NICE National Institute for Health and Care Excellence

Melatonin for treating sleep disorders in adults who are blind

Evidence review

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This evidence review sets out the best available evidence on melatonin for treating sleep disorders in adults who are blind. It should be read in conjunction with the evidence summary, which gives the likely place in therapy and factors for decision making.

Evidence review commissioned by NHS England.

Product overview

Mode of action

Melatonin is a hormone that occurs naturally in the body. It acts on the melatonin receptors (MT1, MT2 and MT3), which are involved in the regulation of circadian rhythms and sleep (summaries of product characteristics for melatonin).

Regulatory status

Several licensed melatonin products are available including tablets, capsules, prolonged-release tablets, and oral solutions. Melatonin is also available in various unlicensed formulations.

Marketing authorisations differ depending on the particular product and include:

- as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in people who are aged 55 or over,
- short-term treatment of jet lag in adults,
- treatment of insomnia in children and adolescents aged 2 to 18 with autism spectrum disorder or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.

See the summaries of product characteristics for further information.

The use of melatonin for treating sleep disorders in adults who are blind is off-label. See NICE's information on prescribing medicines.

Dosing information

For treating primary insomnia characterised by poor quality of sleep in people who are aged 55 or over the recommended dose using modified-release tablets is 2 mg once daily taken 1 to 2 hours before for bedtime for up to 13 weeks.

For short-term treatment of jet lag the recommended standard dose is 3 mg once daily for a maximum of 5 days. The dose may be increased up to 6 mg if the standard dose does not adequately relieve symptoms.

For treating insomnia in children and adolescents aged 2 to 18 with autism spectrum disorder or Smith-Magenis syndrome, the recommended starting dose using modified release tablets is 2 mg once daily taken 30 to 60 minutes before bedtime. If response is inadequate, the dose should be increased to 5 mg, with a maximum dose of 10 mg.

Disclaimer

The content of this evidence review was up to date in August 2021. See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

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Background

The daily rhythm of sleep and wakefulness in people is regulated by an intrinsic body clock. This body clock usually runs longer than 24 hours (average 24.2 hours) but is synchronised by the daily light to dark cycle to match the environmental 24-hour day (Roth et al. 2015). In people who are totally blind, in whom environmental light cues are unavailable, disturbances of the daily rhythm of sleep and wakefulness are common. This can lead to recurrent insomnia, sleep disruption and daytime sleepiness (Sack et al. 2000).

Melatonin is a hormone which is secreted by the pineal gland. It helps to regulate sleep by synchronising the internal body clock to the light-dark cycle. It also has a sedative effect and increases the propensity for sleep (summary of product characteristics).

Related NICE guidance

NICE has not produced any guidance on treating sleep disorders in adults who are blind.

Some related NICE guidelines include recommendations for considering melatonin (often off-label) in people with sleep disorders due to other underlying conditions. In the guideline on autistic spectrum disorder in under 19s and also the guideline on challenging behaviour and learning disabilities, NICE recommends that melatonin is only considered for persistent sleep problems after non-pharmacological interventions have been tried and following consultation with a specialist with expertise in this area. It should be used in conjunction with non-pharmacological interventions, such as having a sleep plan. NICE also recommends that the use of melatonin in these circumstances is reviewed regularly to ensure the benefits continue to outweigh the side effects and risks. The NICE guideline on chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) recommends that melatonin may be considered for children and young people who have sleep difficulties, but only under specialist supervision because it is not licensed in the UK for this indication. Similarly, in the guideline on cerebral palsy in under 25s, NICE recommends considering a trial of melatonin to manage sleep disturbances if no treatable cause is found, particularly for problems with falling asleep. For rapid eye

movement sleep behaviour disorder in people with Parkinson's disease, NICE recommends considering clonazepam or melatonin if a medicines review has addressed possible pharmacological causes (see the NICE guideline on Parkinson's disease in adults).

Melatonin was included in the scope of the NICE guidelines on attention deficit hyperactivity disorder in children, young people and adults and autism spectrum disorder in adults, but there was insufficient evidence to make recommendations on its use for sleep disorders.

