Canadian Journal of Health Technologies

CADTH

May 2022 Volume 2 Issue 5

CADTH Health Technology Review

Melatonin for the Treatment of Insomnia: A 2022 Update

Rapid Review

CADTH

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ISSN: 2563-6596

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AGREE	Appraisal of Guidelines for Research and Evaluation
AMSTAR	A Measurement Tool to Assess Systematic Reviews
CBT-I	cognitive behavioural therapy for insomnia
DSM	Diagnostic and Statistical Manual of Mental Disorders
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICD	International Disease Classification
LSEQ	Leeds Sleep Evaluation Questionnaire
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSQI	Pittsburgh Sleep Quality Index
RCT	randomized controlled trials
SR	systematic review

Key Messages

- Two umbrella reviews, 7 systematic reviews, and 2 randomized controlled trials provided mixed results on the clinical effectiveness of melatonin for insomnia, when compared to placebo. Some studies reported improvement in sleep and quality of life outcomes with melatonin, and some studies reported no difference between patients who received melatonin and those who received placebo.
- Efficacy of melatonin was measured both objectively (e.g., polysomnography, actigraphy) and subjectively (e.g., validated questionnaires, sleep diaries), and was measured across multiple outcomes.
- Two guidelines recommend melatonin for insomnia, but the strength of the recommendations was not reported. One guideline recommends melatonin for insomnia, based on very low evidence (but the evidence was unclear). One guideline recommends against melatonin for chronic insomnia disorder (weak recommendation). The evidence for these recommendations was not well reported across the guidelines.
- No studies were found that evaluated the clinical effectiveness of melatonin compared to prescription sedatives in people with insomnia that met the criteria for this review.
- No studies were found for the cost-effectiveness of melatonin in people with insomnia that met the criteria for this review.

Context and Policy Issues

Insomnia is a sleep disorder which can be situational, recurrent, or chronic.[1] The 4th cycle (2014 to 2015) of the Canadian Health Measures Survey classified 21.8% to 28.9% of adults 18 to 64 years old and 18.6% to 25.8% of adults 65 years and older of having nighttime insomnia (i.e., trouble going to sleep or staying asleep). Insomnia was more prevalent among females than males in both age groups.[1]

Several organizations have developed classifications for insomnia disorder, including the WHO International Disease Classification 11 (ICD-11),[2] section 7A00 Chronic Insomnia, and the International Classification of Sleep Disorders.[3] Chronic insomnia is described as: having sleep disturbances (e.g., difficulty falling asleep, difficulty staying asleep); having associated daytime symptoms (e.g., daytime sleepiness, mood disturbance/irritability); a situation that cannot be explained by inadequate opportunity or inadequate circumstances (e.g., safe, dark environment) to sleep; sleep disturbance and associated daytime symptoms occur at least 3 times a week for at least 3 months; sleep/wake difficulty cannot be better explained by another sleep disorder.[2]

Management and treatment options for insomnia include cognitive behavioural therapy for insomnia (CBT-I), light therapy, prescribed medications (e.g., benzodiazepine), over the counter sleep aids (e.g., doxylamine), and dietary supplements (e.g., melatonin).[4,5] An UpToDate report states that the evidence base for CBT-I is stronger than for medications, therefore, CBT-I should be a part of the management approach for insomnia.[4] The selection of medication for insomnia is highly individualized and should consider symptom pattern, past treatment response, medication availability and cost, side effects and contraindications, comorbidities, and patient preference.[4]

Melatonin is a dietary supplement which may help facilitate sleep onset. It is rapidly absorbed and although side effects from controlled studies are not well established, it is reported to have mild side effects (e.g., vivid dreams, headache, stomach cramps) from short-term and intermediate-term administration.[4,6] However, the effectiveness of melatonin for the treatment of insomnia in adults is not clear, and may depend on type of insomnia (e.g., sleep onset insomnia, sleep maintenance insomnia) and comorbidities (e.g., dementia).[4]

This report is an update to a previous CADTH report published in 2019, which include 4 systematic reviews (SRs) and 2 randomized controlled trials (RCTs). All studies included in the previous report answered the clinical effectiveness question (i.e., no cost-effectiveness studies or guidelines were identified). The included SRs and RCTs suggested favourable effects of melatonin on global sleep outcomes, specific sleep outcomes, and outcomes related to functioning and mood. Effects around quality of life were unclear.[7] The objective of this report is to summarize the evidence regarding the clinical effectiveness, cost-effectiveness, and guidelines pertaining to the use of melatonin for the treatment of insomnia in adults.

Research Questions

1. What is the clinical effectiveness of melatonin versus no treatment or placebo for the treatment of insomnia in adults?
2. What is the clinical effectiveness of melatonin versus prescription sedatives for the treatment of insomnia in adults?
3. What is the cost-effectiveness of melatonin versus no treatment or placebo for the treatment of insomnia in adults?
4. What is the cost-effectiveness of melatonin versus prescription sedatives for the treatment of insomnia in adults?
5. What are the evidence-based guidelines regarding the use of melatonin for the treatment of insomnia in adults?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were melatonin and insomnia. CADTH-developed search filters were applied to limit retrieval to health technology assessments, SR, meta-analyses, or network meta-analyses; RCTs, controlled clinical trials, or any other type of clinical trial; economic studies; and guidelines. Where possible, retrieval was limited to the human

population. The search was also limited to English language documents published between January 1, 2019 and April 6, 2022.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2019. SRs in which all relevant studies were captured in other more recent or more comprehensive SRs or were captured in the 2019 CADTH report were excluded (unless additional outcomes were reported). Primary studies retrieved by the search were excluded if they were captured in 1 or more included SRs. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess Systematic Reviews 2 (AMSTAR 2)[8] for SRs, the "Questionnaire to assess the relevance and credibility of a network meta-analysis"[9] for network meta-analyses, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[10] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Table 1: Selection Criteria

Criteria	Description
Population	Adults with insomnia
Intervention	Melatonin
Comparator	Q1 and Q3: No treatment, placebo Q2 and Q4: Prescription sedatives (e.g., benzodiazepines [e.g., zopiclone, eszopiclone, zolpidem, temazepam, oxazepam], doxepin) Q5: Not applicable
Outcomes	Q1 and Q2: Clinical effectiveness (e.g., objective sleep parameters [e.g., total sleep time, sleep latency, sleep efficiency, percentage of rapid eye movement sleep, etc.], quality of life), safety Q3 and Q4: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained, incremental cost-effectiveness ratios) Q5: Recommendations regarding the use of melatonin for the treatment of insomnia
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, economic evaluations, evidence-based guidelines

Summary of Evidence

Quantity of Research Available

A total of 410 citations were identified in the literature search. Following screening of titles and abstracts, 355 citations were excluded and 55 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 41 publications were excluded for various reasons, and 15 publications met the inclusion criteria and were included in this report. These comprised 2 umbrella reviews, 7 SRs (including 1 network meta-analysis), 2 RCTs, and 4 evidence-based guidelines. Appendix 1 presents the PRISMA[11] flow chart of the study selection.

One cohort study was also identified but was not eligible for inclusion based on the criteria for this review. Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Two umbrella reviews,[12,13] 7 SRs,[14-20] (1 of which was a network meta-analysis[17]), 2 RCTs,[21,22] and 4 guidelines[23-26] were identified for inclusion in this review. No relevant economic evaluation studies were identified.

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Two umbrella reviews published in 2019[13] and 2020[12] were identified for inclusion in this review. The 18 relevant SRs or meta-analyses in these umbrella reviews were published between 1997 and 2018, and 1 review was included in both umbrella reviews. Seven SRs[14-20] were identified for inclusion in this review. Reviews were published between 2019 and 2022. The relevant primary studies included in these reviews were published between 1995 and 2018. The SRs included meta-analyses, RCTs, crossover RCTs, prospective and retrospective cohort studies, and placebo-drug-placebo studies. Searches ranges from database inception up to August 20, 2021. There were 14 primary studies included in the SRs, with some overlap of inclusion of primary studies between the SRs, particularly between Sys et al. (2020)[19] and Pierce et al. (2019).[20] Two SRs[15,19] included Garfinkel et al. 1995, 2 SRs[19,20] included Lemoine et al. 2007, 3 SRs[17,19,20] included Wade et al. 2007, and 2 SRs included Wade et al. 2010.[19,20] The overlap of included primary studies in included SRs is presented in Appendix 5. The outcome results of the overlapping primary studies were only reported once in this review. Some primary studies were captured in both this review and the 2019 CADTH report,[7] as they provided additional outcomes not captured in the 2019 CADTH review. One umbrella review and SR included the same meta-analysis (Olde Rikkert et al. 2001). Both umbrella reviews and the 7 SRs had broader inclusion criteria than the present review. Specifically, eligible participants could include children and/or those with sleep problems, disorders, or difficulties, not specific to insomnia. Additionally, eligible interventions included non-pharmacological interventions (e.g., cognitive behavioural therapy, sleep restriction, yoga), other pharmacological interventions (e.g., benzodiazepines, over the counter sleep aids), other dietary supplements (e.g., Ayurveda, valerian), and melatonin receptor agonists. Only the characteristics and results of the subset of relevant studies will be described in this report.

Two RCTs published in 2021[21] and 2020[22] were identified in Appendix 2

Four guidelines, published between 2019 and 2021 were identified. One guideline was developed with several German medical societies,[23] 1 from Italian and French societies,[24] 1 from 5 Italian scientific societies,[25] and 1 from the Department of Veterans Affairs and Department of Defense in the US.[26] All 4 guidelines used a systematic review approach to form the evidence base for recommendations. SRs performed in the guidelines included guidelines,[25] SRs and meta-analyses,[24,25] RCTs,[23,26] and cohort studies.[26] One guidelines' review also included "studies of lower evidence" if studies with high evidence were lacking.[23] One guideline used an evidence classification according to standardized European Procedures, with a citation provided, but was not further described.[23] Two guidelines used the RAND/UCLA Appropriateness Method,[24,25] and 1 guideline used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[26] Three guidelines used a Delphi method for recommendations development,[23-25] and 1 used GRADE.[26] Most guidelines did not adequately describe their rating system; however, the guideline that used GRADE to provide the strength of the recommendation described strong recommendations as those that "generally indicates high confidence in the quality of the available scientific evidence, a clear difference in magnitude between the benefits and harms of an intervention, similarity among patient or provider values and preferences, and the apparent influence of other implications (e.g., resource use, feasibility [p.12])"[26] and weak recommendations if "the Work Group has less confidence after the assessment across these domains and believes that additional evidence may change the recommendation (p. 12)."[26]

Country of Origin

The 2 umbrella reviews had authorship teams in Canada[13] and Singapore.[12] One SR was published with the first author in Belgium,[19] China,[14] Germany,[17] and the UK.[18] Three SRs were published with the first author in the US.[15,16,20]

One RCT was conducted in Korea[21] and the other in China.[22]

One guideline was meant to apply to the Italy as only available options in Italy were taken into consideration.[25] The other 3 guidelines did not specifically state which country they were meant to apply; however, they were conducted by several German medical societies,[23] Italian and French societies,[24] and the US Department of Veterans Affairs and Department of Defense.[26]

Patient Population

The SRs included in the umbrella reviews included patients 18 years and older with primary or comorbid insomnia[12] and adults 18 years and older with acute (< 3 months) or chronic (> 3 months) insomnia disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria, International Classification of Sleep Disorders, or Research Diagnostic Criteria for insomnia.[13] Participants of the included studies were not always described but could have included adults (not otherwise described), elderly (not otherwise described), elderly patients with schizophrenia, dementia, Alzheimer disease, and patients who were medically ill.

Participants in the relevant studies of the included SRs include patients with Parkinson disease with insomnia,[14] patients 65 years and older with long-term or chronic insomnia,[15] patients with type 2 diabetes and insomnia,[16] patients 55 years and older with insomnia disorder defined by DSM-IV and/or ICD-10,[17] patients with dementia with insomnia (DSM-5

circadian cycle sleep disorder with insomnia),[18] patients with long-term insomnia or DSM-IV insomnia,[19] and patients 65 years and older with primary insomnia.[20] Five reviews included patients with mean ages of 60 years or more,[14-16,19,20] and 1 review included with patients 55 years and older.[17]

Participants in the RCTs included women 55 years of age and older with insomnia (i.e., PSQI score ≥ 5)[21] and individuals aged 45 to 60 years old with primary insomnia (i.e., DSM-IV criteria).[22] Both studies were in the hospital, either via recruitment or to measure objective outcomes. Participants were all female in 1 study[21] and 47.5% male in the other.[22]

The target population for the guidelines included individuals with neurologic diseases and insomnia,[23] adults with neuropsychiatric disorders (e.g., mood disorders, autism spectrum disorder, eating disorders) and insomnia,[24] adults with insomnia,[25] and adults treated in any Veterans Affairs or Department of Defense in the primary care setting with chronic insomnia disorder.[26] Intended users include psychiatric clinical practice, clinical practice, and health care providers.

Interventions and Comparators

Two umbrella reviews, 7 SRs, and 2 RCTs examined immediate-release melatonin, prolonged-release melatonin, controlled-release melatonin, and melatonin (not otherwise described). The prescribed doses ranged from 0.5 to 6 mg. Duration of treatment ranged from 3 days to 6 months. Most studies were short-term (e.g., 8 weeks or less). Comparators consisted of placebo or inactive control (e.g., placebo/sham, wait list). One SR did not specify the comparator in the inclusion details, but stated in the discussion that all of the included studies reported adverse effects between melatonin and placebo.[20] For this reason, we assumed the comparison was placebo in the relevant included studies.

