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SUMMARY WITH CRITICAL APPRAISAL

Melatonin for the Treatment of Insomnia: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale – cognitive subscale
AE	Adverse effects
AIS	Athens Insomnia Scale
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
CI	Confidence Interval
CRD	Centre for Reviews and Dissemination
DSM	Diagnostic and statistical manual of mental disorders
DSPS	Delayed sleep phase syndrome
ESS	Epworth Sleepiness Scale
FSS	Fatigue Severity Scale
HADS	Hospital Anxiety and Depression Scale
IADL	Instrumental Activities of Daily Living
ICSD	International Classification of Sleep Disorders
ICD-10	International Classification of Diseases
MMSE	Mini-Mental States Examination
N	Total sample
n	Subsample
PR	Prolonged release
PSQI	Pittsburg Sleep Quality Index
QoL	Quality of Life
RoB 2.0	Cochrane Risk of Bias tool version 2.0
SCZ	Schizophrenia
SD	Standard deviation
SF-36	36-item Short Form Health Survey
SR	Systematic review
TBI	Traumatic brain injury
WHO	World Health Organization

Context and Policy Issues

Between 2007 and 2013 64.8% of Canadian adults aged 18 to 64 reported accumulating the recommended seven to nine hours of sleep per night.[1] While not of those who do not get enough sleep have a sleep disorder, 13.4% of Canadian adults meet the criteria for an insomnia disorder.[2] Insomnia disorder has been described as the most prevalent of the sleep disorders, which include restless legs syndrome, periodic limb movement disorder, sleep apnea, and delayed phase sleep.[3]

The main diagnostic classifications for insomnia disorder are: the International Classification of Sleep Disorders (ICSD), the World Health Organization's (WHO) International Classification of Diseases (ICD-10) and the American Psychiatric Association's Diagnostic and Statistical Manual. Each defines insomnia similarly. Insomnia disorder involves dissatisfaction with the quality or quantity of sleep, characterized by difficulty falling asleep, staying asleep, or falling back asleep after waking early, which is associated with distress and impairment in daily functioning.[4] To be considered as insomnia, the sleep disturbance cannot be the result of another sleep disorder or the physiological effects of a substance.[4] Symptoms should be present several times a week for a minimum of three months, despite having adequate opportunities for sleep.[4]

Management of insomnia normally includes complex therapies that often involve conventional drugs and psychological interventions.[5] Drawbacks of many pharmaceutical

treatments include hang-over effects and the potential for dependence and tolerance, while drawbacks of psychological treatments include adherence issues.[5]

Melatonin has been examined as a potential treatment for various sleep disorders in adults. Exogenous melatonin has several apparent benefits. It appears not to have the potential for development of tolerance, dependence, or hang-over effect; it has minimal side-effects at low doses, and has a short half-life.[5] However, the effectiveness of melatonin for the treatment of insomnia in adults is not clear.

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 for the treatment of insomnia in adults?
2. What is the cost-effectiveness of melatonin for the treatment of insomnia in adults?
3. What are the evidence-based guidelines regarding the use of melatonin for the treatment of insomnia in adults?

Key Findings

Evidence of limited quality from four systematic reviews and two randomized controlled trials suggested modest favourable effects of melatonin on global sleep outcomes, specific sleep outcomes, and outcomes related to functioning and mood, as well as unclear effects on quality of life for adults with primary and comorbid insomnia. Evidence from one systematic review showed no statistical difference between melatonin and placebo for safety outcomes. No evidence-based guidelines or evidence regarding the cost-effectiveness of melatonin for the treatment of insomnia were identified.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, randomized controlled trials, non-randomized studies, 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, 2014 and January 24, 2019.

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.

Table 1: Selection Criteria

Population	Adults (≥18 years) with insomnia
Intervention	Melatonin
Comparator	Any comparator (e.g., no treatment, pharmacological sedatives, other doses of melatonin)
Outcomes	Q1: Clinical effectiveness, safety Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessments, randomized controlled trials, economic evaluations, non-randomized studies, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using AMSTAR 2[6] and randomized studies were critically appraised using the Cochrane Risk of Bias tool 2 (RoB 2).[7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 473 citations were identified in the literature search. Following screening of titles and abstracts, 447 citations were excluded and 26 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 19 publications were excluded for various reasons, and seven publications met the inclusion criteria and were included in this report. These comprised five systematic reviews and two randomized controlled trials (RCTs). Appendix 1 presents the PRISMA[8] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

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

Study Design

Four systematic reviews published between 2015 and 2018 were eligible for inclusion. Date ranges covered by the included studies' searches were 1950 to 2017. Study designs eligible for the included reviews were systematic reviews and RCTs. Longitudinal studies were included for harm-related outcomes only. There was a degree of overlap between reviews, with Auld and Brasure both including data from Wade 2011.[5,9] In the review by

Brasure, data from Wade 2011 and Wade 2010 (both papers used data from the same study) were the only results reported of relevance to this report. The overlap about primary studies in included systematic reviews is presented in Appendix 5.

Two double-blind, placebo-controlled RCTs published in 2016 and 2018 were included. One study was a multi-centre study with a cross-over design[10] and the other was a single centre study.[11]

Country of Origin

The systematic reviews were conducted by authors in Portugal[12], the United Kingdom,[5,13] and the United States.[9] The primary clinical studies were conducted in Australia[10] and India.[11]

Patient Population

Data from a total of 1,449 adults with insomnia are summarized in this report. Participants in the systematic reviews were eligible if they were aged 18 years or older. Baseline characteristics for participants included in this report from systematic reviews were not available as these data represent a subsample of the populations included in the reviews. Data were published for the total samples but not the subsamples included in this report. Included participant mean ages were 37[10] and 52.42 years[11] in the two RCTs. Participants in the systematic reviews and RCTs were identified as having primary insomnia or comorbid insomnia. Participants with comorbid insomnia had diagnoses of Schizophrenia, dementia, mild to severe traumatic brain injury, and cancer (any type or stage).

