Kaffashan, 1979			+		1
Mitchell, 1979			+		1
Lacks, 1983			+		1
Espie, 1989			+		1
Haynes, 1974			+		1
Haynes, 1977			+		1
Friedman, 2000		+			1
Taylor, 2010		+			1
Bliwise, 1995		+			1
Jacobs, 1993				+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

Table 133: Total Sleep Time

Primary Studies (n = 7)	Systematic Reviews			Times Cited
	Brasure, 2015[a] n = 4	McCurry, 2007 n = 1	Miller, 2014 n = 4	
Edinger, 2001	+			1
Espie, 1989	+			1
Epstein, 2012	+		+	2
Lichstein, 2001	+			1
Friedman, 2000		+	+	2
Taylor, 2010			+	1
Bliwise, 1995			+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

Table 134: Wake After Sleep Onset

Primary Studies (n = 9)	Systematic Reviews			Times Cited
	Brasure, 2015[a] n = 3	Buscemi, 2005[a] n = 3	Miller, 2014 n = 3	
Buysse, 2011	+			1
McCrae, 2007	+			1
Soeffing, 2008	+			1
Sanavio, 1990		+		1
Edinger, 2001		+		1
Lichstein, 2001		+		1
Epstein, 2012			+	1
Friedman, 2000			+	1
Taylor, 2010			+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

Table 135: Sleep Quality

Primary Studies (n = 13)	Systematic Reviews						Times Cited
	Hwang, 2016[a] n = 5	Bogdanov, 2017 n = 1	Brooks, 2014 n = 1	Hellström, 2011 n = 1	Tamrat, 2013 n = 3	Miller, 2014 n = 1	
Hong and Kim, 2009	+						1
McCurry, 2013	+						1
Buysse, 2011	+						1
Germain, 2006	+						1
Alessi, 2005	+						1
Vuletic, 2016		+					1
Greeff and Conradie, 1998			+				1
Richardson, 2003				+			1
Lareau, 2008					+		1
Toth, 2007					+		1
McDowell, 1998					+		1
Epstein, 2012						+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

Table 136: Sleep Efficiency

Primary Studies (n = 4)	Systematic Reviews		Times Cited
	McCurry, 2007 n = 2	Miller, 2014 n = 3	
Friedman, 2000	+	+	2
Lichstein, 2001	+		1
Epstein, 2012		+	1
Taylor, 2010		+	1

+ = Primary study included in systematic review.

10.12 Overlap of Primary Studies Across Included Systematic Reviews That Compared Mindfulness-Based Interventions to Inactive Controls

Table 137: Sleep Quality

Primary Studies (n = 4)	Systematic Reviews		Times Cited
	Gong, 2016[a] n = 3	Venables, 2014 n = 1	
Britton, 2012	+		1
Zhang, 2015	+		1
Black, 2015	+		1
Carlson, 2005		+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

Table 138: Sleep Efficiency

Primary Studies (n = 5)	Systematic Reviews		Times Cited
	Gong, 2016[a] n = 2	Venables, 2014 n = 3	
Britton, 2012	+		1
Ong, 2014	+		1
Lengacher, 2013		+	1
Shapiro, 2003		+	1
Carlson, 2005		+	1

+ = Primary study included in systematic review.

[a] Systematic review with meta-analysis.

10.13 Overlap of Primary Studies Across Included Systematic Reviews That Compared Combination Therapy to Inactive Controls

Table 139: Total Sleep Time

Primary Studies (n = 4)	Systematic Reviews		Times Cited
	Buscemi, 2005[a] n = 2	Chiesa, 2009 n = 2	
Milby, 1993	+		1
Morin, 1999	+		1
Heidenreich, 2006		+	1
Ong, 2008		+	1

+ = Primary study included in systematic review.
[a] Systematic review with meta-analysis.