The 4 guidelines evaluated immediate release, prolonged-release, and melatonin (not otherwise described). One guideline specified 2 mg of prolonged-release melatonin.[25]

Outcomes

Sleep Outcomes

Sleep outcomes were reported in the umbrella reviews using objective, subjective, or combined measures and were reported by sleep efficiency or quality,[12,13] sleep onset latency,[12,13] total sleep time,[12,13] wake after sleep onset,[12,13] and sleep satisfaction.[13] Four SRs and 1 RCT measured sleep outcomes objectively through polysomnography or actigraphy using several sleep outcomes including sleep efficiency,[15-17,22] total sleep time,[14,15,17,22] wake time after sleep onset,[15-17] sleep onset latency,[15,17,22] number of awakenings,[15-17] wake during sleep,[22] and early wake.[22] Four SRs and 2 RCTs measured sleep outcomes subjectively through sleep questionnaires (e.g., PSQI, Leeds Sleep Evaluation Questionnaire [LSEQ]), and sleep diaries, and reported several sleep outcomes including sleep quality,[14,17-19,21,22] sleep onset latency,[19] quality of night,[19] and insomnia severity index.[19] Last, 1 SR[20] reported sleep outcomes using undefined measurement (i.e., no indication if objective or subjective), including sleep efficiency, sleep quality, sleep latency, night time awakenings, and nocturnal wake time. This SR also qualitatively reported combined sleep-related outcomes.

Functioning, Mood, and Quality of Life

Daytime parameters were measured with self-reported sleep questionnaires or scales (e.g., Epworth Sleepiness Scale), or were not described. These included morning alertness,[12,19,20] behaviour following awakening,[19] daytime sleepiness,[14,17,22] quality of day,[19] and overall

functioning. Quality of life outcomes were measured with the Short Form Health Survey (SF-36) and reported on physical function and mental health,[17] quality of life measured with the WHO-5 index,[19] clinical global impression,[19] and health-related quality of life[12,13] or quality of life[18] without clearly providing the measurement tool used. One SR that included patients with dementia evaluated cognition using the Mini Mental State Examination and activities of daily living measured with Lawton's Instrumental Activities of Daily Living Scale.[18]

Adverse Events

Adverse events were reported in 1 umbrella review,[12] 3 SRs,[15,18,19] and 1 RCT.[22]

Most guidelines did not report which outcomes were considered by the guideline panels. The guideline that used GRADE methodology included various outcomes depending on the key question being answered.[26] Only outcomes that were rated as critical and important for decision-making were included, such as daytime functioning, insomnia severity, sleep efficiency, sleep onset latency, wake after sleep onset, sleep quality, total sleep time, quality of life, and harms.

Summary of Critical Appraisal

The critical appraisal of the included umbrella reviews, SRs, RCTs, and guidelines is presented here. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Umbrella Reviews

The umbrella reviews[12,13] were assessed using AMSTAR 2[8] with additional questions specifically related to umbrella reviews (e.g., evaluating overlap of primary studies included in the SRs). Several strengths were identified. Both umbrella reviews were prospectively registered in the PROSPERO database, several electronic databases were searched with supplemental searching performed to identify reviews not found in electronic databases, and PRISMA flow diagrams were provided. One umbrella review[13] described the method for study selection and critical appraisal and is considered sufficiently robust, performed a matrix of evidence to ascertain the degree of overlap, and used GRADE to ascertain the strength of the evidence. One umbrella review[12] did not describe the method of study selection or critical appraisal, though they did sufficiently report the method for data extraction. Neither umbrella review provided a list of excluded studies or the source of funding of the included reviews.

Systematic Reviews

The SRs[14-16,18-20] and the network meta-analysis[17] were assessed using AMSTAR 2[8] and the network meta-analysis was further assessed using the ISPOR Questionnaire.[9] There were strengths across the reviews. A PRISMA flow diagram was provided in all reviews. All but 1 review[20] searched 2 or more electronic databases and provided details around the method for study selection. One Cochrane review[18] provided the list of excluded studies and reported the funding of the included primary studies. This was not provided in any other review. There was also difference in limitations in quality of conduct and reporting across reviews. Four SRs did not mention a protocol.[14,15,19,20] Three SRs did not perform any supplemental searching to identify studies not published in electronic databases.[14,15,20] Not all elements of PICO were described for the inclusion criteria, primarily around comparators[15,16,19,20] and outcomes.[15,20] Three SRs did not report the method of data extraction.[15,17,20] Two SRs did not report if critical appraisal or risk of bias of the included studies was performed,[19,20] and 1 SR reported that critical appraisal was performed, but did not provide the results.[15] At least some level of the

characteristics of the included studies (e.g., population, control, dosage, setting) was not sufficiently reported in the reviews, in all but 3 reviews.[15,18,19] The source of funding of the primary included studies was only reported in 1 SR,[18] A formal assessment of publication bias was not performed in any of the reviews. Among the reviews that addressed reasons for not performing an assessment of publication bias was because there were too few studies[16,18] or because there is still debate on how to perform publication bias for network meta-analyses.[17] The network meta-analysis[17] provided a rationale for using random-effects models, and graphical representation of the evidence networks for several outcomes were provided.

Randomized Controlled Trials

The RCTs[21,22] were assessed using the Downs and Black checklist and several strengths were identified in both studies.[27] The aim of the study, inclusion and exclusion criteria, intervention and comparison, main outcomes, and characteristics of the included patients of the studies were clearly described. In both studies, the placebo tablet was identical in appearance to the melatonin tablet, which would reduce the chance of patients knowing which group they were assigned to. Patients in both groups were recruited from the same population and follow-up was the same. Reporting of the outcomes was sufficient in both studies and included the number of patients contributing to the data in both groups, and results at baseline and at follow-up. However, the method of randomization was not well reported in 1 study[22] and not reported at all in the other.[21] Allocation concealment was not reported in 1 study.[21] Neither study measured adherence to the medication.

Guidelines

The guidelines were assessed using the AGREE-II tool.[10] All guidelines provided a description of the scope and purpose of the guideline, clearly presented the recommendations, and provided a statement around the competing interests of the members of the guideline development group. There was a lack of reporting around the methods of the conduct of the SRs (e.g., method of study selection, strengths and limitation of the body of evidence), if the guideline was externally reviewed, a procedure for updating the guideline, description of facilitators and barriers to guideline application, and resource implications in 3 guidelines.[23-25] In the other guideline those items were well reported.[26]

Summary of Findings

There was some overlap in the primary studies that were included in the SRs; therefore, to avoid duplication of results, outcome data from an individual primary study are only reported once. A citation matrix illustrating the degree of overlap is presented in Appendix 5.

Appendix 4 presents the main study findings and authors' conclusions.

Clinical Effectiveness of Melatonin Versus No treatment or Placebo

Sleep Measures

The 2 umbrella reviews reported the outcomes as either subjective, objective, or combined. For this reason, the outcomes from the umbrella reviews are reported separately from the SRs and RCTs.

Results From Umbrella Reviews

Sleep efficiency or quality. Results from the included meta-analyses and SRs within the umbrella reviews were mixed with some reporting a statistically significant increase in sleep efficiency or quality with melatonin, while other reported no change or difference.[12,13]

Sleep latency, total sleep time, wake after sleep onset. Results from the included meta-analyses and SRs within the umbrella reviews were mixed with some reporting a statistically significant improvement in these sleep outcomes, while other reported no change or difference.[12,13]

Sleep satisfaction. Sleep satisfaction was reported in one included SR (with one included study) within the umbrella review and reported a significant increase in both percentage of nights scored "good" and percentage of "good mood."[13]

Quality of life. One umbrella review reported a significant increase in health-related quality of life (undefined subjective measurement tool; evidence from 1 included primary study in 1 SR).[13]

Results From Primary Studies Within SRs and Primary Studies Identified in This Review

Objective sleep measures (i.e., polysomnography, actigraphy)

Sleep efficiency. Two SRs and 1 RCT reported on sleep efficiency using objective sleep measures. The 2 SRs reported on sleep efficiency comparing melatonin (2 mg or 3 mg) to placebo. In patients with primary insomnia, 2 RCTs in the SR by Almond et al.[15] and in patients with type 2 diabetes with insomnia, 1 RCT in the SR by Kothari et al.,[16] reported statistically significant improvements in sleep efficiency. In a RCT of patients with primary insomnia, there was no difference in sleep efficiency in patients who received melatonin (3 mg) compared to placebo.[22]

Total sleep time. Two SR, 1 network meta-analysis, and 1 RCT reported on total sleep time using objective sleep measures. The 2 SRs reported on total sleep time comparing melatonin (2 mg or 3 mg) to placebo. There were mixed results between the SRs and the studies within the reviews. One RCT in the SR by Ma et al.[14] reported non-significant results in patients with Parkinson disease. In patients with primary insomnia in the SR by Almond et al.,[15] 1 RCT reported no difference in total sleep time and 1 placebo-drug-placebo study reported a significant increase in total sleep time. Additionally, the network meta-analysis by Baglioni et al. 2020[17] included outcome data on 1 RCT in patients with insomnia disorder (DSM-IV and/or ICD-10), but did not provide details around the impact of melatonin compared to placebo. In a RCT of patients with primary insomnia, there was no difference in total sleep time in patients who received melatonin (3 mg) compared to placebo.[22]

Wake time after sleep onset. Two SRs, 1 network meta-analysis, and 1 RCT reported on wake time after sleep onset using objective sleep measures. The 2 SRs reported on wake time after sleep onset comparing melatonin (2 mg or 3 mg) to placebo. In patients with primary insomnia, 2 RCTs in the SR by Almond et al.[15] and in patients with type 2 diabetes with insomnia, 1 RCT in the SR by Kothari et al.,[16] reported that melatonin significantly reduced wake time after sleep onset. Additionally, the network meta-analysis by Baglioni et al. 2020[17] included outcome data on 1 RCT in patients with insomnia disorder (DSM-IV and/or ICD-10), but did not provide details around the impact of melatonin compared to placebo. In a RCT of patients with primary insomnia, there was no difference in wake after sleep onset in patients who received melatonin (3 mg) compared to placebo.[22]

Sleep onset latency. One SR, 1 network meta-analysis, and 1 RCT reported on sleep latency using objective sleep measures. The 1 SR reported on sleep latency comparing melatonin (2 mg or 3 mg) to placebo. In patients with primary insomnia, 2 RCTs in the SR by Almond et al.[15] reported no difference in sleep onset latency between melatonin and placebo. Additionally, the network meta-analysis by Baglioni et al. 2020[17] included outcome data on 1 RCT in patients with insomnia disorder (DSM-IV and/or ICD-10), but did not provide details around the impact of melatonin compared to placebo. In a RCT of patients with primary insomnia, there was no difference in sleep latency in patients who received melatonin (3 mg) compared to placebo.[22]

Number of awakenings. Two SRs and 1 network meta-analysis reported on number of awakening using objective sleep measures. The 2 SRs reported on number of awakenings in patients receiving melatonin (2 mg or 3 mg) or placebo. In patients with primary insomnia, 1 placebo-drug-placebo study in the SR by Almond et al.[15] reported that the number of awakenings was not significantly affected. In patients with type 2 diabetes with insomnia, 1 RCT in the SR by Kothari et al.[16] reported there was a significant effect of melatonin compared to placebo. Additionally, the network meta-analysis by Baglioni et al. 2020[17] included outcome data on 1 RCT in patients with insomnia disorder (DSM-IV and/or ICD-10), but did not provide details around the impact of melatonin compared to placebo.

Wake during sleep. In a RCT of patients with primary insomnia, there was no difference in wake during sleep (measured in minutes) in patients who received melatonin (3 mg) compared to placebo.[22]

Early wake. In a RCT of patients with primary insomnia, there was a significant decrease in early wake (measured in minutes) in patients who received melatonin (3 mg) compared to placebo.[22]

Subjective sleep measures (e.g., sleep questionnaires, sleep diary)

Sleep quality. Three SRs, 1 network meta-analysis, and 2 RCTs reported on sleep quality using sleep questionnaires and sleep diaries. In the 3 SRs, sleep quality was measured using subjective measures (e.g., PSQI, LSEQ, sleep diaries). In patients with Parkinson disease taking melatonin (3 mg), 1 SR found a statistically significant increase in sleep quality compared to placebo (measured with PSQI; evidence from 1 relevant RCT).[14] In another SR in patients with dementia, there was no difference in carer-rated sleep quality between patients who received melatonin (5 mg) and placebo (measured with PSQI; evidence from 1 relevant RCT).[18] In another SR, in patients with long-term insomnia, there was a statistically significant increase in sleep quality in those taking melatonin (2 mg) when measured with LSEQ and PSQI,[19] but no difference was observed when reported in sleep diaries (evidence from 3 relevant RCTs).[19] Additionally, the network meta-analysis by Baglioni et al. 2020[17] included outcome data on 2 RCTs in patients with insomnia disorder (DSM-IV and/or ICD-10). This was measured through LSEQ, PSQI, and sleep diaries, but did not provide details around the impact of melatonin compared to placebo. In 1 RCT, there was a significant difference in sleep quality in the patients who received melatonin (2 mg), but not in the patients who received placebo. However, there was no difference between groups (P = 0.158).[21] In another RCT of patients with primary insomnia, there was no difference in the PSQI total score in patients who received melatonin (3 mg) compared to placebo.[22]

Sleep onset latency. In patients with long-term insomnia, 1 SR reported a statistically significant shortening of sleep latency with melatonin compared to placebo (measured with

PSQI or undefined subjective measurement tool; evidence from 2 relevant RCTs), which continued up to 29 weeks in 1 included primary study.[19]

Quality of night. In patients with long-term insomnia, 1 SR reported no difference in sleep maintenance in patients who received melatonin (2 mg) compared to placebo (measured using sleep diaries; evidence from 1 relevant RCT).[19]