The NICE guideline on dementia states that melatonin should not be offered to manage insomnia in adults with Alzheimer's disease. No evidence was found for the use of melatonin for treating sleep disorders in adults with other types of dementia.

Objective

This evidence review aims to review the best available evidence on the effectiveness and safety of melatonin for treating sleep disorders in adults who are blind.

Review questions

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review questions for this evidence review are:

1. What is the clinical effectiveness of melatonin for treating sleep disorders in adults who are blind?

2. What is the safety of melatonin for treating sleep disorders in adults who are blind?

Summary of included studies

A literature search for melatonin identified 1,872 references (see appendix E for full details). These references were screened using their titles and abstracts and 19 full text references were obtained and assessed for relevance.

Three studies are included in this evidence summary. A summary of the included studies is shown in appendix B. Quality assessment of the included studies is in appendix C.

One study is a randomised, double-blind, placebo-controlled, proof-of-principle study (Roth et al. 2015). Two studies (Sack et al. 2000 and Hack et al 2003) are placebo-controlled crossover studies.

Sixteen studies were excluded. Details of these excluded studies are in appendix F.

Effectiveness and safety

Full details of the results are in appendix D.

Review question 1: What is the clinical effectiveness of melatonin for treating sleep disorders in adults who are blind?

Total night sleep duration

Roth et al. (2015) found that mean total night sleep duration (the primary outcome) increased by 43 minutes from baseline with melatonin 2 mg prolonged release compared with 16 minutes with placebo. The mean difference between the groups was 27 minutes (95% confidence interval [CI] −14.4 to 69.0 minutes; p=0.18). Although this outcome did not reach statistical significance, the authors report that it met the primary endpoint because there was a clinically relevant effect on sleep duration, which they pre-specified as an upper limit of the 95% CI greater than 20 minutes.

Hack et al. (2003) found that mean total night sleep duration was greater with melatonin 0.5 mg (6.64 hours) compared with placebo (5.99 hours). The difference between the groups was statistically significant (p<0.01).

Sack et al. (2000) found no statistically significant difference in total time asleep at the end of treatment with melatonin 10 mg compared with the end of treatment with placebo.

Sleep latency

Roth et al. (2015) found no statistically significant difference in sleep latency (time it takes to fall asleep) between melatonin 2 mg prolonged release and placebo.

Hack et al. (2003) and Sack et al. (2000) also found no statistically significant difference in sleep latency between melatonin (0.5 mg and 10 mg respectively) and placebo.

Time spent awake after the onset of sleep

Hack et al. (2003) found no statistically significant difference in the number of night awakenings with melatonin 0.5 mg compared with placebo. However, the duration of night awakenings was statistically significantly less with melatonin (0.56 hours) compared with placebo (0.79 hours; $p<0.05$). The clinical relevance of this difference is unclear.

At the end of treatment, Sack et al. (2000) found a statistically significant difference in the time spent awake after the onset of asleep with melatonin 10 mg (88 minutes) compared with placebo (166 minutes; $p=0.05$).

Early awakenings

Roth et al. (2015) found no statistically significant difference in sleep offset (the time that participants woke up) with melatonin compared with placebo.

Hack et al. (2003) found a statistically significant delay in the time that participants woke up on melatonin 0.5 mg compared with the time they woke on placebo.

Quality of life

Roth et al. (2015) found no difference between melatonin and placebo in the Clinical Global Impression of Change score for severity of illness and global improvement, and the WHO-5 well-being index. No statistical analyses were reported.

Review question 2: What is the safety of melatonin for treating sleep disorders in adults who are blind?

Roth et al. (2015) report that 1 out of 5 (20%) people in the melatonin 2 mg prolonged-release group and 2 out of 8 (25%) people in the placebo group

experienced one or more treatment-emergent adverse events during the study. These were all considered to be mild in severity and none led to withdrawal from the study. No serious adverse events were reported during the study.

The BNF states that common and very common adverse effects reported with melatonin include arthralgia, headaches, increased risk of infection, and pain (see the BNF for more information).

For further information on the safety profile of individual melatonin preparations see the summaries of product characteristics for melatonin.