Interventions and Comparators

Four systematic reviews and two RCTs examined standard melatonin or prolonged release melatonin. The prescribed doses ranged from 0.01 milligrams (mg) per night[5] to 12 mg per night,[12] with most studies prescribing 2 mg doses. Studies that reported timing of melatonin dose instructed participants to take their treatment dose one to two hours before bedtime.[5,13] Duration of treatment ranged from 7 days to a total of 24 weeks. Comparator conditions consisted of no change in treatment or placebo.

Outcomes

Global sleep outcomes were assessed three studies using the Pittsburg Sleep Quality Index (PSQI)[9,10] and the Athens Insomnia Scale.[11]

Specific sleep outcomes were assessed in five studies. Sleep-efficiency was objectively assessed in two studies using Actigraphy.[10,12] Quality and depth of nighttime sleep were assed in one review by an unspecified method of self-report.[12] Sleep onset latency was assessed in three studies by sleep diary,[9] Actigraphy[10] and an unspecified method.[5] Sleep quality was carer-rated using an unspecified measure.[13] Instrumental activities of daily living were assessed in one study using an unspecified measure.[13] Daytime sleepiness in the previous four weeks was assessed in one study using the Epworth Sleepiness Scale.[10]

Functioning, mood, and quality of life were assessed in one study. This included subjective fatigue, which was assessed using the Fatigue Severity Scale,[10] anxiety and depression, which were assessed by self-report with the Hospital Anxiety and Depression Scale,[10] and health related quality of life (subscales: physical functioning, role-physical, role-emotional, vitality, mental health, social functioning, bodily pain, and general health) assessed by self-report with the 36-item Short Form Health Survey (SF-36).[10]

Adverse effects/events were assessed in one study.[9]

Summary of Critical Appraisal

The critical appraisal of the included systematic reviews and primary clinical studies is presented here. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews

The systematic reviews[5,9,12,13] were assessed using AMSTAR 2[6] and several strengths and limitations were identified. First, the search strategy for each review was guided by a research question and/or inclusion criteria that clearly identified the participants, interventions, comparators, and outcomes of interest to the review.[5,9,12,13] In addition, multiple strategies were used in each review to identify relevant studies for inclusion, and study selection and data extraction were performed in duplicate, reducing the potential for selection bias.

Randomized Studies

The two RCTs[10,11] were assessed using RoB 2[7] and few limitations were identified.[10,11] The sole risk of bias concern identified in one study was the absence of information about the measurement properties of outcome measures in the reporting of one review, raising concerns about the accuracy outcome measures, and therefore study findings. [10] Limitations in the other study were questionable reporting of participant baseline characteristics and an absence of any mention of allocation concealment, both concerns potentially indicative of a problem with the randomization process, opening up the possibility that findings were due to factors other than the intervention itself.[10] These issues aside, strengths of the RCTs included blinding of participants and outcome assessors, and availability of data for nearly all participants randomized.[10,11]

Summary of Findings

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

Clinical Effectiveness of Melatonin

Global Sleep Outcomes

One systematic review that included studies relevant to adults with Schizophrenia and comorbid insomnia[12] and two RCTs that included patients with traumatic brain injury[10] and cancer[11] with comorbid insomnia examined global sleep outcomes. These studies showed a statistically significant, albeit small improvement in PSQI scores whereby melatonin improved global sleep outcomes compared with placebo.[9-11] The RCT by Kurdi et al. showed that the greatest improvements in global sleep outcomes came during the second week of a two week trial.[11]

Specific Sleep Outcomes

Two systematic reviews[5,9] and one RCT[10] assessed self-reported sleep onset latency. While the systematic reviews showed a significant reduction in time to fall asleep for patients in the melatonin group compared with the placebo group,[5,9] the RCT of 31 participants showed no difference between groups.[10]

One systematic review that included studies examining adults with dementia and comorbid insomnia showed there was no significant difference between melatonin and placebo for change from baseline in carer-rated sleep quality.[13]

One systematic review of studies that included adults with Schizophrenia and insomnia[12] and one RCT of studies that included adults with traumatic brain injury and insomnia[10] examined sleep efficiency. Both studies showed a statistically significant improvement in nighttime sleep efficiency with melatonin compared with placebo.[10,12]

One systematic review of patients with Schizophrenia and comorbid insomnia showed melatonin significantly improved nighttime sleep quality and depth compared with placebo.[12]

One RCT (n = 33) that included adults with traumatic brain injury and insomnia showed no significant effect of melatonin on daytime sleepiness as compared with placebo.[10]

Functioning, Mood, QoL

One systematic review of studies that included patients with Alzheimer's disease and comorbid insomnia showed no effect of melatonin on change in instrumental activities of daily living.[13] The same review showed conflicting findings with regard to cognitive abilities, with no differential effect of melatonin versus placebo on cognition as assessed by the cognitive subscale of the Alzheimer's Disease Assessment Scale compared with placebo,[13] whereas there were significantly greater improvements in cognitive abilities with melatonin compared with placebo when assessed by the Mini-Mental State Examination versus placebo.[13]

One RCT of patients with traumatic brain injury and insomnia showed melatonin improved self-reported anxiety, depression, and fatigue severity compared with placebo in a sample of 32 participants with insomnia.[10]

One systematic review showed that prolonged release melatonin significantly improved self-reported QoL compared with placebo, although the difference was small. [9] In contrast, one RCT of patients with traumatic brain injury showed that melatonin significantly improved mental health related QoL compared with placebo, but there was no difference for the following subcategories of QoL: physical functioning, role-physical, role-emotional, vitality, social functioning, bodily pain, or general health.[10]

Adverse Effects

One systematic review with one study included study of relevance to this report showed no statistical difference between prolonged release melatonin and placebo with respect to overall withdrawals from the study, withdrawals due to adverse effects, or participants with one or more adverse effects.[9]

Cost-Effectiveness of Melatonin

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

Guidelines

No relevant guidelines for the use of melatonin for insomnia were identified; therefore, no summary can be provided.