Insomnia severity index. In 1 RCT of patients with primary insomnia, there was no difference on the Insomnia Sleep Index in patients who received melatonin (3 mg) compared to placebo.[22]

Other Sleep Outcomes Using Undefined Measurement

Sleep efficiency. In patients with primary insomnia, 1 SR reported a trend for improved efficiency (undefined measure; evidence from 1 relevant RCT).[20]

Sleep quality. In patients with primary insomnia, 1 SR reported no positive effect or improvement on sleep quality (undefined measure; evidence from 2 relevant RCTs).[20]

Sleep latency. In patients with primary insomnia, 1 SR reported a significant decrease in sleep latency (undefined measure; evidence from 1 relevant RCT).[20]

Nighttime awakenings. In patients with primary insomnia, 1 SR reported a decreased number of nighttime awakenings (undefined measure; evidence from 1 relevant RCT).[20]

Nocturnal wake time. In patients with primary insomnia, 1 SR reported a significant increase in nocturnal wake time (undefined measure; evidence from 1 relevant RCT).[20]

Combined sleep-related outcomes. In patients with long-term insomnia, 1 SR reported no difference in total sleep time and sleep maintenance (measured with sleep diaries; evidence from 1 relevant RCT). In another SR in patients with primary insomnia, there was no statistically significant improvement or difference in total sleep time, sleep latency, sleep efficiency, or wake time (undefined measure; evidence from 3 relevant RCTs).[20]

Functioning, Mood, Quality of Life

Behaviour following wakening. In patients with long-term insomnia, 1 SR reported a statistically significant improvement with melatonin compared to placebo (measured with LSEQ; evidence from 1 relevant RCT).[19]

Alertness in morning. In patients with long-term insomnia and primary insomnia, 2 SR reported a significantly more alertness in the morning with melatonin compared to placebo or an increase in morning alertness (undefined measure; evidence from 2 relevant RCTs).[19]

Sleepiness. One SR, 1 umbrella review, and 1 RCT reported on sleepiness measured with the Epworth Sleepiness Scale (ESS). In patients with Parkinson disease, 1 SR reported that daytime sleepiness is not affected by melatonin (3 mg) compared to placebo (evidence from 1 relevant RCT).[14] Additionally, the network meta-analysis by Baglioni et al. 2020[17] included outcome data on 1 RCT in patients with insomnia disorder (DSM-IV and/or ICD-10), but did not provide details around the impact of melatonin compared to placebo (evidence from 1 relevant RCT). In a RCT of patients with primary insomnia, there was no difference in on the ESS in patients who received melatonin (3 mg) compared to placebo.[22]

Quality of day. In patients with long-term insomnia, 1 SR reported no difference in quality of day (measured with sleep diaries; evidence from 1 relevant RCT).[19]

Quality of life. In patients with long-term insomnia, 1 SR reported mixed results for quality of life (measured with WHO-5 index; evidence from 2 relevant RCTs).[19]

Clinical Global Impression (CGI). In patients with long-term insomnia, 1 SR reported both no difference and a significant improvement in patients who received melatonin (2 mg) compared to placebo (measured using CGI scale; evidence from 2 relevant RCTs).[19]

Cognition and activities of daily living. In patients with dementia, 1 SR reported that there is no evidence that melatonin had either beneficial or harmful effects in these patients (cognition measured with Mini Mental State Examination, activities of daily living measured with Lawton's Instrumental Activities of Daily Living Scale; evidence from 1 relevant RCT).[18]

Physical and mental function. The network meta-analysis by Baglioni et al. 2020[17] included outcome data on 1 RCT in patients with insomnia disorder (DSM-IV and/or ICD-10), but did not provide details around the impact of melatonin compared to placebo (measured with SF-36).

Adverse Events

Adverse events were reported in 3 SRs.[15,18,19] Overall, these were reported as no or infrequent adverse events, mild or not serious (e.g., pruritus, headache), treatment was well-tolerated, or no difference between patients who received melatonin and placebo. In a RCT of patients with primary insomnia, there was no difference in the incidence of adverse events in patients who received melatonin (3 mg) compared to placebo, and melatonin was well-tolerated. Additionally, the RCT reported there were no clinically relevant changes in vital signs and laboratory blood and urine tests.[22]

Clinical Effectiveness of Melatonin Versus Prescription Sedatives

No relevant evidence regarding the clinical effectiveness of melatonin versus prescription sedatives for insomnia was identified; therefore, no summary can be provided.

Cost-Effectiveness of Melatonin Versus No Treatment or Placebo

No relevant evidence regarding the cost-effectiveness of melatonin versus no treatment or placebo for insomnia was identified; therefore, no summary can be provided.

Cost-Effectiveness of Melatonin Versus Prescription Sedatives

No relevant evidence regarding the cost-effectiveness of melatonin versus prescription sedatives for insomnia was identified; therefore, no summary can be provided.

Guidelines

Four evidence-based guidelines[23-26] were identified providing recommendations for melatonin for treatment of insomnia.

Neurologic Disease and Neuropsychiatric Disorders

One guideline, by Mayer et al. (2021), recommends melatonin for patients with neurologic diseases (i.e., movement disorders, multiple sclerosis, epilepsy, dementia and prion-diseases),[23] although the authors reported that these recommendations were based on very low evidence. However, it is unclear if this "low evidence" was specific to

the recommendations for dementia and prion-diseases or for all recommendations in the guideline.

One guideline, by Pagalini et al. (2021), provides recommendations for patients with various neuropsychiatric disorders and recommends prolonged-release melatonin at 2 mg to 10 mg, 1 to 2 hours before bedtime for the treatment of insomnia symptoms or comorbid insomnia in mood disorders.[24] Recommendations for anxiety disorders, attention-deficit/hyperactivity disorder, autism spectrum disorder, and eating disorders are given in the absence of well-conducted RCTs in adults and state that melatonin "might be useful" or "could be of interest."[24] Prolonged-release melatonin at 2 mg given 1 to 2 hours before bedtime and immediate-release melatonin at 2 mg to 6 mg given at bedtime might be useful in the treatment of insomnia in neurocognitive disorders.[24] Prolonged-release melatonin at 2 mg given 1 to 2 hours before bedtime could be used in individuals 55 years of age and older with substance use disorder and in individuals with schizophrenia. Immediate-release melatonin for individuals with schizophrenia gave uncertain results and more studies are needed to be able to provide recommendations.[24] The quality of evidence and strength of each recommendation was not reported in this guideline.

Insomnia

Two guidelines provided recommendations for insomnia, not specific to any other comorbidity. One guideline, by Palagini et al. (2020)[25] recommends pharmacological treatments as the first-line option when CBT-Insomnia is not available. The drug selected should be based on factors such as type of insomnia, age, comorbidities, and potential side effects. If the choice is prolonged-release melatonin, in individuals 55 years of age and older, use it within 13 weeks. The quality of evidence and strength of the recommendations was not reported in this guideline. The guideline by the Department of Veterans Affairs and Department of Defense[26] suggest against the use of melatonin for the treatment of chronic insomnia disorder (weak recommendation).

Limitations

Two umbrella reviews and 7 SRs were identified with primary studies that evaluated melatonin for insomnia. Overall, the quality of conduct and reporting for these reviews was mixed (e.g., no supplemental searching, lack of details around the methods of study selection, no list of excluded studies), making it difficult to determine if all relevant primary studies were captured by the SR and to determine which primary studies were relevant to this current review. For example, some reviews identified the primary studies as patients with insomnia. However, when evaluating those primary studies as part of this review, they did not qualify as having insomnia, but rather poor sleep quality.[14] The definition of what was considered insomnia in general was mixed, with some reviews requiring a clinical diagnosis of insomnia (e.g., DSM-IV) and others accepting self-reported insomnia. This difference may impact the certainty of the results across the reviews. One umbrella review included a SR where the comparator was labelled as "control," making it unclear if this group was given placebo, no treatment, or some other inactive comparison.[13] The quality of reporting of the outcomes was insufficient in several reviews. It was not always stated how the outcome was measured, as some reviews combined subjective (e.g., polysomnography) and objective (e.g., validated questionnaires, sleep diaries) measures. Additionally, when the name of the questionnaire used to evaluate subjective sleep outcomes was provided, the scale of the questionnaire

and the interpretation of the value (e.g., higher score is better sleep efficiency) was not provided. Some reviews provided results in which it is not possible to determine if the result was improved or worse for the melatonin group (e.g., mean difference with no descriptor if a negative or positive value was better). The network meta-analysis reported the mean and standard deviations for the comparisons, but did not provide an indication if the was a difference or no difference pre- and post-treatment or between those who received melatonin and those who received placebo. However, the authors did conclude that their findings do not support any of the selected therapies for insomnia disorder.[17]

Two RCTs were also identified for inclusion. One RCT stated that randomization was performed using a random number method,[22] but did not further describe this process (e.g., computer-generated random number generation, selecting a number from a hat), so it is difficult to determine if there is any bias associated with the process that was used. The other RCT did not report on either the method of randomization or the process of allocation concealment, therefore it is unclear if there was any selection bias in this study.[21] Neither RCT reported on if compliance (or nonadherence) to treatment was measured,[21,22] which may lead to a failure to detect a true treatment effect.

The SRs were often conducted in specific populations (e.g., patients with cancer, patients with schizophrenia), resulting in few relevant included studies, often among a small group of patients. This heterogeneity makes it difficult to determine any trends across reviews. Primary studies were often short-term (e.g., < 8 weeks), therefore they did not provide any long-term evidence for the efficacy and safety of melatonin. Even among the short-term primary studies, harms data were rarely reported.

Both subjective and objective outcomes are reported using several different measures, including sleep efficiency, sleep quality, latency of sleep onset, total sleep time/duration of sleep, depth of sleep, wake time after sleep onset, number of awakenings, freshness on awakening, alertness in morning, morning headaches, morning mental dullness, daytime sleepiness, mood, overall functioning, physical function, mental status, quality of life. Therefore, depending on the individual and the measure that might be the most important to them, any or all of these measures could be considered when recommending melatonin.

Most guidelines did not provide a detailed description of the method of conduct of the systematic review that informed the recommendations. For example, the process of study selection was only reported in 1 guideline. Therefore, we cannot determine if all relevant studies were captured. Additionally, 3 of 4 guidelines did not provide formal ratings for the certainty of the evidence for each recommendation.[23-25] One guideline provides 1 statement around the certainty of the evidence, but it is not clear if it is for all recommendations in the guideline or only in that particular section (i.e., dementia and prion-diseases).[23] Veterans Affairs is the only guideline to recommend against melatonin for insomnia, but it also specifies that this recommendation if for chronic insomnia, which is defined as lasting longer than 3 months. This might be why it differs from Palagini et al. (2020), who state that it be used within 13 weeks (i.e., before it becomes chronic). Although none of the guidelines were produced specifically for the Canadian health care system, melatonin in the formulations included in the recommendations are available in Canada, making these recommendations generalizable to the Canadian health care system.

Last, we were not able to find any evidence for 3 of the research questions in this review. There was no evidence to evaluate the clinical effectiveness of melatonin versus prescription

sedatives, the cost-effectiveness of melatonin versus no treatment or placebo, and the cost-effectiveness of melatonin versus prescription sedatives.

Conclusions and Implications for Decision- or Policy-Making

Two umbrella reviews, 7 SRs, and 2 RCTs were identified to address the effectiveness of melatonin versus no treatment or placebo for the treatment of insomnia. No evidence was identified to evaluate the clinical effectiveness of melatonin versus prescription sedatives for the treatment of insomnia. All included reviews were broader in scope than this review (e.g., broader population, broader interventions). Where possible, depending on the quality of the reporting, relevant primary studies were identified from these reviews. Generally, findings suggested that melatonin may be effective for some sleep-related outcomes, but may differ depending on how it is measured. For example, in patients with insomnia, the use of melatonin did not have any impact on sleep onset latency when measured objectively (evidence from 2 RCTs in 1 SR and 1 primary RCT),[15,22] but significantly reduced sleep onset latency when measured subjectively (evidence from 2 RCTs in 1 SR).[19] Efficacy may also be dependent on the population. For example, the systematic review by McCleery et al. (2020) found no beneficial or harmful effects in people with dementia due to Alzheimer disease.[18] However, Ma et al. (2022) concluded that melatonin could be considered an effective treatment in patients with Parkinson disease.[14] As the majority of the primary studies were 8 weeks or less, there is inadequate evidence to confirm the long-term efficacy of melatonin.[13]

Among the included reviews and primary studies, there is heterogeneity in terms of the included population and the methods of measuring the outcomes, which leads to uncertainty in the effectiveness of melatonin. For example, the reviews and primary studies included patients with clinically defined insomnia disorder (i.e., DSM-VI or ICD-10),[13,17,22] either long-term (undefined) or DSM-IV defined insomnia combined,[15,19] undefined primary insomnia,[12,20] Parkinson disease,[14] type 2 diabetes,[16] dementia,[18] or were all female.[21] Authors of these studies often concluded that larger studies should be performed. The safety and harms of melatonin is poorly reported in primary studies, and 1 umbrella review,[12] 3 SRs,[15,18,19] and 1 RCT[22] reported that short-term use of melatonin was considered safe and well-tolerated. Interpretation of the results across these reviews was often hampered by the poor reporting in the details of the included primary studies (e.g., patients, setting, intervention, outcome measurement, outcome data). The 7 SRs and 2 RCTs included patients aged 55 years and older, which may impact the generalizability of the results to adults between the ages of 18 and 54.