Limitations of the evidence

The evidence for using melatonin to treat sleep disorders in adults who are blind is limited. Only 1 study (Roth et al. 2015) was randomised. The other studies (Hack et al. 2003 and Sack et al. 2000) were crossover studies and the authors do not report if the studies were randomised, and as such are subject to potential bias.

The study by Roth et al. was the largest (n=13) but as reported by the authors, was underpowered to find a statistically significant difference between melatonin and placebo. Roth et al. report that a total of 42 participants would have been needed to have at least an 80% chance of detecting a difference between the placebo and melatonin groups at the 0.1 significance level for the primary outcome. The studies by Hack et al. and Sack et al. were smaller including 10 and 7 participants respectively.

The primary outcome in the study by Roth et al was total night sleep duration. The studies by Hack et al. and Sack et al. did not specify which outcomes in the studies were primary or secondary. However, most of the outcomes reported in these studies related to entrainment of the free-running circadian rhythms of people who were totally blind (regulating sleep by synchronising the internal body clock to the light-dark cycle), rather than effects on sleep.

The study by Roth et al. was funded by a pharmaceutical company that include the prolonged-release melatonin product used in the study in their approved drug product list. Two of the authors who were employees of the company were involved

in the conception and design of the study, drafting of the protocol, interpretation of the data and preparation of the manuscript. Not all elements of study design were reported, such as the randomisation process or if allocation was concealed, and as such may be subject to potential bias.

The dose and formulation of melatonin used in the studies varied. Roth et al. used a 2 mg prolonged-release formulation of melatonin whereas Hack et al. and Sack et al. used immediate-release formulations at dosages of 0.5 mg and 10 mg daily, respectively. The durations of treatment varied from around 3 to 12 weeks. This makes it difficult to determine what dose should be used for treating sleep disorders in adults who are blind, and how long treatment should be continued for.

Safety data for using melatonin to treat sleep disorders in adults who are blind are limited. Roth et al. reported safety outcomes but only provided overall numbers of people who experienced treatment-emergent adverse events, rather than the types of events experienced. No safety information was reported by Hack et al. or Sack et al.

Overall, the limitations of the available evidence make it difficult to determine the clinical effectiveness and safety of melatonin for treating sleep disorders in adults who are blind.

Person-centred factors

Safety data were poorly reported in the studies. In the study by Roth et al. (2015), 1 out of 5 people had treatment-emergent adverse events with melatonin but these were considered to be mild. All the studies were short term and long-term safety data are lacking.

Melatonin is taken once a day, usually between 30 minutes and 2 hours before a person’s usual bedtime, depending on which product is prescribed.

Melatonin is taken by mouth as tablets, capsules, prolonged-release tablets, and oral solution, depending on the person’s needs and preferences.

Resource implications

The cost of prescribing melatonin for treating sleep disorders in adults who are blind will vary depending on the dose and product that is prescribed. The cost of a year's treatment with melatonin is estimated to be between £187 and £1278. See the resource impact assessment accompanying this evidence review for more information.

References

Hack LM, Lockley SW, Arendt J et al. (2003) The effects of low-dose 0.5 mg melatonin on free-running circadian rhythms of blind subjects. Journal of Biological Rhythms 18(5): 420−9

Roth T, Nir T, Zisapel N (2015) Prolonged release melatonin for improving sleep in totally blind subjects: a pilot placebo-controlled multicenter trial. Nature and Science of Sleep 7: 13−23

Sack RL, Brandes RW, Kendall AR et al. (2000) Entrainment of free-running circadian rhythms by melatonin in blind people. The New England Journal of Medicine 343(15): 1070−77

Development of the evidence review

Process

The evidence summary: process guide sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers

Details of expert advisers and any declarations of interest

Name, job title and organisation	Declaration of interest
Matthew Walker. Professor of Neurology, UCL Queen Square Institute of Neurology and Honorary Consultant Neurologist, National Hospital for Neurology and Neurosurgery, UCLH NHS Foundation Trust	Eisai consultancy about sleep (16/3/2021 to 30/04/2021) Expert witness opinion on relationship between vaccination and narcolepsy (ongoing)

Name, job title and organisation	Declaration of interest
	Undertake some private practice at Queen Square Consulting rooms seeing sleep and epilepsy referrals (ongoing)