Limitations

Overall, the included studies were at high risk of bias. Beyond concerns with methodological quality, there are a few limitations to note. The first relates to the paucity of evidence identified. Two systematic reviews, accounting for five primary studies of 1,315 participants, that examined adults in the general population were identified for inclusion in this review, and small studies conducted in special populations (i.e., adults with traumatic brain injury, cancer, Schizophrenia, and dementia) comprised the remaining studies. The data are generally consistent with respect to the direction (i.e., favourable) and size (small effect sizes) of the findings. However, it is difficult to draw definitive conclusions from few studies of heterogeneous populations.

A second limitation relates to the lack of studies examining the long-term safety of melatonin use among adults with insomnia. Although one systematic review searched for observational studies with follow-up durations of at least six months to assess safety and harms, no relevant melatonin studies were identified.[9] The primary study included in the reviews by Auld et al and Brasure et al. provided patients with melatonin for up to 24 weeks.[5,9] Therefore, the safety of melatonin use beyond 24 weeks cannot be ascertained from this report.

It can be considered a limitation that the systematic review by Auld et al. was conducted using a definition of insomnia that is currently out of date.[5] During the study the International classification of sleep disorders and the Diagnostic and Statistical Manual of Mental Disorders were updated. In the update primary insomnia was renamed as insomnia disorder, and the definition was slightly altered. Auld et al., identified the possibility that if the studies in their review were replicated according to the newer, more inclusive criteria, study findings may differ.[5] This limitation is likely to be true of other studies included in this review where the older criteria were used.

Finally, no evidence-based guidelines or studies regarding the cost-effectiveness of melatonin for the treatment of insomnia were identified. However, with little clinical evidence identified, the lack of guidelines and cost-effectiveness studies specifically pertaining to melatonin for the treatment of insomnia may be related to the limited clinical information available.

Conclusions and Implications for Decision or Policy Making

Four systematic reviews and two RCTs of limited quality evidence were identified to address the effectiveness of melatonin for the treatment of insomnia. Generally, findings suggested melatonin had modest, favourable effects on global sleep outcomes; sleep outcomes; and outcomes related to functioning and mood across a broad array of populations. Evidence for quality of life was less clear. Findings from one study suggested melatonin did not differ from placebo with respect to safety and harms.

Although the findings are relatively consistent across studies, there remains some degree of uncertainty about the conclusions due to the small number of participants, paucity of safety and harms data, and lack of information about the validity and reliability outcome measures assessed in included studies. Large studies with long follow-up durations, and improved reporting with respect to the measurement properties of outcome assessment instruments would reduce this uncertainty.

An important gap in the literature is the lack of identified guidelines or studies regarding the cost-effectiveness of melatonin for the treatment of insomnia, particularly in a Canadian context. This may be related to the small amount of clinical evidence identified and the small effect sizes.