Four guidelines were identified providing recommendations for melatonin for the treatment of insomnia in general,[25,26] and for several neurologic diseases[23] and neuropsychiatric disorders.[24] Although the guidelines state that there is insufficient evidence[23]or an absence of well-conducted RCTs[24] to help support the recommendations, they often state that melatonin may be used to treat insomnia. However, 1 guideline specific to chronic insomnia, recommends against the use of melatonin.[26]

This review is an update to a previously published CADTH from 2019.[7] The results from this updated report are similar in terms of the clinical effectiveness of melatonin versus no

treatment or placebo. The 2019 CADTH report did not identify any guidelines; however, this report has identified 4 guidelines published between 2019 and 2021. There was no evidence to evaluate the cost-effectiveness of melatonin in the 2019 report and no evidence was found in this update.

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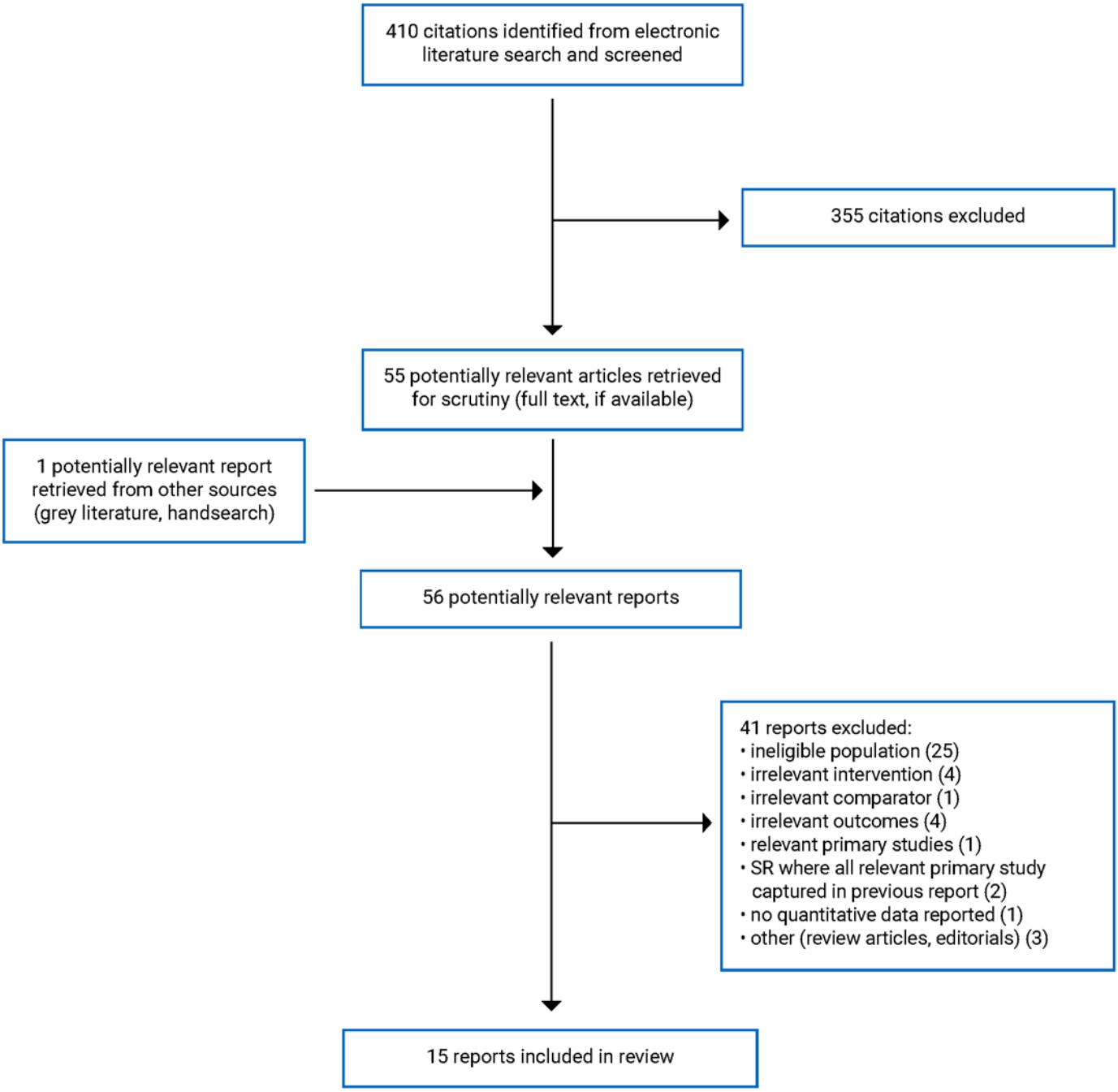
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Umbrella Reviews

Study citation, country, funding source	Study designs and numbers of studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Low et al. (2020)[12] Singapore **Funding**: NR	Systematic reviews and meta-analyses Reviews published up to July 2018 were searched Number of reviews included: 18 Number of relevant reviews: 7 published between 2001 and 2018 (2 additional reviews on Ramelteon in adults)	Eligibility criteria: Treatment in primary or comorbid insomnia in any age group that included RCTs Included patients were 18 years and older (one study was > 16 years) who had primary or comorbid insomnia N studies included in reviews = 33 N patients included in reviews = 3654	**Eligible interventions:** Melatonin/ melatonin receptor agonists **Eligible comparators:** Placebo or other medications **Relevant intervention:** Melatonin 0.3 to 75 mg **Relevant comparators:** Placebo Duration of interventions ranged from 3 days to 6 months (where reported)	Outcomes in included reviews: Sleep quality; Sleep efficiency; Sleep latency; Sleep onset; Total sleep time; REM latency; Ease of getting to sleep; Quality of night/day; Wake after sleep onset; Number of awakening; Morning alertness; Quality of Life; WHO-5 well-being index; Safety Outcomes reported in relevant reviews: Sleep efficiency; Total sleep time; Sleep latency
Rios et al. (2019)[13] Canada **Funding**: Canadian Institutes of Health Research	Systematic knowledge syntheses including primary studies of any design with or without a meta-analysis Reviews published up to June 14, 2017 Number of included reviews: 64 Number of relevant reviews: 12 (8 with meta-analyses) published between 1997 and 2017	Eligibility criteria: Adults > 18 years of age diagnosed with acute (< 3 months) or chronic (> 3 months) insomnia disorder according to the DSM diagnostic criteria, International Classification of Sleep Disorders, or Research Diagnostic Criteria for insomnia N patients included in reviews = NR (reported in some reviews, but not all)	**Eligible interventions:** Prescription or non-prescription Pharmacological interventions, Non-pharmacological interventions (e.g., cognitive behavioural therapy, sleep restriction, Melatonin) **Eligible comparators:** Inactive controls (e.g., placebo/ sham, wait list, symptom monitoring), Active controls (e.g., another available intervention) **Relevant intervention:** Melatonin **Relevant comparator:** Inactive controls (mostly placebo; one included systematic review states 'control')	Eligible outcomes: Effectiveness (e.g., sleep onset latency, total sleep time, wake after sleep onset); Harms (e.g., hangover/ morning sedation, accidental injuries) Outcomes reported in relevant reviews: Sleep onset latency; Total sleep time; Wake after sleep onset; Sleep quality; Sleep satisfaction; Sleep efficiency; Health-related quality of life

Table 3: Characteristics of Included Systematic Reviews and Network Meta-Analyses

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Ma et al. (2022)[14] China **Funding**: Project of Henan Province Science and Technology, the Key Projects of Medical Science and Technology in Henan Province and Medical Science and Technology Research in Henan Province	RCTs Studies published up to August 20, 2021 were searched Number of primary studies: 7 Number of relevant primary studies: 1 (2 other studies were categorized as insomnia but were evaluated at full-text as part of this review and were not for insomnia). Study published in 2007.	Inclusion criteria: Patients with Parkinson disease Relevant population: Patients who had Parkinson disease for an average of 6.4 years and insomnia. Average age was 62.9 years in the intervention group and 60.7 years in the control group; 77.8% male. N = 18	**Eligible interventions:** Melatonin or prolonged-release melatonin **Eligible comparator:** Placebo or clonazepam **Relevant interventions:** 3 mg melatonin **Relevant comparators:** Placebo Duration of intervention: 4 weeks	Outcomes: At least one of the following: Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), RBD questionnaire (RBDQ) and polysomnography (PSG) sleep parameters Follow-up: End of treatment (4 weeks)
Almond et al. (2021)[15] US **Funding**: NR	Crossover RCTs, Placebo-drug-placebo Studies published up to May 8, 2020 were searched Number of primary studies: 5 Number of relevant primary studies: 2 (1 crossover RCT, 1 placebo-drug-placebo). Studies published in 1995 and 1999.	Inclusion criteria: Adult 65 years of age and older being evaluated on over the counter sleep aids for primary insomnia or sleep disorders in the outpatient setting Relevant population: Patients who had complained of long-term insomnia in one study and were diagnosed with chronic primary insomnia according to DSM-IV in the other. Patients were 68 to 93 and 66 to 86 years old; 40.9% male. N = 22	**Eligible interventions:** Over the counter sleep aids **Eligible comparators:** NR **Relevant interventions:** 2 mg controlled-released melatonin in one study, 3 mg melatonin capsules in the other **Relevant comparators:** Placebo Duration of the included studies were 7 weeks (3 weeks melatonin/placebo, 1 week washout, 3 weeks melatonin/ placebo), and 19 days (placebo nights 1 to 3, melatonin nights 4 to 16, placebo nights 17 to 18)	Outcomes: Subjective and objective measures of changes in sleep, such as mean total sleep time, sleep latency, sleep efficiency, and number of awakenings; Safety end points, such as psychomotor ability, cognitive ability, and adverse effect profile Follow-up: Assessments were done at the end of the 3-week treatment period in one study, and on nights 1 to 5, 17 and 18 in the other
Kothari et al. (2021)[16] US **Funding**: No funding	RCTs, crossover RCTs, single-arm prospective studies Studies published up to August 1, 2019 were searched Number of primary	Inclusion criteria: Adults aged ≥ 18 years with problems of sleep disturbances eg: insomnia, short sleep, poor sleep quality	**Eligible interventions:** Sleep extension, sleep education or cognitive behavioural therapy for insomnia, and pharmacological interventions **Eligible comparators:** NR **Relevant interventions:** 2 mg of	Relevant outcomes: Sleep-related outcomes (e.g., objective sleep assessment, sleep parameters from questionnaires and sleep diaries)

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	studies: 22 Number of relevant studies: 1 crossover RCT (1 additional study evaluating Ramelteon). Study published in 2011.	Relevant population: Patients with type 2 diabetes with insomnia. Average age of patients was 63 years old; 30.5% male. N = 36	prolonged-release melatonin **Relevant comparators:** Placebo Duration of intervention: 3 weeks, followed by 5 months of open-label melatonin for all patients	Other outcomes: At least one of the glycemic outcomes must be measured: glucose, insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) or hemoglobin A1C (A1C). Follow-up: 3 weeks
Baglioni et al. (2020)[17] Germany **Funding**: German Ministry for Education and Research	RCTs Studies published between January 1994 and September 2019 were searched Number of primary studies: 40 Number of relevant primary studies: 3 RCTs (4 additional studies evaluating Ramelteon). Studies published in 2007, 2009, and 2011.	Inclusion criteria: Individuals with insomnia disorder of any age Relevant population: Individuals aged 55 years and older with insomnia disorder (defined by DSM-IV and/or ICD-10); 37.5 to 60.5% male. N = 437	**Eligible interventions:** Ayurveda, chelation, diet-based therapy, energy healing therapy, exercise, folk medicine, homeopathy, hypnosis, light exposure, massage, meditation, melatonin, music therapy, natural herbs, naturopathy, qi gong, reiki, tai chi, transcranial magnetic stimulation, valerian, vitamin, and yoga **Eligible comparators:** waiting list, no treatment, pharmacological and psychological (e.g., psychoeducation) placebo, standard therapy for insomnia: sleep pharmacotherapy (hypnotics: benzodiazepine and benzodiazepine receptor agonists and recommended psychological treatment, i.e., CBT-I [CBT-I, sleep restriction, stimulus control]). **Relevant interventions:** Melatonin **Relevant comparators:** Placebo	Outcomes: Objective and subjective standardized measures of sleep and/or insomnia Outcomes in relevant studies: Self-report questionnaires, polysomnography Follow-up: NR
McCleery et al. (2020)[18] UK **Funding**: National Institute for Health Research	RCTs Studies published up until February 19, 2020 were searched Number of primary studies: 9 Number of relevant primary studies: 2 RCTs. Studies published in 2014 and 2018.	Inclusion criteria: People with dementia with sleep problems identified on the basis of subjective and objectives measures Relevant population: Patients with mild or moderate dementia (CDR 1 and 2) with DSM-5 circadian cycle sleep disorder with insomnia in one	**Eligible interventions:** Any drug primarily intended to improve patients' sleep **Eligible comparators:** Placebo **Relevant interventions:** 5 mg immediate-release melatonin in one study, 2 mg slow-release melatonin in the other **Relevant comparators:** Placebo Duration of intervention: 8 weeks in one study, 28 weeks (2-week run-in phase, 24-weeks treatment	Relevant outcomes: Objective sleep outcomes measured with polysomnography or actigraphy; Quality of life; Adverse events Other outcomes: Carer ratings of patient's sleep using sleep diaries or validated observer scales; Cognition measured with any validated scale; Activities of daily