Appendices

Appendix A: PICO table

PICO table

Criteria	Details
P – Population and indication	Sleep disorders in adults who are blind
I – Intervention	Oral melatonin - all formulations
C – Comparator(s)	Standard care, including: • antihistamines • alpha-adrenergic agonists • antidepressants • antipsychotics • benzodiazepines • chloral hydrate • sleep hygiene measures • behavioural therapies • 'Z-drugs' (zaleplon, zolpidem and zopiclone). Placebo or no treatment. Most of these are used off-label.
O – Outcomes	Total sleep time Sleep onset latency Number of night awakenings Longest sleep period Early awakenings Ability to wake in the morning Daytime functioning, mood, behaviour and performance (at home and school) Quality of sleep and quality of life or wellbeing of child and family members Impact on other family members especially siblings Long-term efficacy and maintenance of response Adverse effects including effects on mental health, sexual development, and growth Medicines adherence
Inclusion criteria	-
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, observational studies including case series
Language	English
Patients	Human studies only
Age	Adults aged 18 and above
Date limits	None
Exclusion criteria	-
Publication type	Pre-prints before peer review, letters, conference abstracts or studies that have not been published in full
Study design	Case reports

Appendix B: Summary of included studies

Summary of included studies

Study	Number of participants	Population	Intervention	Comparison	Outcomes
Roth et al. 2015 Double-blind RCT	n=13	Adults aged 37 to 67 years (38% male) who were totally blind. Participants had a history of periodic sleep difficulty for at least 6 weeks including difficultly in initiating sleep or difficulty awakening, average total sleep per night of less than 6 hours, progressive delays of the sleep phase and inability to maintain entrainment to a 24-hour day. Use of melatonin, benzodiazepines, or other hypnotics was not allowed for 2 weeks before the study (or 5 half-lives of the medicine if longer), or during the study	Placebo for 2 weeks then melatonin prolonged release 2 mg at 9pm to 10pm (n=5) for 6 weeks. This was followed by a 2-week washout period	Placebo for 2 weeks then placebo at 9pm to 10pm (n=8) for 6 weeks. This was followed by a 2-week washout period	Primary outcome: total night sleep duration. Secondary outcomes: sleep onset and offset times, sleep latency, night awakenings, sleep quality, number of naps, total duration of naps, feeling upon awakening, morning alertness
Hack et al. 2003 Single-blind, placebo-controlled, crossover study	n=10	Adults (90% male) aged 32 to 65 years who were totally blind. Use of any medicines that could affect melatonin or cortisol production, or sleep (for example beta	Melatonin 0.5 mg once daily at 9pm for 26 to 81 days	Placebo	Sleep latency, sleep onset, number and duration of night awakenings, sleep offset, total night sleep duration, and number and duration of naps.

Study	Number of participants	Population	Intervention	Comparison	Outcomes
		blockers, monoamine oxidase inhibitors, tricyclic antidepressants, or benzodiazepines) was not allowed throughout the study			The study did not specify whether outcomes were primary or secondary
Sack et al. 2000 Placebo-controlled, crossover study	n=7	Adults (57% male) aged 42 to 57 years who were totally blind. At the time of screening participants were not taking any medications that could affect plasma melatonin concentration or sleep	Melatonin 10 mg once daily for 3 to 9 weeks. The dose was taken one hour before the person's preferred bedtime	Placebo	Total time asleep, sleep latency, sleep efficiency, and time spent awake after the onset of sleep. The study did not specify whether outcomes were primary or secondary

Abbreviations: RCT, randomised controlled trial.

Sleep latency is the time it takes to fall asleep at night. Sleep onset is the time that a person starts trying to fall asleep. Sleep offset is the time that a person wakes up.

In Roth el al. (2015), sleep parameters were assessed using a diary recorded over a daily telephone call to participants. In Hack et al. (2003), sleep parameters were obtained from daily sleep and nap diaries kept by participants. In Sack et al. (2000), sleep parameters were assessed by polysomnography performed in a sleep laboratory. Measurements were taken once during screening, then at the beginning, middle and end of the melatonin and placebo treatment periods.