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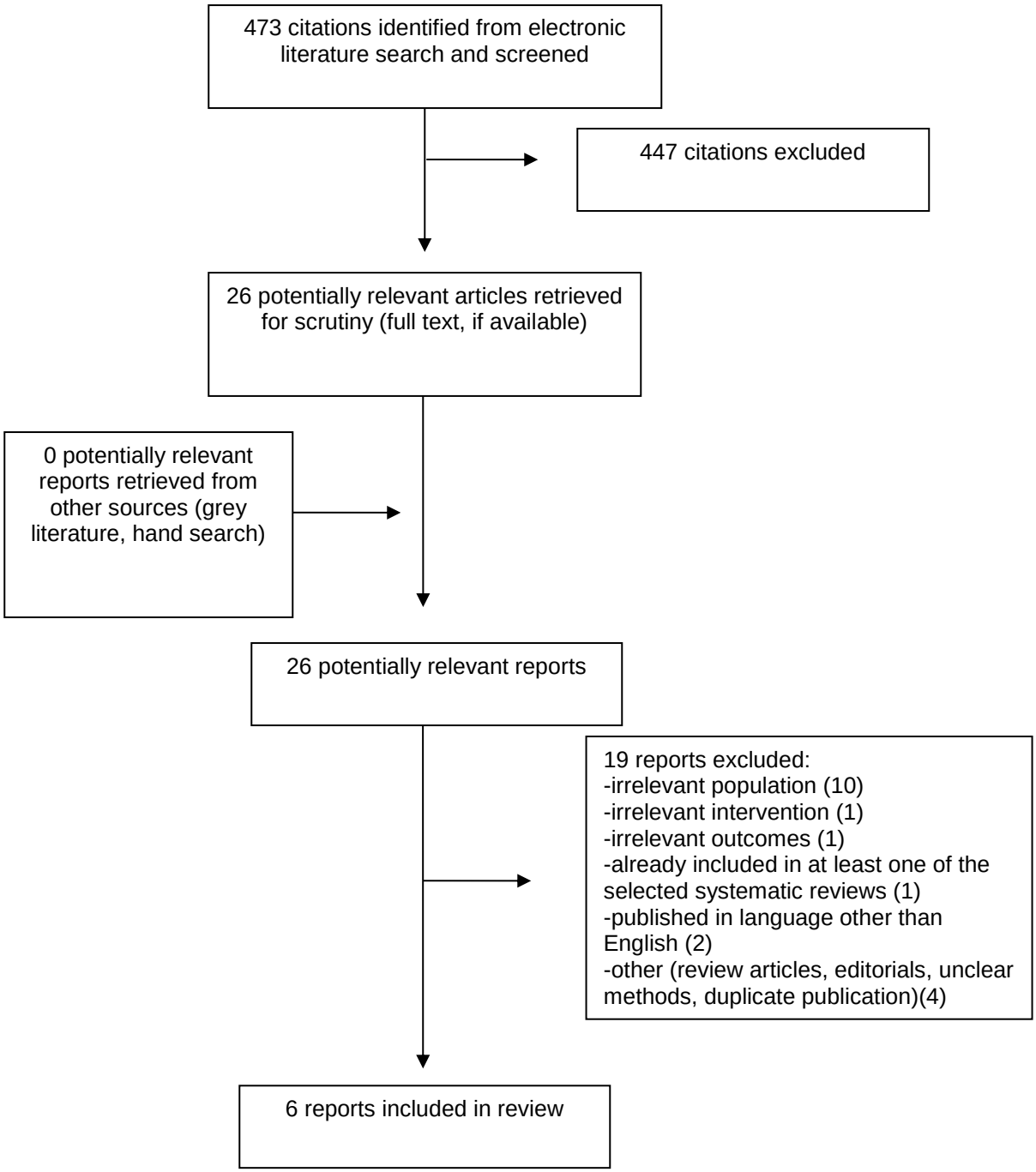
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Oliveira, 2018[12] Portugal	RCT 2 primary study eligible for this report Studies published between January 1970 to July 2017 were searched	N = 39 Inclusion criteria: Adults ≥18 years with Schizophrenia and comorbid insomnia Included participants had Schizophrenia and Insomnia defined using DSM-IV in one study and outpatients with stable Schizophrenia and initial insomnia of ≥2 weeks in the other	Intervention: Melatonin Daily dose: 2 mg of controlled release and 3-12 mg standard melatonin Duration of the included studies were 7 weeks (included 2 x 3 week intervention periods with one week between in one study, and 15 days in the other study Comparator: No change in treatment	Sleep Outcomes **Sleep efficiency** measured by Actigraphy **Quality and depth of nighttime sleep** assessed by unspecified questionnaire No description of measures, minimal clinically important difference, or description of what direction represents clinical improvements or worsening was provided. Follow-up for 3 days following each treatment period
Auld, 2017[5] UK	Placebo-controlled RCTs: single or double-blind; cross-over or parallel 6 studies examined primary insomnia (only 5 included in meta-analysis) Studies published between 1950 and 2015 were searched	N = 1,315 Inclusion criteria: Adults ≥18 years with a primary sleep disorder; subsample with primary insomnia is included in this report Eligible age ranges spanned 18 years to ≥80 years (an upper limit was not provided for 2 studies) Participant descriptive statistics not provided	Intervention: Melatonin Daily doses were: 0.01 mg , 0.3 mg, 1.0 mg, 2.0 mg, and 3.0 mg Timing was 2 hours before bed, where reported Study duration ranged from 7 days to 9 weeks, including washout periods, where they were included Comparator: Placebo Doses, frequency, and duration same as intervention group	Sleep Outcomes **Sleep onset latency** No description of measure, minimal clinically important difference, or description of what direction represents clinical improvements or worsening was provided. Follow-up immediately post intervention

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
McCleery, 2016[13] UK	Placebo-controlled RCTs were eligible 1 study was relevant to this report: a multi-centre, single blind, 2-arm parallel treatment group RCT Studies published between 2012 to March 2016 were searched	N = 13 Inclusion criteria: Adults with dementia (MMSE score ≥15) and a sleep disturbance; Subsample of 13 patients with comorbid insomnia included in this report Other information: • Participants had been taking stable doses of acetylcholinesterase inhibitor with or without memantine for 2 months prior to recruitment; • Participants were instructed to spend 2 hours per day outdoors during daylight hours	Intervention: 2 mg melatonin PR, once daily, 1 to 2 hours before bed Comparator: Placebo Duration of treatment: 6 months (i.e., 2 weeks run-in phase, 24-week double-blind randomized treatment phase, 2-week placebo run-out phase)	Sleep outcomes **Carer-rated sleep quality** **Cognition** assessed with ADAS-cog and MMSE Functioning, Mood, QoL: **IADL** No description of measures, minimal clinically important difference, or description of what direction represents clinical improvements or worsening was provided. Follow-up immediately post intervention
Brasure, 2015[9] US	SRs, RCTs, and longitudinal studies were eligible 1 study (published in two manuscripts) was relevant to this report Studies published between 2004 to January 2015	N = 711 Inclusion criteria for SRs and RCTs: Adults (age ≥18) with insomnia disorder according to unspecified diagnostic criteria; studies with at least 4 weeks follow-up; reported global or sleep outcomes Inclusion criteria for observational studies that reported harms: adults with chronic insomnia without major comorbidities; ≥6 month duration; N ≥100 Adults with comorbid medical or mental health disorders were	Intervention: Melatonin prolonged release Dose = 2mg Comparator: Placebo 3 weeks randomized to melatonin or placebo After 3 weeks, placebo group re-randomized to melatonin or placebo and melatonin group remained on melatonin for 26 week extension. Only extension included in the review(n = 711)	Global outcomes (sleep symptoms and daytime functioning or distress associated with sleep symptoms) Assessed by PSQI Sleep outcomes: **Sleep onset latency** (minutes); Assessed by sleep diary **AE** Method of assessment not reported

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		eligible Actual demographic data for the 711 participants included in this report not available. Data for the 722 of the full study: mean age 62 years, 99% white, 69% female		

AE = adverse effects; DSM = Diagnostic and statistical manual of mental disorders; IADL = Instrumental activities of daily living; mg = milligrams; MMSE = Mini-Mental State Examination; N = total sample; n = subsample; PSQI = Pittsburg Sleep Quality Index; PR = prolonged release; QoL = Quality of Life; RCT = randomized controlled trials; SR = systematic review