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		study, and patients with dementia (diagnostic criteria not specified) with insomnia at baseline (defined as Pittsburgh Sleep Quality Index score ≥ 6). Mean age were 92.2 and 83.1 years in one study, and NR for the subgroup in the other; 22.6% male in one study, and NR for the subgroup in the other. N = 53 (one study included a subgroup with insomnia and reported on these patients)	phase, 2-week run out phase) in the other	living (ADLs) measured with any validated scale; Carer outcomes (well-being, quality of life, burden, sleep). Follow-up: End of treatment
Sys et al. (2020)[19] Belgium **Funding**: NR	RCTs, non-RCTs with parallel groups, prospective or retrospective cohort studies with control groups, and observational studies Studies published up until September 1, 2019 were searched Number of primary studies: 24 Number of relevant studies: 4 (3 RCTs and 1 crossover RCT) (4 additional studies evaluating Ramelteon). Studies published between 1995 and 2010.	Inclusion criteria: Patients ≥ 65 years with insomnia Relevant population: Patients with long-term insomnia or DSM-IV insomnia in outpatient clinics. Patients in all studies were ≥ 55 years' old. N = 817	**Eligible interventions:** Antidepressants, antipsychotic drugs, anticonvulsive medications, antihistamines, herbal therapies, melatonin receptor agonists, and orexin receptor antagonists **Eligible comparators:** NR **Relevant interventions:** 2 mg prolonged-release melatonin **Relevant comparators:** Placebo Duration of intervention: Studies ranged from 3 to 29 weeks, with some including run-in and run out periods or washout periods	Relevant outcomes: Sleep duration; Subjective sleep quality; Safety profile, number of adverse events Follow-up: End of treatment
Pierce et al. (2019)[20] US **Funding**: No funding	Meta-analyses, RCTs, and prospective and retrospective cohort studies Studies published up until October 10, 2018	Inclusion criteria: Adults 65 years of age and older Relevant population: Adults with primary insomnia. Mean age	**Eligible interventions:** Exogenous melatonin **Included comparators:** Unclear **Eligible interventions:** 0.5 to 6 mg of controlled-release, immediate-release and prolonged-re-	Reported outcomes: Sleep efficiency; Sleep latency; Wake time following initiation; Follow-up: End of treatment

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	were searched Number of studies: 3 meta-analyses, 21 RCTs, 1 cohort study Number of relevant studies: 1 meta-analysis, 7 RCTs (2 RCTs, 5 crossover RCTs). Studies published between 1998 to 2010.	of the patients ranged from 65.67 to 71.7 years old; % male NR N = 874	lease melatonin **Relevant comparators:** Unclear (assumption has been made that comparator was placebo based on a statement made in the discussion section) Duration of intervention: Studies ranged from 8 nights to 26 weeks	

NR = not reported; RCT = randomized controlled trials.

Table 4: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Kim et al. 2021[21] Korea **Funding**: Kuhnil Pharmacy (Seoul, Korea)	RCT	N = 38 **Eligibility criteria:** Women > 55 years old with insomnia (Pittsburgh Sleep Quality Index (PSQI) ≥ 5) who had not taken medication for depression, insomnia, or tranquilization in the past 3 months. **Exclusion criteria:** History of menopausal hormone replacement therapy; cerebrovascular diseases (including ischemic stroke and cerebral hemorrhage), cardiovascular diseases (including unstable angina, myocardial infarction, and coronary revascularization); chronic liver disease (including chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma); chronic renal disease (including previous chronic kidney disease and kidney transplantation); malignant neoplasm; any treatment for depression, insomnia, or tranquilization at least 3 months before this study; aspartate aminotransferase (AST) > 100 IU/L, alanine aminotransferase (ALT) > 100 IU/L, or creatinine > 1.4 mg/dL. **Setting:** Patients recruited via Severance Hospital **Age** median (interquartile range): Melatonin: 61 (58, 71); Placebo: 61 (59, 65) **% male:** 0%	**Intervention**: 2 mg prolonged-release melatonin (Circadian) **Comparator:** Placebo Treatment was taken daily 2 hours before sleep	Relevant outcomes: Pittsburgh Sleep Quality Index Other outcomes: Arterial stiffness; Mitochondrial DNA Follow-up: 6 weeks

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Xu et al. 2020[22] China **Funding**: Shanghai Municipal Commission of Science and Technology	RCT	N = 61 **Eligibility criteria:** Chinese individuals aged 45 to 60 years who had primary insomnia according to the DSM-IV criteria **Exclusion criteria:** Use of hypnotics within the previous one month or any psychoactive treatment, had drugs such as neuroleptic, antidepressants and anticholinergic agents which could interfere on sleep structure within the previous 3 months; moderate-severe OSA or relevant periodic leg movements; sleep disorders associated with a psychiatric disorder; severe psychiatric disorders, especially psychosis, anxiety and depression; sleep disorders secondary to another medical condition; a lifestyle likely to interfere with sleep patterns; use of prohibited medication or alcoholism; patients with severe organic diseases or with other conditions not suitable for participating in the study at the investigator's discreet. **Setting:** Tertiary hospital **Age** mean (SD): Melatonin: 57.24 (5.59); Placebo: 56.53 (4.65) **% male:** 47.5%	**Intervention:** 3 mg fast-release melatonin tablet **Comparator:** Placebo Treatment was taken daily 1 hour before bedtime	Outcomes: Sleep quality (polysomnography); Subjective sleep performance and daytime somnolence (PSQI), Insomnia Severity Index; Epworth Sleepiness Scale; Serious adverse events and side effects Follow-up: 4 weeks

DNA = DNA; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation.

Table 5: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Mayer et al. (2021)[23]						
Intended Users: NR Target Population: Insomnias in headaches, neurodegenerative movement disorders, multiple sclerosis, traumatic brain injury, epilepsies, stroke, neuromuscular disease and dementia	Cognitive behavioural therapy; Light therapy; Physical exercise; Pharmacological therapy (e.g., benzodiazepine); Non-pharmacological therapy (e.g., melatonin) Chronic insomnia (ICD 10)	Treatment of insomnia	Systematic review of randomized controlled trials, and "studies of lower evidence (p. 9)"[23] if studies of high evidence were lacking	Literature was categorized independently by 2 experts according to Oxford Centre for Evidence-based Medicine Levels of Evidence (2001)	Nominal group process and Delphi technique Evidence classification (class 1-IV) was performed according to standardized European Procedures Levels of recommendation are A-D (not further described)	NR
Palagini et al. (2021)[24]						
Intended users: Psychiatric clinical practice Target population: Adults with neuropsychiatric disorders and insomnia and circadian sleep disturbances	Prolonged-release and immediate-release exogenous melatonin	Treatment of insomnia symptoms; Use of melatonin during sedative-hypnotics discontinuation	Systematic literature review including systematic reviews and meta-analyses	RAND/UCLA Appropriateness method which include critical appraisal of the evidence (not otherwise described)	RAND/UCLA Appropriateness Method for conceptualizing, designing, and carrying out the appropriateness procedures. Recommendation formulated using a modified Delphi method	NR
Palagini et al. (2020)[25]						
Intended users: Clinical practice Target population: Adult population with insomnia	Cognitive behavioural therapy; Pharmacological therapy (i.e., Melatonin 2 mg prolonged-release, sedating antidepressants, short/	Treatment of insomnia	Systematic literature review of guidelines, with additional systematic review of systematic reviews or meta-analyses	RAND/UCLA Appropriateness method which include critical appraisal of the evidence (not otherwise described)	RAND/UCLA Appropriateness Method for conceptualizing, designing, and carrying out the appropriateness procedures. Recommendation formulated using a modified Delphi method	NR

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
	medium-acting benzodiazepines, Zdrugs)					
Department of Veterans Affairs (2019)[26]						
Intended Users: Health care providers Target Population: Adults 18 years or older treated in any VA/DoD primary care setting who have experienced sleep disorders	Key Question 1: Pharmacotherapy, including over the counter preparations (e.g., melatonin)	Patient health outcomes; Quality of life	Systematic review of clinical studies and systematic reviews, RCTs, and cohort studies	Not clearly reported, but included blinding of patients and professionals, allocation concealment	VA and DoD Evidence-Based Practice Work Group (www.healthquality.va.gov/policy/index.asp) Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, considering: • Balance of desirable and undesirable outcomes • Confidence in the quality of the evidence • Patient or provider values and preferences • Other implications, as appropriate (e.g., resource use, equity, acceptability, feasibility, subgroup consideration) Recommendations were strong (generally indicates high confidence in the quality of the available scientific evidence, a clear difference in magnitude between the benefits and harms of an intervention, similarity among patient or provider values and preferences, and the apparent influence of other implications) (e.g., resource use, feasibility) or	Posted on a wiki website for a period of 14 business days; American Academy of Sleep Medicine

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
					weak (If the Work Group has less confidence after the assessment across these domains and believes that additional evidence may change the recommendation).	

DoD = Department of Defense; ICD = International Classification of Diseases; NR = not reported; VA = Veterans Affairs.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 6: Strengths and Limitations of Umbrella Reviews Using AMSTAR 2[8]

Strengths	Limitations
Low et al. 2020[12]	
• The protocol for the review was registered prospectively with PROSPERO and the registration number was provided • Five electronic databases were searched. Supplemental grey literature searching, PROSPERO, and reference list searching was conducted • No language restriction; non-English articles were translated via Google Translate • Data extraction was performed by 2 reviewers independently, with disagreement resolved through discussion • Details of the reviews were sufficiently reported • Methodological quality of the systematic reviews was performed using AMSTAR 2, although the process of conducting this was not reported • A PRISMA flow diagram was provided • Conflict of interest were reported (i.e., none)	• Some elements of PICO for inclusion not described (e.g., outcomes) • No description on how study selection was conducted • No description on how critical appraisal (i.e., AMSTAR 2) was conducted • A list of excluded studies was not provided, and no reasons were provided in the PRISMA flow diagram • No assessment of overlap in the primary studies between the included systematic reviews • Source of funding of the included reviews was not provided • Source of funding for the umbrella review not reported
Rios et al. 2019[13]	
• The protocol for the review was registered prospectively with PROSPERO and the registration number was provided • Five electronic databases were searched. Supplemental searching for grey literature using the Grey Matters checklist, reviewing bibliographies of included reviews, and contacting authors of conference abstracts and review protocols was performed • PICO elements were well defined for inclusion • Study selection performed independently by 2 reviewers, disagreements were solved with a third reviewer • A PRISMA flow diagram was provided • Data extraction was completed by one reviewer and verified by a second reviewer • Details of the reviews and included studies well reported in supplemental files • Any SRs that completely overlapped primary studies and did not contribute any new evidence were excluded • A list of primary studies in each review were collated in a matrix of evidence tables to ascertain the degree of overlap. Additionally, a matrix of evidence for the entire review was prepared, which was also used to calculate the corrected covered area • Methodological quality of the systematic reviews was performed using AMSTAR 2, and was completed by one reviewer and verified by a second reviewer	• A list of excluded studies and reason for exclusion was not provided, but high-level reasons were provided in the PRISMA flow diagram • Interpretation of reported outcomes in the supplementary file are not always clear what the outcome is reporting (e.g., decrease vs increase) • Source of funding of the included reviews was not provided • Competing interests were reported, but not all provided a description on how they were managed

Strengths	Limitations
• A GRADE algorithm developed for overviews was used to ascertain the strength of evidence of the included reviews • Sources of funding for the overview was provided • Competing interests were reported, but not all provided a description on how they were managed	

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2.

Table 7: Strengths and Limitations of Systematic Reviews and Network Meta-Analyses Using AMSTAR 2[8] and the ISPOR Questionnaire[9]

Strengths	Limitations
Ma et al. (2022)[14]	
• Four electronic databases were searched • Elements of PICO were well described for inclusion • Study selection performed independently by 2 reviewers • A PRISMA flow diagram was provided • Two reviewers extracted data, with a third independent reviewer involved in disagreements • Risk of bias assessed independently by 2 reviewers with a third reviewer involved in disagreements • Statistical analysis well described, and heterogeneity assessed for meta-analysis • PICO elements of primary studies described, but missing some details (e.g., setting, dosage of melatonin) • Sources of funding for the review was provided	• There was no statement that the review methods were established before the review conduct and no mention of a protocol • Although PICO elements well described, definition of 'insomnia' was not included • No supplemental searching performed (e.g., grey literature, bibliography hand searching) • A list of excluded studies and reason for exclusion was not provided, but high-level reasons were provided in the PRISMA flow diagram • Some elements of study characteristics missing (i.e., setting, dosage of melatonin) • No mention of assessment for publication bias • Source of funding of the included primary studies not provided • Authors did not report on any competing interests
Almond et al. (2021)[15]	
• Three electronic databases were searched • Study selection performed independently by 2 or more reviewers with disagreements resolved with first author of the review • A PRISMA flow diagram was provided • Risk of bias assessment rated by 2 reviewers independently • PICO elements of primary studies described	• There was no statement that the review methods were established before the review conduct and no mention of a protocol • Some elements of PICO were not well described (e.g., comparators, outcomes). There is no explanation of study designs for inclusion in the review • No supplemental searching was performed to identify studies not included in electronic databases • Review authors did not explain their selection of the study designs for inclusion and exclusion in the review • A list of excluded studies was not provided, but high-level reasons were provided in the PRISMA flow diagram • No description of data extraction process (e.g., 2 independent extractors) • Source of funding of the included primary studies not provided • Although it is stated that risk of bias was performed, the results are not presented or discussed