Appendix C: Quality assessment of included studies

Quality assessment of Roth et al. 2015

Question	Roth et al. (2015)
Domain 1: Risk of bias arising from the randomisation process	-
1.1 Was the allocation sequence random?	No information
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
Risk of bias judgement	Some concerns
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	-
2.1. Were participants aware of their assigned intervention during the trial?	Probably no
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably no
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Not applicable
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Not applicable
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Not applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Probably yes
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable
Risk of bias judgement	Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	-
2.1. Were participants aware of their assigned intervention during the trial?	Probably no
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably no
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Not applicable
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	No information
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	No information
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Probably no
Risk of bias judgement	High
Domain 3: Missing outcome data	-
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Not applicable

Question	Roth et al. (2015)
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Risk of bias judgement	Low
Domain 4: Risk of bias in measurement of the outcome	-
4.1 Was the method of measuring the outcome inappropriate?	No
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably no
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Risk of bias judgement	Low
Domain 5: Risk of bias in selection of the reported result	-
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example scales, definitions, time points) within the outcome domain?	Probably no
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	Probably no
Risk of bias judgement	Some concerns
Overall risk of bias judgement	High

Checklist used: Cochrane risk of bias 2 tool.

Quality assessment of Hack et al. 2003

Question	Hack et al. (2003)
Domain 1a: Risk of bias arising from the randomisation process	-
1.1 Was the allocation sequence random?	Probably no
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Probably no
1.3 Did baseline differences between intervention groups at the start of the first period suggest a problem with the randomisation process?	No information
Risk of bias judgement	High
Domain S: Risk of bias arising from period and carryover effects	-
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	No information
S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?	No information
S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	No information
Risk of bias judgement	Some concerns

Question	Hack et al. (2003)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	-
2.1. Were participants aware of their assigned intervention during each period of the trial?	No information
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?	No information
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	No information
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Not applicable
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Not applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	No information
Risk of bias judgement	High
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	-
2.1. Were participants aware of their assigned intervention during each period of the trial?	No information
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?	No information
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced between interventions?	No information
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	Not applicable
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Not applicable
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	No information
Risk of bias judgement	High
Domain 3: Risk of bias due to missing data	-
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No information
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	No
3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?	No information
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No information
Risk of bias judgement	High
Domain 4: Risk of bias in measurement of the outcome	-
4.1 Was the method of measuring the outcome inappropriate?	Probably no
4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?	Probably no
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No information

Question	Hack et al. (2003)
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Yes
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
Risk of bias judgement	Some concerns
Domain 5: Risk of bias in selection of the reported result	-
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
5.2 Is the numerical result being assessed likely to have been selected on the basis of the results from multiple eligible outcome measurements (for example scales, definitions, time points) within the outcome domain?	No information
5.3 Is the numerical result being assessed likely to have been selected on the basis of the results from multiple eligible analyses of the data?	Probably no
5.4 Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?	No
Risk of bias judgement	Some concerns
Overall risk of bias judgement	High

Checklist used: Cochrane risk of bias 2 tool for crossover trials

Quality assessment of Sack et al. 2000

Question	Sack et al. (2000)
Domain 1a: Risk of bias arising from the randomisation process	-
1.1 Was the allocation sequence random?	Probably no
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Probably no
1.3 Did baseline differences between intervention groups at the start of the first period suggest a problem with the randomisation process?	No information
Risk of bias judgement	High
Domain S: Risk of bias arising from period and carryover effects	-
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	No information
S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?	No information
S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	No information
Risk of bias judgement	Some concerns
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	-
2.1. Were participants aware of their assigned intervention during each period of the trial?	No
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?	No
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Not applicable
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Not applicable

Question	Sack et al. (2000)
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Not applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	No information
Risk of bias judgement	High
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	-
2.1. Were participants aware of their assigned intervention during each period of the trial?	No
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?	No
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced between interventions?	Not applicable
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	Not applicable
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Not applicable
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
Risk of bias judgement	Low
Domain 3: Risk of bias due to missing data	-
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No information
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	No
3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?	No information
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No information
Risk of bias judgement	High
Domain 4: Risk of bias in measurement of the outcome	-
4.1 Was the method of measuring the outcome inappropriate?	No
4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?	No
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably no
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Risk of bias judgement	Low
Domain 5: Risk of bias in selection of the reported result	-
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
5.2 Is the numerical result being assessed likely to have been selected on the basis of the results from multiple eligible outcome	Probably no