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Grima, 2018[10] Australia	Multi-centre, randomized, double-blind, placebo-controlled, two-period, two-treatment crossover The study was conducted from August 2011 to November 2016	N = 33 Mean age = 37 Female, 33%; Male, 67% Median (IQR Q1 to Q3) months since TBI = 46 (13 to 102) Inclusion criteria: Community dwelling adults (aged 18 to 65) with mild to severe acquired TBI (history of blunt head trauma with loss of consciousness, initial Glasgow Coma Scale of 3 to 14; post-traumatic amnesia) Sleep complaint corroborated by PSQI global score ≥8 and confirmed diagnosis of chronic insomnia (ICSD, 3rd ed) Exclusion criteria: Sleep problems, fatigue or neurological conditions before their TBI; Pregnant; Trans meridian travel across >1 time zone or worked night shifts in previous 3 months; high risk of obstructive sleep apnea; Use of non-prescription sleep medication in previous 6 weeks; Psychoactive substances in previous 12 months	<u>Intervention:</u> Prolonged-release melatonin Dose; 2 mg Frequency: 1/night Duration: 4 weeks Timing: ~same time each night within 2 hours of bed time <u>Comparator</u>: Placebo Dose: Mannitol (106 mg) Acacia (11 mg) Pure icing sugar (106 mg) Duration: 4 weeks Timing: ~same time each night within 2 hours of bed time	<u>Sleep outcomes:</u> **Global sleep outcomes** were assessed over the previous over the previous month using the 19-item PSQI global score, which combines subdomains of sleep duration, sleep disturbance, sleep latency, sleep efficiency, daytime dysfunction, overall sleep quality and medication use (Score range 0 to 21) higher values indicate poorer sleep quality No description of minimal clinically important difference or measurement properties were provided. **Sleep onset latency** (time elapsed between the start of the rest interval relative to the sleep start time) was measured using wrist Actigraphy (Actiwatch-2, Phillips Respironics), collected in 1 minute epochs at medium sensitivity; the average value across nights measured was taken Authors reported validity for wrist Actigraphy generally but not for Actiwatch specifically. Cut points used to classify activity counts as sleep were not provided by authors No description of minimal clinically important difference, description of what direction represents clinical improvements or worsening were provided **Sleep efficiency** was measured by Actigraphy

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
				and calculated as total sleep time / total duration of the sleep episode (%) averaged across nights **Daytime sleepiness** was assessed with a modified version of the ESS to assess "daytime somnolence in the preceding 4 weeks" **Anxiety** was assessed by self-report with the HADS **Depression** was assessed by self-report with the HADS **Subjective fatigue** was assessed by self-report with the FSS Health related QoL was assessed by self-report with the SF-36 v1, which included the following subscales: Physical functioning; Role-physical; Role-emotional; Vitality; Mental health; Social functioning; Bodily pain; General health Adverse events were assessed by showing participants a list of symptoms and asking if they had experienced any in the previous period Follow-up was immediately post-test
Kurdi, 2016[11] India	Single-centre, double-blind RCT	N = 50 Mean age = 52.42 Female, 48%; Male, 52%;	Intervention: Melatonin Dose: 3 mg daily Timing: 2 hours before bedtime	<u>Global Sleep Outcomes:</u> **Sleep quality/ severity of insomnia** assessed with the self-report 8-item AIS. Scales range from 0 (no problem) to

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Unclear reporting of cancer stage overall and per group Inclusion criteria: Age: 20 to 65 years Cancer patients; Primary insomnia (DSM IV criteria) with sleep complaints >1 month; not using sleep medication in previous 2 weeks Exclusion criteria: Pregnancy or lactation; cognitive impairment; History of psychiatric disorders; On antipsychotic treatment; Language or communication difficulties; Other sleep disorders; Liver and renal dysfunction	Duration = 14 days Comparator: Multivitamin tablets Duration = 6 months	3 (did not sleep); Individual components assessed by AIS (subscales: Sleep induction; Awakenings during the night; Final awakening; Total sleep duration; Sleep quality; Well-being; Functional capacity; Sleepiness during the day) Measurement properties were not reported Follow-up was immediately post-test

AIS = Athens Insomnia Scale; DSM = Diagnostic and statistical manual of mental disorders; ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; HADS = Hospital Anxiety and Depression Scale; ICSD = International Classification of Sleep Disorders; mg = milligrams; N = total sample; PSQI = Pittsburg Sleep Quality Index; QoL = Quality of Life; RCT = randomized controlled trial; SF-36 = Short-Form Health Survey; TBI = traumatic brain injury

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[6]