Strengths	Limitations
	• No mention of assessment for publication bias • Source of funding for the systematic review not reported
Kothari et al. (2021)[16]	
• The review protocol was prospectively registered on PROSPERO and the registration number was provided • Two electronic databases were searched. Reference lists of included studies were reviewed for additional studies. • Elements of PICO were well described for inclusion, with the exception of comparators • Study selection performed independently by 2 reviewers, disagreements were solved by senior authors • A PRISMA flow diagram was provided • Data extraction performed independently by 2 reviewers, disagreements were solved by senior authors • Risk of bias performed independently by 2 reviewers, who met to compare results and reach consensus • Primary study authors contacted if data were not clearly reported in included study • Statistical analysis well described, and heterogeneity assessed for meta-analysis • Elements of primary studies described, but missing some details (e.g., setting) • Addressed why publication bias was not performed (i.e., low number of included studies) • Source of funding (i.e., none) and conflicts of interest reported	• Review authors did not explain their selection of the study designs for inclusion and exclusion in the review • Minimal supplemental searching performed (e.g., no relevant websites, no contacting experts) • Comparators not described in the inclusion criteria • A list of excluded studies was not provided, but high-level reasons were provided in the PRISMA flow diagram • Some elements of study characteristics missing (i.e., setting) • Source of funding of the included primary studies not provided
Baglioni et al. (2020)[17]	
• The study protocol was reviewed and approved for funding • Eligibility criteria were clearly defined, and covered the elements of PICO and included study designs • Studies published in several languages were included • Several electronic databases were searched, and supplemental searching was performed (i.e., bibliographic searching, contacting authors and experts in the field) • Study selection performed by 2 or more independent reviewers with disagreements resolved with first author of the review • A PRISMA flow diagram was provided • Risk of bias assessment rated by 2 independent reviewers with divergences discussed with other reviewers • A valid rationale for using random-effects model was provided • A graphical representation of the evidence network is provided for several outcomes	• Although there was a mention of a protocol, there was no explicit statement that the review methods were established before the conduct of the review • Review authors did not explain their selection of the study designs for inclusion and exclusion in the review • No description of data extraction process (e.g., 2 independent extractors) • A list of excluded studies was not provided, but high-level (i.e., PICO) reasons were provided in the PRISMA flow diagram • Inadequate detail of the included studies (e.g., setting, dosage of melatonin) • Source of funding of the included primary studies not provided • No formal publication bias was performed, however, authors state that there is still debate on how to perform this in network meta-analyses

Strengths	Limitations
McCleery et al. (2020)[18]	
• The review protocol was published before the conduct of the review. Deviations from the protocol were described. • Several electronic databases were searched. Supplemental searching included grey literature sources, reference lists of selected studies. • Elements of PICO were well described • Study selection performed independently by 2 reviewers, disagreements were resolved through discussion. Study authors were contacted when further information was required for inclusion. • A PRISMA flow diagram was provided; A list of excluded studies was provided • Data extraction performed independently by 2 reviewers, disagreements were resolved through discussion • Risk of bias performed independently by 2 reviewers, disagreements were resolved through discussion. Study authors were contacted when further information was required to be able to assess risk of bias. • Statistical analysis well described, and heterogeneity assessed for meta-analysis • Elements of primary studies described, including source of funding (when reported) • Addressed why publication bias was not performed (i.e., low number of included studies) • The overall strength of the evidence was evaluated using the GRADE approach • Source of funding for the review was reported and conflicts of interest reported	• Review authors did not explain their selection of the study designs for inclusion and exclusion in the review
Sys et al. (2020)[19]	
• Three electronic databases were searched. Additional searching of reference lists in retrieved articles and systematic reviews was performed. • Articles in English, Dutch, and French were included • Elements of PICO were sufficiently described, with the exception of comparators • Study selection performed independently by 2 reviewers, with consensus reached • A PRISMA flow diagram was provided • Data extraction performed independently by 2 reviewers • Elements of primary studies described • Authors declared conflicts of interest (i.e., none)	• There was no statement that the review methods were established before the review conduct and no mention of a protocol • Comparators not well described in the PICO for inclusion • A list of excluded studies was not provided, but high-level reasons were provided in the PRISMA flow diagram • No description on of how quality appraisal of the included studies was performed (e.g., independently) • No mention of assessment for publication bias • Source of funding of the included primary studies not provided • Source of funding for the systematic review not reported

Strengths	Limitations
Pierce et al. (2020)[20]	
• One database searched • A PRISMA flow diagram was provided • Source of funding for the review was reported (i.e., none) and conflicts of interest reported	• There was no statement that the review methods were established before the review conduct and no mention of a protocol • Only one database searched and no supplemental searching performed • Elements of PICO for inclusion/exclusion were not well described • No details around the methods of study selection, data extraction, and risk of bias assessment • A list of excluded studies was not provided, but high-level reasons were provided in the PRISMA flow diagram • PICO elements of the studies were not well described (e.g., no setting, little description of the population). It is possible studies not listed under the primary insomnia category included patients with insomnia. • Inadequate outcome reporting for several studies • No mention of assessment for publication bias • Authors did not report on the sources of funding for the studies included in the review

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NR = not reported; PICO = participants, intervention, comparator, outcomes.

Table 8: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[27]

Strengths	Limitations
Kim et al. (2021)[21]	
• The aim of the study was clearly described • The main outcomes were clearly described • The characteristics of the included patients were well described, including the inclusion and exclusion criteria • The intervention and comparator were clearly described • Patients were recruited from the same population (i.e., single-centre) • Trial described as "double-blind," although there is no information on who was blinded • Placebo tablet had the same appearance as the melatonin pill, therefore assuming patients were blinded to group • No patients lost to follow-up; all included in the results • Follow-up was the same for all patients • Reporting of the outcomes was sufficient, including median and interquartile range at baseline and follow-up, and the intergroup difference (reported as a p-value)	• There is no description around the method of randomization or allocation concealment, so we do not know if there is selection bias, although the baseline study characteristics were similar with exception of total cholesterol and insulin • Only women > 55 years old were included, so results would not be generalization to men or those under the age of 55 • It is unclear if compliance (or nonadherence) of the intervention was measured and how this may have impacted the results

Strengths	Limitations
Xu et al. (2020)[22]	
• The aim of the study was clearly described • The main outcomes were clearly described, including the scales and interpretation of the scales for questionnaires • The characteristics of the included patients were well described, including the inclusion and exclusion criteria • The intervention and comparator were clearly described • Allocation concealment in sequentially numbered, opaque envelopes • Patients were recruited from the same population and were similar at baseline • Patients and investigators were blind to treatment group • Placebo tablets were identical in appearance to melatonin tablets • Patients not included in the final analysis were described and reasons for exclusion were justified • Follow-up was the same for all patients • Reporting of the outcomes was sufficient, including means at baseline and follow-up, the difference in the change between groups and confidence intervals	• Randomization was performed with a "random number method" with the method not further described • Patients were pre-screened by their general practitioner and are therefore health-seeking individuals. This may not be representative of the general population who have insomnia. • Patients were 45 to 60 years old, so results would not be generalizable to those under the age of 45 years or over the age of 60 years' old • It is unclear if compliance (or nonadherence) of the intervention was measured and how this may have impacted the results

Table 9: Strengths and Limitations of Guidelines Using AGREE II[10]

AGREE scale item	Mayer et al. (2021)[23]	Palagini et al. (2021)[24]	Palagini et al. (2020)[25]	Veterans Affairs (2019)[26]
Domain 1: Scope and Purpose				
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes
Domain 2: Stakeholder Involvement				
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	Unclear	Unclear	Yes
6. The target users of the guideline are clearly defined.	No	Yes	Yes	Yes
Domain 3: Rigour of Development				
7. Systematic methods were used to search for evidence.	Yes	Yes	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	No	No	No	Yes

AGREE scale item	Mayer et al. (2021)[23]	Palagini et al. (2021)[24]	Palagini et al. (2020)[25]	Veterans Affairs (2019)[26]
9. The strengths and limitations of the body of evidence are clearly described.	No	No	No	Yes
10. The methods for formulating the recommendations are clearly described.	No	Yes	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts before its publication.	Unclear	Unclear	Unclear	Yes
14. A procedure for updating the guideline is provided.	No	No	No	Yes
Domain 4: Clarity of Presentation				
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes
Domain 5: Applicability				
18. The guideline describes facilitators and barriers to its application.	No	No	No	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No	No	No	Yes
20. The potential resource implications of applying the recommendations have been considered.	No	No	No	Yes
21. The guideline presents monitoring and/or auditing criteria.	No	No	No	Yes
Domain 6: Editorial Independence				
22. The views of the funding body have not influenced the content of the guideline.	Yes (no funding)	Unclear	Unclear	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes (none)	Yes (none)	Yes (none)	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II.

Appendix 4: Main Study Findings and Authors' Conclusions

Note that this appendix has not been copy-edited.

Table 10: Summary of Findings Included Umbrella Reviews

Main study findings	Authors' conclusion
Low et al. 2020[12]	
Sleep outcomes 1. 3/5 studies showed improved sleep latency and sleep efficiency; Statistically significant improvement in sleep latency (Olde Rikkert et al. 2001) 2. "In 3 of 4 trials, sleep efficiency was significantly improved compared to placebo, while sleep latency was significantly improved in 2. In 2 others, total sleep time improved significantly. In 3 studies, melatonin significantly improved at least one actigraphic measure of sleep quality. (p. 19)"[12]; Statistically significant improvement in sleep latency (Harrington 2004) 3. 1/4 studies reported improvement in sleep quality; No statistically significant improvement in total sleep time or sleep latency (MacMahon et al. 2005) 4. Out of 4 studies, 2 favoured melatonin and 2 did not favour either melatonin or control (Costello et al. 2014) 5. Melatonin significantly lowers sleep latency [-2.48 (−4.56 to −0.40)] and significantly increases total sleep time [29.27 (6.68 to 51.86)], but had little effect on sleep efficiency (Li et al. 2018) 6. "Circadin 1–2 h before bedtime was associated with significant improvements in many sleep and daytime parameters, including sleep quality and latency, morning alertness and health-related quality of life. (p. 21)"[12]; Statistically significant improvement in sleep latency (Lyseng-Williamson et al. 2012) **Adverse events** • Headaches, with no serious events (MacMahon et al. 2005) • Adverse events were infrequent and non-serious (Costello et al. 2014) • "It is very well tolerated, with a tolerability profile similar to that of placebo. Short- or longer-term treatment with circadian was not associated with dependence, tolerance, rebound insomnia or withdrawal symptoms. (p. 21)"[12] (Lyseng-Williamson et al. 2012) Other relevant review already captured in the 2019 CADTH report: Auld et al. 2017.	Findings were fairly consistently across reviews, however, there was considerable heterogeneity, which leads to uncertainty Most reviews did not specify timing of melatonin administration, and among those that did, timing was variable. "Hence, it is possible that conflicting conclusions are contributed by different and/or suboptimal timing of administration of melatonin. (p. 22)"[12] "It appears that there is inadequate evidence to confirm the efficacy of melatonin in primary insomnia. (p. 22)"[12]

Main study findings	Authors' conclusion
Rios et al. 2019[13]	
Sleep onset latency (reported in 4 MAs and 3 SRs) measured with sleep diaries, polysomnography and/or actigraphy • 4 MAs (2 high and 2 critically low AMSTAR rating), with 8 to 12 primary studies, all reported a significant mean difference in sleep onset latency • 3 SRs (all critically low AMSTAR rating) reported mixed primary study results with significant improvement, non-significant improvement, and no change **Total sleep time** (reported in 6 MAs and 4 SRs) measured with polysomnography, actigraphy, sleep diary, subjective report, and PSQI • 2 of 6 MAs (2 critically low, 1 moderate, 2 High AMSTAR rating), with 2 to 11 primary studies, reported a statistically significant mean difference of total sleep time • 4 SRs (3 critically low, 1 moderate AMSTAR rating) reported mixed primary study results with significant improvement, non-significant improvement, no change, and decrease **Wake after sleep onset** (reported in 3 MAs and 2 SRs) measured with sleep diary, polysomnography, actigraphy • All 3 MAs (1 critically low, 2 high AMSTAR rating), with 2 to 5 primary studies, reported no significant mean difference • Both SR (both critically low AMSTAR rating) reported significant changes (i.e., change in outcome, decrease) **Sleep quality** (reported in 5 MAs and 5 SRs) measured with polysomnography, actigraphy, sleep scales questionnaires, carer-rated sleep quality, and various sleep questionnaires (e.g., LSEQ, PSQI) • 1 of 5 MAs (critically low AMSTAR rating), with 14 primary studies, reported a statistically significant mean change in sleep quality; 4 MAs (2 critically low, 2 high AMSTAR rating), with 2 to 10 primary studies) reported no statistically significant difference • SRs (4 critically low, 1 moderate AMSTAR rating) reported mixed primary study results with significant improvement, and no change/difference **Sleep satisfaction** (reported in 1 SR) measured by % nights scored good; % good mood • SR (critically low AMSTAR rating) reported a significant increase in both % nights scored good and % good mood **Sleep efficiency** (reported in 5 MAs and 3 SRs) measured by polysomnography, actigraphy, and sleep diary • 1 of 4 MAs (critically low AMSTAR rating), with 8 primary studies, reported a statistically significant mean difference in sleep efficiency; 3 MAs (1 moderate, 2 high AMSTAR ratings), with 1 to 9 primary studies, reported no	• Over half of the included reviews were assessed as low or critically low quality on AMSTAR 2 • Most interventions were short duration (< 12 weeks) and had small sample sizes • There was a lack of harm data across studies • Cognitive behavioural therapy can be considered the first-line intervention, but if it is not effective "then other behavioral interventions can be considered or short courses of melatonin, zolpidem, suvorexant, or doxepin can be added to non-pharmacological therapy. However, these agents have only been tested in short-term studies and there is little evidence for their effectiveness or safety beyond 16 weeks of treatment. (p. 14)"[13]

Main study findings	Authors' conclusion
statistically significant difference • 3 SRs (all critically low AMSTAR rating) reported mixed primary study results with significant improvement, and no change/difference **Health-related quality of life** (reported in 1 SR) measurement tool not reported • SR (critically low AMSTAR rating) with 1 primary study reported a significant increase in quality of life	

LSEQ = Leeds Sleep Evaluation Questionnaire; MA = meta-analysis; PSQI = Pittsburgh Sleep Quality Index; SR = systematic review.