Question	Sack et al. (2000)
measurements (for example scales, definitions, time points) within the outcome domain?	
5.3 Is the numerical result being assessed likely to have been selected on the basis of the results from multiple eligible analyses of the data?	Probably no
5.4 Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?	No
Risk of bias judgement	Low
Overall risk of bias judgement	High

Checklist used: Cochrane risk of bias 2 tool for crossover trials

Appendix D: Results tables

Results table for Roth et al. 2015

Outcome	Melatonin 2mg PR	Placebo	Analysis
Primary efficacy outcome	**n=5**	**n=8**	**-**
Mean change from baseline to end of treatment in total night sleep duration (hours) plus or minus SD	0.72 hours (43.0 minutes) ±0.699 hours	0.27 hours (16.2 minutes) ±0.449 hours	Mean difference between the groups 27 minutes; 95% CI −14.4 to 69.0 minutes; p=0.18. The authors report that the primary outcome was met because the upper limit of the confidence interval for the difference between the groups was larger than the pre-specified duration of 20 mins
Secondary efficacy outcomes	--------	----------	---------
Mean change from baseline to end of treatment in sleep latency (hours) plus or minus SD	−0.48 hours (−28.8 minutes) ±0.765	−0.001 hours (−0.06 minutes) ±0.314	Mean difference between the groups 29 minutes; p=0.13, not statistically significant
Mean change in sleep onset time from baseline to the end of treatment	8 minutes earlier	No change	The authors state that there was no difference between the groups. No data reported
Mean change from baseline to the end of treatment in sleep offset time	37 minutes later	8 minutes earlier	Mean difference between the groups 45 minutes; p=0.11, not statistically significant
Mean change from baseline to end of treatment in duration of naps per day (minutes)	−13	2	No statistical analyses reported
CGIC; severity of illness score and global improvement score	No data reported	No data reported	The authors report that there were no differences

			between the groups
WHO-5	No data reported	No data reported	The authors report that there were no differences between the groups
Safety outcomes	-	-	-
Number of participants experience treatment-emergent adverse events	1/5 (20%)	2/8 (25%)	No statistical analyses reported

Abbreviations: Abbreviations: CGIC, Clinical Global Impression of Change; CI, confidence interval; PR, prolonged release; SD, standard deviation; WHO-5, WHO-5 well-being index.

Results table for Hack et al. 2003

Outcome	Melatonin 0.5 mg	Placebo	Analysis
Efficacy outcomes	**n=10**	**n=10**	-
Mean total night sleep duration (hours) plus or minus SD	6.64±1.11	5.99±0.88	Statistically significant difference between melatonin and placebo (p<0.01)
Mean sleep latency (hours) plus or minus SD	0.49±0.42	0.54±0.41	No statistically significant difference between melatonin and placebo
Mean sleep onset time (hours) plus or minus SD	24.01±0.71	24.10±0.73	No statistically significant difference between melatonin and placebo
Mean sleep offset time (hours) plus or minus SD	7.03±1.13	6.78±1.09	Statistically significant difference between melatonin and placebo (p<0.05)
Mean number of night awakenings per day plus or minus SD	1.51±0.84	1.59±1.02	No statistically significant difference between melatonin and placebo
Mean duration of night awakenings per day (hours) plus or minus SD	0.56±0.51	0.79±0.67	Statistically significant difference between melatonin and placebo (p<0.05)
Mean sleep quality score plus or minus SD (Scale 1	4.70±0.95	4.85±0.80	No statistically significant

to 9, with 1 being best and 9 being worst)			difference between melatonin and placebo
Mean number of naps per day plus or minus SD	0.76±1.27	1.09±1.45	Statistically significant difference between melatonin and placebo (p<0.01)
Mean duration of naps per day (hours) plus or minus SD	0.14±0.12	0.45±0.35	Statistically significant difference between melatonin and placebo (p<0.01)

Abbreviations: SD, standard deviation.