Strengths	Limitations
Oliveira, 2018[12]	
• The research question and inclusion criteria for the review included all of the components of PICO • Four databases were searched and key words were provided; reference lists of included studies were hand searched; search was completed within 24 months of completion of the review • Review authors reported using Cochrane's Risk of Bias tool to assess the risk of bias in individual studies included in the review • Review authors reported no competing interests, or described a funding source as a potential conflict. However, the author did not describe how this potential conflict of interest was managed.	• Review report did not contain an explicit statement that the review methods were established prior to the conduct of the review. • Review authors did not explain their selection of the study designs for inclusion in the review • Additional exclusions (i.e., language) and the decision to limit the search dates were not justified • Study selection was not performed in duplication • Number of data extractors was not reported • A list of excluded studies was not provided, but reasons for exclusions were • Included studies were described in partial detail. Usual treatment of comparators, duration of one included intervention, study outcomes and outcome measures, and time frame for follow up were not reported or poorly reported • Review authors did not report on the sources of funding for the studies included in the review • Review authors did not account for risk of bias in individual studies when discussing the results of the review • Review authors reported no competing interests, or described a funding source as a potential conflict. However, the author did not describe how this potential conflict of interest was managed.
Auld, 2017[5]	
• Taken together, the research question and inclusion criteria for the review included all of the components of PICO • Four databases were searched and key words were provided; no additional publication restrictions were identified; search was conducted within 24 months of completion of review • Review authors performed study selection in duplicate • Review authors performed data extraction in duplicate • A list of all exclusions of studies that were read in full-text form was provided and reasons for exclusions were justified. • Authors used appropriate methods for statistical combination of results • Authors assessed the risk of bias in individual studies that were included in the review using the 3-item Jadad scale • Authors accounted for risk of bias in individual studies when discussing the results • Review authors discussed reasons for low heterogeneity in the results of the review	• There was no explicit statement that the review methods were established prior to the conduct of the review. Several sleep-related study outcomes were extracted from included studies, but only sleep onset latency was synthesized or discussed, suggesting the methods may not have been established prior to the conduct of the review. • There was no explanation of the selection of study designs for inclusion in the review • Authors did not report searching reference lists of included studies, trial / study registries, or grey literature • Included studies superficially described eligible populations, interventions, comparators, outcomes, and research designs. Adequate detail was not provided regarding included participant characteristics, study settings, or timeframe for follow up. • Authors used the 3-item Jadad scale to assess risk of bias in individual studies, which assesses randomization, blinding, and reporting of withdrawals and dropouts. The Jadad scale has been shown to have poor inter-rater

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[6]

Strengths	Limitations
• Review authors provided funnel plots and discussed the likelihood (i.e., low) of publication bias • Review authors indicated no conflict of interest	agreement in one study[14] and does not consider allocation concealment, which is described as critical to avoiding bias by the Cochrane Collaboration.[15] • Authors did not report on the sources of funding for the studies included in the review • Review did not assess the potential impact of risk of bias in individual studies on the results of the meta-analysis •
McCleery, 2016[13]	
• The research question and inclusion criteria for the review included all of the components of PICO • The report contained an explicit statement that review methods were published prior to the conduct of the original review, which was published in 2012. The updated review justified deviations from the original protocol and indicated the deviations were made before the updated search was conducted. • The review authors used a somewhat comprehensive literature search strategy. They searched the ALOIS database, which searches 5 databases and trials registries; the search was conducted within 2 months of completion of the report; grey literature was not included • The ALOIS database selects studies using a combination of machine learning an manual selection • Review authors performed data extraction in duplicate • Review authors provided a list of excluded studies and justified the exclusions • Review authors described the included studies in detail • Review authors used Cochrane's risk of bias tool to assess risk of bias in individual studies included in the review • Review authors reported the sources of funding for the studies included in the review. Note – the study of relevance to this report was industry funded • Review authors used appropriate methods for statistical combination. Note - one subsample of one study was eligible for this report • Review authors accounted for risk of bias in individual studies when interpreting the results • Heterogeneity is not of relevance to this report as only one study was included • Authors reported there were insufficient publications to investigate publication bias using graphic tests • Authors reported no competing interests	• Review authors did not explain their selection of the study designs for inclusion in the review
Brasure, 2015[9]	
• The research question and inclusion criteria for the review included all of the components of PICO • The report contained an explicit statement that review	

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[6]

Strengths	Limitations
methods were completed prior to the conduct of the review • Review authors explained their selection of the study designs for inclusion in the review • Review authors used a comprehensive literature search strategy • Review authors performed study selection in duplicate • Review authors performed data extraction in duplicate • Review authors provided a list of excluded studies and justified the exclusions • Review authors described the included studies in adequate detail • Review authors used a satisfactory technique for assessing the risk of bias in individual studies that were included in the review • Review authors reported the sources of funding for the studies included in the review • Review authors accounted for risk of bias in individual studies when discussing the results • Potential for reporting bias was examined and discussed • Review authors reported potential sources of conflict of interest and how it was addressed	

PICO = Participants, Interventions, Comparators, Outcomes

Table 5: Strengths and Limitations of Clinical Studies using Cochrane RoB 2.0[7]

Strengths	Limitations
Grima, 2018[10]	
Risk of bias arising from the randomization process • Allocation sequence was random • Allocation sequence was concealed until participants were enrolled and assigned to interventions • Baseline characteristics were not analyzed for statistical differences between those who started in the intervention group and those who started in the comparator group. However, the crossover design was employed to minimize the influence of any between group baseline differences. **Effect of assignment to intervention** • Participants were not aware of their assigned intervention during the trial • Carers and people delivering the intervention were not aware of participants' assigned intervention during the trial • No deviations from the intervention arose because of the experimental context • Appropriate analysis was used to estimate the effect of assignment to intervention **Missing outcome data** • Data were available for nearly all participants randomized **Risk of bias in the measurement of the outcome** • Measurement of the main outcomes was appropriate. • Measurement of the outcomes could not have differed between intervention groups • Outcome assessors were not aware of the intervention received by study participants **Risk of bias in the selection of the reported result** • The trial was analyzed in accordance with a pre-specified plan that was registered a priori • The numerical result being assessed is not likely to have been selected, on the basis of the results, from multiple outcome measurements within the outcome domain or multiple analyses of the data	**Risk of bias in the measurement of the outcome** • Secondary outcomes may have been appropriately assessed; however measurement properties were not reported.
Kurdi, 2016[11]	
Risk of bias arising from the randomization process • Allocation sequence was reported to be random using the fishbowl method **Effect of assignment to intervention** • Participants were not likely aware of their assigned interventions • Carers and trial personnel were not likely aware of participants' assigned intervention during the trial • No participants were analysed in a group different from the ones to which they were assigned • Analysis was appropriate to estimate the effect of assignment to the intervention **Risk of bias due to missing outcome data** • Outcome data were available for nearly all participants	**Risk of bias arising from the randomization process** • Baseline differences between groups were not statistically assessed. There were similarities between groups that suggest there may have been a problem with the randomization process. I.e., there were equal numbers of males and females in each group and there was no mention of stratification by gender or sex in the allocation process. Additionally, frequencies tables suggest the melatonin group included 19 patients with stage I and II cancer and 19 had stage III and IV cancer, while 6 in the placebo group had each type. The number of patients in each group would add up to 38 intervention and 12 comparator, which is not consistent with the 25 reported participants in each group. • Allocation concealment was not reported