Table 11: Summary of Findings Included Systematic Reviews and Network Meta-Analysis

Main study findings	Authors' conclusion
Ma et al. (2022)[14]	
Data from 1 relevant included study (Medeiros et al. 2007) **Objective outcomes** (measured with polysomnography) **Total sleep time** • Total sleep time: P = 0.09; "A trend of improvement of total sleep time was observed in the melatonin-treated group. (p.6)"[14] **Subjective outcomes** **Sleep quality** (measured with PSQI) • Melatonin vs Placebo Mean (SD): 6.7 (2.7) vs 8.5 (2.6); Mean difference (95% confidence interval): −1.8 (−3.26 to −0.34); P = 0.03 **Daytime sleepiness measured by mean change** (measured with ESS) • Melatonin vs Placebo: 0.3 vs 0.2 (P = 0.84); "Daytime sleepiness is not affected by melatonin administration despite improved subjective sleep quality. (p.6)"[14]	• "The combined data from RCT studies showed that melatonin could significantly improve the subjective and objective sleep quality of patients with PD with good safety and tolerability. (p. 9)"[14] • "Melatonin could be considered an effective treatment for insomnia in patients with Parkinson's disease. (p.9)[14] • Using the Epworth Sleepiness Scale, there was no significant improvement in excessive daytime sleepiness • A larger, multi-centred RCT should be performed
Almond et al. (2021)[15]	
Data from 2 relevant included studies (Garfinkel et al. 1995, Monti et al. 1999) **Objective outcomes** (measured with wrist actigraphy or polysomnography) **Sleep efficiency** • Increased sleep efficiency with melatonin vs. placebo (83% vs 75%; P < 0.001) (Garfinkel et al. 1995) • Sleep efficiency was significantly increased with melatonin compared to placebo (Monti et al. 1999) ◦ Melatonin: nights 4 to 5 [72.1% (3.5); P < 0.05] ◦ Melatonin: nights 15 to 16 [72.7% (3.9); P < 0.03] ◦ Placebo: nights 2 to 3 [63.9% (4.1)] **Wake time after sleep onset**	• "Melatonin was found to significantly increase sleep efficiency, decrease wake time after sleep onset, and increase total sleep time when compared with placebo."[15] (p.91) • Melatonin is likely a safe option as it demonstrated little to no adverse effects

Main study findings	Authors' conclusion

• Reduced wake time after sleep onset with melatonin vs. placebo (49 vs 73 minutes; P < 0.001) (Garfinkel et al. 1995)
• Significantly decreases with melatonin treatment compared to placebo (Monti et al. 1999)
  ◦ Melatonin: nights 4 to 5 (103.7 [15.9] minutes; P < 0.03)
  ◦ Melatonin: nights 15 to 16 (107.3 [15.4] minutes; P < 0.03)
  ◦ Placebo: baseline nights 2 to 3 (144.3 [19.3] minutes]
Total sleep time
• No difference in total sleep time with melatonin vs. placebo (360 vs 365 minutes; P = 0.49) (Garfinkel et al. 1995)
• Significantly increased total sleep time with melatonin compared to placebo (Monti et al. 1999)
  ◦ Melatonin: nights 4 to 5 [345.9 (16.7) minutes; P < 0.03)
  ◦ Melatonin: nights 15 to 16 [349.2 (18.6) minutes; P < 0.03)
  ◦ Placebo: nights 2 to 3 [306.7 (19.7) minutes]
Sleep latency
• Slight decline in sleep latency with melanin compared to placebo (33 vs 19 minutes; P = 0.88) (Garfinkel et al. 1995)
• Sleep latency was not significantly affected (Monti et al. 1999)
Number of awakenings (Monti et al. 1999)
• Number of awakenings was not significantly affected
Safety outcomes
Adverse events
• Pruritus was reported in 2 subjects (1 in each group) and resolve spontaneously (Garfinkel et al. 1995)
• No adverse events were reported (Monti et al. 1999)	

Kothari et al. (2021)[16]	
Data from 1 relevant included study (Garfinkel et al. 2011) Reported as melatonin vs placebo at 3 weeks **Objective outcomes** (measured using actigraphy) **Sleep efficiency** • 79.2% vs 83.0%; P < 0.04 **Wake time after sleep onset** • 66.3 vs 38.0 minutes; P < 0.001 **Number of awakenings** • 16.5 vs 10.8; P < 0.003	• Despite the limitations of the studies "majority of the studies (21 of 22) showed that these interventions (sleep extension, CBT-I and medications) were able to improve certain aspects of sleep including sleep duration, self-reported sleep quality and wake time after sleep onset. (p. 33)"[16] • All studies evaluating melatonin or melatonin agonist resulted in improved sleep (quality, duration). • The change in glycemic parameters in the relevant study was not predicted by improvement in sleep parameters.
Baglioni et al. (2020)[17]	
Data from 2 relevant included studies (Lurthinger et al. 2019; Rondanelli et al. 2007) Other relevant primary studies already captured in 2019 CADTH review and not reported here: Wade et al. 2007	• The network meta-analysis did not show any evidence that any of the included interventions were effective for either nighttime sleep symptoms and perception of severity of insomnia. • "Our findings do not support any of the selected therapies

Main study findings	Authors' conclusion
Reported as Melatonin pre-mean (SD) vs Placebo pre-mean (SD); Melatonin post mean (SD) vs Placebo post mean (SD) **Objective outcomes** (measured by polysomnography, actigraphy) **Sleep onset latency** (Luthringer et al. 2009) • 20.6 (8.6) vs 24.3 (13.8); 13.7 (6.6) vs 22.6 (13.4) **Wake after sleep onset** (Luthringer et al. 2009) • 84.9 (38.5) vs 85.7 (30.8); 81.7 (36.3) vs 73.2 (28.6) **Total sleep time** (Luthringer et al. 2009) • 381.1 (41.4) vs 381 (30); 391.7(35.6) vs 389.5 (33.2) **Number of awakenings** (Luthringer et al. 2009) • 21.9 (9.8) vs 21.3 (9.6); 21.3 (10.4) vs 19.9 (8.9) Additional objective outcomes not reported here: Stage 1 sleep Stage 2 sleep, Stage 3 sleep, REM sleep **Subjective outcomes** **Sleep** (measured with PSQI) (Rondanelli et al. 2007) • 12.7 (2.6) vs 12.3 (3.6); 5.5 (1.9) vs 12 (4.4) **Sleep quality** (measured with LSEQ) (Luthringer et al. 2009, Rondanelli et al. 2007) • 49.5 (16.5) vs 34.7 (20.5); 42.1 (14.8) vs 33.8 (17.3) • 54.5 (9.3) vs 53.7 (9.7); 45.9 (16) vs 49.5 (14.8) **Sleep quality** (measured with sleep diary) (Luthringer et al. 2009, Rondanelli et al. 2007) • 49.5 (16.5) vs 34.7 (20.5); 42.1 (14.8) vs 33.8 (17.3) • 3.2 (1.3) vs 3 (1.4); 7.65 (0.32) vs 4.95 (0.30) **Sleepiness** (measured with ESS) (Rondanelli et al. 2007) • Mean change from baseline (SD): 10.9 (5.1) vs 11 (3.9); 8.0 (1.49) vs 10.2 (0.8) **Physical function** (measured with SF36) (Rondanelli et al. 2007) • 32.1 (6.7) vs 35.1 (5.9); 29.6 (1.0) vs 34.0 (0.8) **Mental** (measured with SF36) (Rondanelli et al. 2007) • 49.5 (10) vs 47.8 (10.4); 51.5 (1.1) vs 47.8 (1.2)	to be recommended for insomnia disorder. (p. 20)"[17]
McCleery et al. (2020)[18]	
Data from 1 relevant included study (Morales-Delgado et al. 2018) Other relevant primary study already captured in 2019 CADTH review and not reported here: Wade et al. 2014 **Subjective outcomes** **Carer-rated sleep quality** (measured with PSQI) • Mean (SD) melatonin vs placebo: 6.4 (1.99) vs 7.3 (3.36); MD (95% CI): −0.32 (−1.03 to 0.39) **Cognition** (measured with Mini Mental State Examination) • Median (interquartile range) at 8-weeks melatonin vs placebo:	• "We found no evidence from 4 RCTs, reporting data on 222 participants, that melatonin had either beneficial or harmful effects on any major sleep outcome in people with sleep disorders with moderate-to-severe dementia due to Alzheimer's Disease. There were no serious adverse events reported in the trials. (p 21-22)"[18]

Main study findings	Authors' conclusion
17 (9) in both groups **Activities of Daily Living** (Lawton's Instrumental ADLs Scale) • Mean (SD) at 8 weeks melatonin vs placebo: −0.5 (1.38) vs −0.1 (1.17); Std MD (95% CI): −0.30 (−1.01 to 0.41) **Adverse events** • "Morales-Delgado 2018 reported only that "the treatment was well-tolerated in all cases," and that no serious adverse events occurred during the trial, although they also reported that one participant in the placebo group died." (p. 20)"[18]	
Sys et al. (2020)[19]	
Data from 3 relevant included primary studies (Lemoine et al. 2017; Wade et al. 2007; Wade et al. 2010) Other relevant primary studies already captured and reported in a systematic review in this report: Garfinkel et al. 1995 **Subjective outcomes** **Sleep quality** • Improved with melatonin vs placebo: −22.5 vs −16.5 mm; P = 0.047 on LSEQ (Lemoine et al. 2007) • Improved with melatonin vs placebo: 26 vs 15%; P = 0.014 on LSEQ and Behaviour following wakening scales (Wade et al. 2007) • "No difference in diaries (p. 372)"[19] (Wade et al. 2010) • Score better on PSQI in: (Wade et al. 2010) ◦ Short-term: −0.64 (95% CI, −1.25 to −0.02); P = 0.042 ◦ Long-term: −0.70 (95% CI, −1.17 to −0.23); P = 0.003 **Sleep latency** • Shortening with melatonin vs placebo: −24.3 vs −12.9 minutes; P = 0.028 on PSQI (Wade et al. 2007) • Reduced with melatonin vs placebo (Wade et al. 2010) [subjective outcome, but not clearly stated how this was measured]: ◦ at 3 weeks: −15.6 minutes (95% CI, −25.3 to −6.0); P = 0.002 ◦ at 29 weeks: −14.5 minutes (95% CI, −21.4 to −7.7); P < 0.001 **Total sleep time and sleep maintenance** • "No difference in diaries (p. 372)"[19] (Wade et al. 2010) **Quality of night** (sleep diaries) • 0.2 (95% CI, 0.0 to 0.2); P = 0.21 (Wade et al. 2007) **Quality of day** (sleep diaries) • 0.1 (95% CI, 0.0 to 0.2); P = 0.21 (Wade et al. 2007) **Quality of life** • Improved significantly with melatonin vs placebo: 0.8 (95% CI, 0.1 to 1.5); P = 0.034 on WHO-5 index (Wade et al. 2007) • "WHO-5 index improved not significantly at short and long-term	• Three major observations were made around the use of melatonin: "First, the use of melatonin in older persons appears to be safe. Second, we should take into account the large heterogeneity between the tested doses, tablet formulation (slow versus immediate-release form), and outcome measures, which precluded making strong statements on its place in the management of insomnia in older adults. Third, inconsistent results were found for multiple outcomes across all studies included in our review. (p. 378)"[19] • "There is insufficient evidence to recommend the use of melatonin for the management of sleep problems in hospital and evidence for its use in an outpatient setting seems equivocal. (p. 379)"[19] • "Evidence for melatonin seems more equivocal. (p. 379)"[19]

Main study findings	Authors' conclusion
(p. 372)"[19] (Wade et al. 2010) **Next-day alertness, well-being, feelings and mood** **Behaviour following wakening** (LSEQ) • Improved with melatonin vs placebo: −15.7 vs −6.8 mm; P = 0.02 (Lemoine et al. 2007) **Alertness in morning** • More alertness in morning with melatonin vs placebo [subjective outcome, but not clearly stated how this was measured]: −0.10 (95% CI, −0.19 to −0.01); P = 0.032 (Wade et al. 2010) **Clinical Global Impression Scores** • No difference: −0.2; P = 0.14 (Wade et al. 2007) • Improved in long-term: −0.20 (95% CI, −0.38 to −0.02); P = 0.027 (Wade et al. 2010) **Adverse events** • 9 AEs in each group, most were mild. No rebound insomnia or withdrawal effects after treatment discontinuation (Lemoine et al. 2007) • 24% in melatonin group, 21% in the placebo group (Wade et al. 2007) • No difference between groups; most AEs where mild (Wade et al. 2010)	
Pierce et al. (2019)[20]	
Meta-analysis including 6 RCTs (Olde Rikkert et al. 2001) • Increased to no change in sleep efficiency, decreased to no change in sleep latency • 3/6 showed improved sleep efficiency • 4/6 showed decreased sleep latency • 2/6 studies showed decrease wake time following sleep initiation when treated with melatonin • 1/6 showed no change in any sleep outcome Also captured in the Low et al. 2021 umbrella review in this report, but this systematic review reported additional details Data from 4 relevant included primary studies (Baskett et al. 2003, Jean-Louis et al. 1998; Hughes et al. 1998, Dawson et al. 1998) Other relevant primary studies already captured and reported in a systematic review in this report: Wade et al. 2007; Lemoine et al. 2017 **Method of measurement not reported** **Multiple outcomes reported qualitatively** • "No statistically significant improvement in total sleep time, sleep latency, or sleep efficiency; 95% CI crosses zero (p. 425)"[20] (Baskett et al. 2003) • "No significant difference on total sleep time or wake time; p not reported (p. 425)"[20] (Jean-Louis et al. 1998)	• "Evidence assessing the use of melatonin for sleep disorders in older adults is limited (p. 429)"[20] • Improvement in sleep were found in RCTs evaluating doses of melatonin 1 mg to 6 mg, but not in those evaluating doses of melatonin of 0.5 mg • "Adverse effects were minimal among all 26 clinical studies, with no studies reporting statistically significant variance in adverse effects between melatonin and placebo (p. 429)"[20]

Main study findings	Authors' conclusion
• "No significant reduction in total sleep time or nocturnal wake time (p. 426)"[20] (Hughes et al. 1998) **Sleep quality** • No significant positive effect on sleep quality (p not reported) (Dawson et al. 1998) • "No improvement in subjective sleep (p not reported) (p. 426)"[20] (Hughes et al. 1998) **Sleep efficiency** • Trend for improved efficiency (P = 0.09) (Jean-Louis et al. 1998) **Sleep latency** • Decreased (P ≤ 0.05) (Jean-Louis et al. 1998) **Night time awakenings** • Decreased: 36.4 vs 40.2 (95% CI, −7.0 to −1.0) (Baskett et al. 1998) **Nocturnal wake time** • Increased nocturnal wake time (P ≤ 0.05) (Dawson et al. 1998) **Morning alertness** • Increased (P = 0.001) (Lemoine et al. 2007)	

AEs = adverse events; CI = confidence interval; ESS = Epworth Sleepiness Scale; LSEQ = Leeds Sleep Evaluation Questionnaire; MD = mean difference; PSQI = Pittsburgh Sleep Quality Index; RCT = randomized controlled trials; Std MD = standardized mean difference.

Table 12: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Kim et al. (2021)[21]	
Median score (Interquartile range) at baseline and 6-weeks **Subjective outcome** **Sleep quality index** (PSQI) • Melatonin: 11 (3) to 8 (5); P = 0.01 • Placebo: 12 (6) to 9 (6); P = 0.23 • Intergroup difference p-value: 0.158	• Melatonin improved sleep quality
Xu et al. (2020)[22]	
Outcomes reported as Reported as Difference in change (95% CI); p-value [calculated as (change in melatonin group) - (change in placebo group)] **Objective outcomes** (measured by polysomnography) **Sleep efficiency** (%) 3.19 (−3.23 to 9.60); 0.324 **Total sleep time** (in minutes) • 20.90 (−12.67 to 54.47); 0.218 **Wake after sleep onset** (in minutes) • −20.84 (−46.14 to 4.46); 0.105	• Sleep latency was not improved (on polysomnography) • There was a reduction in morning early awakening after treatment of melatonin • "Since early morning awakening could lead to the reduction on total sleep time, the total sleep time that also increased in our population might be due to the improvement in early morning awakening. (p. 117)"[22] • Melatonin did no effect any of the subjective outcomes • "Future studies should investigate whether melatonin combined with cognitive behavioral therapy for insomnia (CBT-I) or light therapy will improve sleep performance for

Main study findings	Authors' conclusion
Sleep latency (in minutes) • 53.89 (−41.27 to 149.05); 0.262 **Wake during sleep** (in minutes) • 1.74 (−18.22 to 21.71); 0.862 **Early wake** (in minutes) • −30.63 (−53.92 to −7.34); 0.011 **Subjective outcomes** **PSQI total score** • 1.53 (−0.55 to 3.61); 0.504 **Insomnia Severity Index** • 0.81 (−2.27 to 3.88); 0.165 **Epworth Sleepiness Scale** • −0.83 (−3.53 to 1.88); 0.147 **Safety** • "There was no significant difference in regard to the incidence of adverse events. The study melatonin was well tolerated and no clinically relevant changes in vital signs and laboratory blood and urine tests were observed. (p. 117)"[22] Other outcomes reported but not extracted: Objective: REM latency, Micro-arousal index, N1%, N2%, N3%, REM%; Subjective: Component 1 to 7 scores of the PSQI	such a population than melatonin supplementation alone. (p. 118)"[22]

CI = confidence interval; PSQI = Pittsburgh Sleep Quality Index; REM = rapid eye movement.

Table 13: Summary of Recommendations in Included Guidelines

Recommendations	Quality of evidence and strength of recommendations
Mayer et al. (2021)[23]	
Movement disorders • Eszopiclone, doxepin, zolpidem, trazodone, ramelteon and melatonin can be used for the treatment of insomnia in Parkinson Disease patients. However, evidence for the efficacy is insufficient. • Optimizing sleep hygiene, CBT-I, light therapy and melatonin can be used for the treatment of insomnia in Parkinson Disease **Multiple sclerosis** • Melatonin is recommended despite insufficient data from RCTs. **Epilepsy** • Slow-release melatonin can be used in epilepsy to shorten sleep latency (although this has only been verified in children so far). **Dementia and prion-diseases** • Immediate release, slow release melatonin and melatonin agonists may be options in the treatment of insomnia patients with AD.	**Movement disorders** NR **Multiple sclerosis** NR **Epilepsy** NR **Dementia and prion-diseases** "The recommendations are therefore of very low evidence and do not imply that certain treatments may not be helpful or efficacious. (p. 8)"[23]

Recommendations	Quality of evidence and strength of recommendations
Palagini et al. (2021)[24]	
Mood disorders 1. "The administration of prolonged-release melatonin at 2–10 mg, 1–2 h before bedtime, should be used in the treatment of insomnia symptoms or comorbid insomnia in mood disorders." (p.8) 2. "The chronotype of patients should be taken into account to adapt the timing of the administration." (p.8) 3. "The administration of immediate-release melatonin in the treatment of insomnia symptoms or comorbid insomnia in mood disorders gave uncertain results, more studies are needed for recommendation in the clinical practice." (p.8) **Anxiety disorders** 1. "In the absence to date of well-conducted RCTs, the administration of melatonin might be useful in the treatment of insomnia symptoms or comorbid insomnia disorder in anxiety disorders according to international guidelines for insomnia disorder treatment (> 55 years 2 mg PR melatonin 1–2 h before bedtime)." (p.8) **Attention-Deficit/Hyperactivity Disorder (ADHD)** 1. "In the absence of well-conducted trials, the administration of immediate-release melatonin at sleep-promoting dose (2–6mg) before bedtime could be of interest to treat insomnia symptoms associated with ADHD." (p.9) **Autism Spectrum Disorder (ASD)** 1. "In the absence to date of well-conducted trials in adults, the administration of prolonged-release melatonin at 2–5mg 1–2 h before bedtime could be useful in the treatment of insomnia in adults with ASD, as an extrapolation from solid available data in children." (p.9) **Eating Disorders** 1. "In the absence to date of well-conducted trials, the administration of melatonin might be useful in the treatment of insomnia symptoms or comorbid insomnia in eating disorders according to international guidelines for insomnia treatment (prolonged-release melatonin at 2mg, 1–2 h before bedtime), but consensus was uncertain, more studies are needed for recommendation in the clinical practice." (p.10) **Neurocognitive Disorders** 1. "The administration of prolonged-release melatonin at 2mg might be useful 1–2 h before bedtime in the treatment of insomnia in Neurocognitive Disorders." (p.11) 2. "The administration of immediate-release melatonin 2–6mg at bedtime might be useful in the treatment of insomnia in Neurocognitive Disorders." (p.11) 3. "The administration of prolonged-release melatonin at 2mg may be particularly useful in patients with Parkinson Disease and may contribute to improve sleep quality and other sleep disturbances including Rem Behavioral Disorder." (p.11)	Not reported

Recommendations	Quality of evidence and strength of recommendations
Substance Use Disorder 1. "Melatonin might be useful in the treatment of insomnia symptoms or insomnia comorbid related to substances use disorders according to international guidelines for insomnia treatment, using prolonged-release melatonin at 2mg 1–2 h before bedtime if >55 years old." (p.12) **Schizophrenia** 1. "Melatonin might be useful in the treatment of insomnia symptoms or co-morbid insomnia in schizophrenia; the administration of prolonged-release melatonin at 2 mg, 1–2 h before bedtime, could be used in schizophrenia." (p.12) 2. "The administration of immediate-release melatonin in the treatment of insomnia symptoms or comorbid insomnia in schizophrenia gave uncertain results, more studies are needed for recommendation in the clinical practice." (p.12)	
Palagini et al. (2020)[25]	
1. "Pharmacological treatment should be first-line option when CBT-Insomnia is not available. The choice of the drug should be based on different factors such as type of insomnia, age, comorbidities, and potential side effects among drugs available in Italy." (p.2) 2. "If the choice is prolonged-release melatonin (>55 years old) use it in within 13 weeks." (p.2)	Not reported
Veteran Affairs (2019)[26]	
"32. We suggest against the use of melatonin for the treatment of chronic insomnia disorder. (p. 60)"[26]	Weak against

AD = Alzheimer dementia; ADHD = Attention-Deficit/Hyperactivity Disorder; ASD = Autism Spectrum Disorder; CBT = cognitive behavioural therapy; h = hours; PR = prolonged-release; RCT = randomized controlled trial.

Appendix 5: Overlap Between Included Systematic Reviews

Note that this appendix has not been copy-edited.

Table 14: Overlap in Relevant Primary Studies between Included Systematic Reviews

Primary study citation	Ma (2022)[14]	Almond (2021)[15]	Kothari (2021)[16]	Baglioni (2020)[17]	McCleery (2020)[18]	Sys (2020)[19]	Pierce (2019)[20]
Baskett et al. *Age Aging* 2003; 32:164 to 70	—	—	—	—	—	—	Yes
Dawson et al. *J Biol Rhythms* 1998; 13:532 to 8.	—	—	—	—	—	—	Yes
Garfinkel et al. *Lancet Long Engl*. 1995; 346(8974):541 to 544.	—	Yes	—	—	—	Yes	—
Garfinkel et al. *Diabetes, Metab Syndrome Obes Targets Ther* 2011; 4:307e13.	—	—	Yes	—	—	—	—
Hughes et al. *Sleep* 1998;21: 52 to 68.	—	—	—	—	—	—	Yes
Jean-Louis et al. *J Pineal Res* 1998;25:177 to 83.	—	—	—	—	—	—	Yes
Lemoine et al. *J Sleep Res* 2007; 16:372 to 80.	—	—	—	—	—	Yes	Yes
Luthringer et al. *Int. Clin. Psychopharmacol*. 2009; 24: 239 to 249.	—	—	—	Yes	—	—	—
Medeiros et al. *J. Neurol*. 2007; 254:459 to 464.	Yes	—	—	—	—	—	—
Monti et al. *Arch Gerontol Geriatr.* 1999; 28(2):85 to 98.	—	Yes	—	—	—	—	—
Morales-Delgado et al. *Euro. Ger. Med.* 2018;9(4):449 to 54.	—	—	—	—	Yes	—	—
Rondanelli et al. *J. Am. Geriatr. Soc*. 2011; 59: 82 to 90.	—	—	—	Yes	—	—	—
Wade et al. *Curr. Med. Res. Opin.* 2007, 23, 2597 to 2605.	—	—	—	Yes	—	Yes	Yes
Wade et al. *BMC Medicine* 2010; 8:51.	—	—	—	—	—	Yes	Yes

Appendix 6: References of Potential Interest

Note that this appendix has not been copy-edited.

Previous CADTH Reports

Melatonin for the Treatment of Insomnia: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines Review. Ottawa (ON): CADTH; 2019. https://www.cadth.ca/melatonin-insomnia-review-clinical-effectiveness-cost-effectiveness-and-guidelines Accessed 2022 Apr 12.

Guidelines With Unclear Methods

Insomnia Guideline. Renton (WA): Kaiser Permanente. 2021. https://wa.kaiserpermanente.org/static/pdf/public/guidelines/insomnia.pdf Accessed 2022 Apr 24.

Review Articles

Integrative Review With Unclear Methods

Bueno APR, Savi FM, Alves IA, Bandeira VAC. Regulatory aspects and evidences of melatonin use for sleep disorders and insomnia: an integrative review. Review. *Arquivos de Neuro-Psiquiatria*. 2021;79(8):732-742. PubMed

Additional References

Relevant Primary Studies

Bologna C, Madonna P, Pone E. Efficacy of Prolonged-Release Melatonin 2 mg (PRM 2 mg) Prescribed for Insomnia in Hospitalized Patients for COVID-19: A Retrospective Observational Study. *Journal of Clinical Medicine*. 2021;10(24):14. PubMed

Additional reviews with primary studies evaluating Ramelteon

Moon E, Partonen T, Beaulieu S, Linnaranta O. Melatonergic agents influence the sleep-wake and circadian rhythms in healthy and psychiatric participants: a systematic review and meta-analysis of randomized controlled trials. *Neuropsychopharmacology*. 2022;04:04.
A systematic review which include a few studies on melatonin receptor agonists. There are several studies on melatonin, but none among those with insomnia.

Scharner V, Hasieber L, Sonnichsen A, Mann E. Efficacy and safety of Z-substances in the management of insomnia in older adults: a systematic review for the development of recommendations to reduce potentially inappropriate prescribing. Research Support, Non-U.S. Gov't Review. *BMC Geriatrics.* 2022;22(1):87. PubMed
Includes on study evaluating Benzodiazepine-like medication (BDLM) (Intervention) or selective melatonin receptor agonist {Ramelteon) (comparison).

Roehrs TA, Auciello J, Tseng J, Whiteside G. Current and potential pharmacological treatment options for insomnia in patients with alcohol use disorder in recovery. Research Support, Non-U.S. Gov't Review. *Neuropsychopharmacology Reports*. 2020;40(3):211-223. PubMed
Includes one study on Ramelteon for insomnia in patients with alcohol use disorder in recovery

Gottlieb JF, Benedetti F, Geoffroy PA, et al. The chronotherapeutic treatment of bipolar disorders: A systematic review and practice recommendations from the ISBD task force on chronotherapy and chronobiology. *Bipolar Disorders*. 2019;21(8):741-773. PubMed
A systematic review that includes one study evaluating Ramelteon in patients with bipolar disorders with manic symptoms and insomnia.