Table 5: Strengths and Limitations of Clinical Studies using Cochrane RoB 2.0[7]

Strengths	Limitations
randomized **Risk of bias in measurement of the outcome** • Outcome assessors were not aware of the intervention received by study participants **Risk of bias in selection of the reported result** • Reported outcomes are not likely to have been selected on the basis of the results from multiple outcome measurements within the outcome domain or multiple analyses of the data	

RoB 2.0 = Cochrane Risk of Bias tool, version 2.0;

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Oliveira, 2018[12]	
One study was eligible for this report and narratively described Sleep efficiency Assessed in 1 study Improved sleep efficiency with melatonin (significant) Subgroup: improved sleep efficiency in poorer sleepers (significant) Quality and depth of nighttime sleep Assessed in one study Relative to placebo, melatonin significantly improved the quality and depth of nighttime sleep without producing hangover." (p.3)	"*In conclusion, the evidence base is too scarce to extract robust clinical recommendations regarding the treatment of residual insomnia in SCZ. Despite the limited number of specific studies, all articles have shown good benefit/risk ratios, and the reviewed options—melatonin, eszopiclone, and paliperidone—might represent valid options for residual insomnia in SCZ*." (p.4)
Auld, 2017[5]	
5 studies included in the meta-analysis Sleep onset latency Total MD = -5.05 minutes; 95% CI: -8.51 to 1.59 Overall effect of melatonin Z = 2.86, *P* = 0.004	"*In conclusion, this review has found evidence from a small number of trials for melatonin in treating primary insomnia, DSPS, and non 24-h sleep wake syndrome in people who are blind. Meta-analyses of the data emphasised in particular the improvement of sleep onset latency with melatonin in these patients*." (p.21)
McCleery, 2016[13]	
Subgroup of 13 patients from 1 study eligible for this report Melatonin (n = 7) vs placebo (n = 6) Carer-rated sleep quality, change from baseline M(SD) = 5.29 (3.45) vs 2.83 (2.56) Standard MD = 0.74; 95% CI: -0.40 to 1.89 MMSE, change from baseline M(SD) = 1.5 (2.9) vs -2.8 (2.9) Standard MD = 4.30; 95% CI: 0.86 to 7.74 Favours melatonin ADAS-cog, change from baseline M(SD) = -2.5 (3.1) vs 1 (6) Standard MD = -3.50; 95% CI: -9.31 to 2.31 IADL, change from baseline M(SD) = 0.67 (1.75) vs 1.8 (1.3) Standard MD = -0.66; 95% CI: -1.90 to 0.58	"*From the studies we identified for this review, we found no evidence that melatonin (up to 10mg) helped sleep problems in patients with moderate to severe dementia due to AD*." (p.4) Note, conclusion applies to the overall study and "sleep problems" includes insomnia among other sleep disorders.

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Brasure, 2015[9]	
711 patients from 1 study eligible for this report **Global outcomes** PSQI global score (n = 700) MD = –0.39; 95% CI: –0.71 to –0.08 **Sleep Outcomes** Sleep onset latency self- report, minutes (n = 700) MD = –6; 95% CI: –10 to –2.1 **Adverse Effects** Overall withdrawals MD = 0.87; 95% CI: 0.64); NS Withdrawals due to AE MD = 0.86; 95%CI: 0.42 to 1.75; NS Participants with ≥1 AE MD = 0.96; 95%CI: 0.87 to 1.06; NS	Not relevant to this report

AD = Alzheimer's disease; ADAS-cog = Alzheimer's Disease Assessment Scale – cognitive subscale; AE = adverse effect; CI = confidence interval; DSPS = delayed sleep phase syndrome; h = hours; IADL = instrumental activities of daily living; M = mean; MD = mean difference; MMSE = Mini-Mental State Examination; N = total sample; n = subsample; NS = no statistically significant; P = probability; SCZ = Schizophrenia; SD = standard deviation; SR = systematic review

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Grima, 2018[10]	
Melatonin vs placebo **Global Sleep Outcomes** PSQI global (n = 33) Adjusted mean (95% CI) 7.68 (6.34 to 9.02) vs 9.47 (8.13 to 10.81) Treatment effect estimate = -1.79 (-2.70 to -0.88) Cohen's d = 0.46; *P* < 0.0001 **Sleep Outcomes** Sleep onset latency, minimum (n = 31) Adjusted mean (95% CI) 1.37 (1.26 to 1.48) vs 1.42 (1.31 to 1.53) Treatment effect estimate = -0.05 (-0.14 to 0.03) Cohen's d = 0.18; *P* = 0.23 Sleep efficiency (n = 31) Adjusted mean (95% CI) -3.22 (-3.61 to -2.82) vs -3.54 (-3.94 to -3.13) Treatment effect estimate = 0.32 (0.01 to 0.63) Cohen's d = 0.28; *P* = 0.04 Daytime sleepiness, ESS (n = 33) Adjusted mean (95% CI) 2.36 (2.00 to 2.73) vs 2.53 (2.17 to 2.90) Treatment effect estimate = -0.17 (-0.40 to 0.06) Cohen's d = 0.17; *P* = 0.15 **Functioning, Mood, QoL** HADS anxiety (n = 32) Adjusted mean (95% CI) 7.84 (6.23 to 9.45) vs 9.00 (7.39 to 10.61) Treatment effect estimate = -1.15 (-1.97 to -0.34) Cohen's d = 0.27; *P* = 0.006 HADS depression (n = 32) Adjusted mean (95% CI) 8.53 (6.93 to 10.13) vs 8.34 (6.75 to 9.94) Treatment effect estimate = 0.18 (-0.70 to 1.07) Cohen's d = 0.04; *P* = 0.03 Fatigue Severity, FSS (n = 32)	"*This study provides preliminary evidence for the efficacy of melatonin in alleviating sleep dysfunction in patients with TBI and insomnia*." (p.9)

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Adjusted mean (95% CI) -4.18 (-4.74 to -3.62) vs -3.73 (-4.28 to -3.17) Treatment effect estimate = -0.45 (-0.86 to -0.04) Cohen's d = 0.29; *P* = 0.03 Health Related QoL (SF-36) (n = 33): Physical functioning Adjusted mean (95% CI) 43.17 (39.15 to 47.20) vs 41.72 (37.69 to 45.75) Treatment effect estimate = 1.45 (-0.33 to 3.24) Cohen's d = 0.13; *P* = 0.11 Role-physical Adjusted mean (95% CI) 43.17 (39.15 to 47.20) vs 41.72 (37.69 to 45.75) Treatment effect estimate = 1.45 (-0.33 to 3.24) Cohen's d = 0.13; *P* = 0.11 Role-emotional Adjusted mean (95% CI) 37.58 (33.11 to 42.06) vs 36.85 (32.38 to 41.32) Treatment effect estimate = 0.73 (-3.38 to 4.84) Cohen's d = 0.05; *P* = 0.73 Vitality Adjusted mean (95% CI) 42.43 (38.97 to 45.90) vs 38.76 (35.30 to 42.22) Treatment effect estimate = 3.67 (0.36 to 6.98) Cohen's d = 0.35; *P* = 0.35 Mental health Adjusted mean (95% CI) 43.60 (40.00 to 47.24) vs 41.09 (37.45 to 44.73) Treatment effect estimate = 2.51 (0.58 to 4.42) Cohen's d = 0.23; *P* = 0.01 Social functioning Adjusted mean (95% CI) 37.09 (33.05 to 41.13) vs 34.82 (30.78 to 38.86) Treatment effect estimate = 2.27 (-1.36 to 5.90) Cohen's d = 0.19; *P* = 0.22 Bodily pain Adjusted mean (95% CI) 44.07 (39.85 to 48.30) vs 43.27 (39.05 to 47.50)	

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Treatment effect estimate = 0.80 (-1.39 to 2.99) Cohen's d = 0.06; *P* = 0.48 General health Adjusted mean (95% CI) 40.96 (36.95 to 44.97) vs 40.29 (36.28 to 44.30) Treatment effect estimate = 0.67 (-0.97 to 2.30) Cohen's d = 0.06; *P* = 0.42	
Kurdi, 2016[11]	
Global Sleep Outcomes: **AIS** Melatonin (n = 25) vs placebo (n = 25) *Mean scores at days 1, 7 and 14*: 1 day Mean (SD) = 17.88 (2.03) vs 16.28 (2.62) t = 2.4136; *P* = 0.0197 7 days Mean (SD) = 14.32 (1.49) vs 16.12 (2.52) t = -3.0714; *P* = 0.0035 14 days Mean (SD) = 9.56 (2.58) vs 14.44 (4.69) t = -4.5562; *P* = 0.00001 *Change scores after 1st week, 2nd week, and from day 1 to day 14*: Change from day 1 to day 7 Mean (SD) = 3.56 (2.58) vs 0.16 (0.69) t = 6.3591; *P* = 0.00001 Day 8 to day 14 Mean (SD) = 4.76 (2.26) vs 1.68 (5.60) t = 2.5490; *P* = 0.0141 Day 1 through day 14 Mean (SD) = 8.32 (3.77) vs 1.84 (5.42) t = 4.9059; *P* = 0.00001 Percent sleep improvement: Day 1 to day 7 19.91% (*P* = 0.00001) vs .98% (*P* = 0.2563) Day 8 to day 14 33.24% (*P* = 0.00001) vs 10.42% (*P* = 0.1469) Day 1 to Day 14	"*We conclude that regular daily intake of oral melatonin 3 mg 2 h before bedtime along with nonpharmalogical measures improves sleep induction and the quality of sleep in cancer patients with insomnia*" (p.6)

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
46.53%; *P* = 0.00001 vs 11.30% (*P* = 0.1026)	

AIS = Athens Insomnia Scale; CI = confidence interval; ESS = Epworth Sleepiness Scale; FSS = Fatigue severity scale; h = hours; HADS = hospital anxiety depression scale; MD = mean difference; mg = milligrams; n = subsample; p = page; PSQI = Pittsburg Sleep Quality Index; QoL = quality of life; SD = standard deviation; SF-36 = short form health survey; t = score from paired t-test

Appendix 5: Overlap between Included Systematic Reviews

Table 8: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation			
	Oliveira, 2018[12]	Auld, 2017[5]	McCleery, 2016[13]	Brasure, 2015[9]
Tek, 2014	X			
Wade, 2014			X	
Wade, 2011		X		X
Wade, 2010				X
Kumar, 2007	X			
Lemoine 2007		X		
Wade 2007		X		
Montes 2003		X		
Zhdanova 2001		X		
Shamir, 2000	X			

*Note. Wade 2011 is a re-analysis of Wade 2010

Appendix 6: Additional References of Potential Interest

Guidelines – Other/Unclear Methodology

Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, Espie CA, Garcia‐Borreguero D, Gjerstad M, Gonçalves M, Hertenstein E. European guideline for the diagnosis and treatment of insomnia. *Journal of sleep research*. 2017 Dec;26(6):675-700.

Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *Journal of Clinical Sleep Medicine*. 2017 Feb 15;13(02):307-49