The study did not specify if outcomes were primary or secondary. The total number of participants in the study was ten. The authors reported that all participants received both treatments. No safety outcomes were reported in the study.

Results for Sack et al. 2000

Outcome	**Melatonin 10 mg**	**Placebo**	**Analysis**
Efficacy outcomes	**n=7**	**n=7**	-
Mean total time asleep at end of treatment (minutes) plus or minus SD	382.6±60.0	309.4±91.6	No statistically significant difference between melatonin and placebo
Mean sleep latency at end of treatment (minutes) plus or minus SD	10.5±6.6	13.7±11.0	No statistically significant difference between melatonin and placebo
Mean sleep efficiency at end of treatment (%; total time asleep divided by the time allowed as an opportunity for sleep) plus or minus SD	79.5 ±12.5	62.8 ±16.7	No statistically significant difference between melatonin and placebo (p=0.06)
Mean time spent awake after onset of sleep, at the end of treatment (minutes) plus or minus SD	88.4±61.2	165.9±71.8	Statistically significant difference between melatonin and placebo (p=0.05)

Abbreviations: SD, standard deviation.

The study did not specify if outcomes were primary or secondary. This was a crossover study design, all participants received both treatments. The total number of participants in the study was 7. No safety outcomes were reported in the study.

Appendix E: Literature search strategy

Database search strategies

Database: Medline ALL

Platform: Ovid
Version: Ovid MEDLINE(R) ALL <1946 to May 27, 2021>
Search date: 28th May 2021
Number of results retrieved: 894
Search strategy:

Database: Ovid MEDLINE(R) ALL <1946 to May 27, 2021>

1 exp "Sleep Initiation and Maintenance Disorders"/ (14303)
2 sleep wake disorders/ or exp dyssomnias/ (91819)
3 (sleep* adj5 (disorder* or dysfunction*)).tw. (31474)
4 (insomnia* or sleepless* or agrypnia* or hyposomnia* or dyssomnia*).tw. (23948)
5 or/1-4 (114835)
6 Melatonin/ (20493)
7 (melatonin* or 73-31-4 or jl5dk93rcl or ki 1001 or ki1001 or jan 13004 or jan13004 or sp 13004 or sp13004 or acetyltryptamine* or methoxytryptamine* or Syncrodin* or VesPro* or Slenyto* or Circadin* or Melovine* or Melatonina*).tw. (26440)
8 6 or 7 (28175)
9 5 and 8 (2851)
10 (MEDLINE or pubmed).tw. (238562)
11 systematic review.tw. (187289)
12 systematic review.pt. (155272)
13 meta-analysis.pt. (133139)
14 intervention$.ti. (163386)
15 or/10-14 (522127)
16 randomized controlled trial.pt. (531996)
17 randomi?ed.mp. (939414)
18 placebo.mp. (225443)
19 or/16-18 (1000359)
20 Observational Studies as Topic/ (6343)
21 Observational Study/ (99796)
22 Epidemiologic Studies/ (8673)
23 exp Case-Control Studies/ (1177281)
24 exp Cohort Studies/ (2142077)
25 Cross-Sectional Studies/ (368118)
26 Controlled Before-After Studies/ (618)
27 Historically Controlled Study/ (202)
28 Interrupted Time Series Analysis/ (1244)
29 Comparative Study.pt. (1890420)
30 case control$.tw. (137590)
31 case series.tw. (83244)

32 (cohort adj (study or studies)).tw. (236223)
33 cohort analy$.tw. (9083)
34 (follow up adj (study or studies)).tw. (51179)
35 (observational adj (study or studies)).tw. (122194)
36 longitudinal.tw. (266486)
37 prospective.tw. (611776)
38 retrospective.tw. (592154)
39 cross sectional.tw. (396874)
40 or/20-39 (4918170)
41 15 or 19 or 40 (5813353)
42 9 and 41 (963)
43 limit 42 to english language (909)
44 animals/ not humans/ (4800877)
45 43 not 44 (894)

Database: Embase

Platform: Ovid
Version: Embase <1974 to 2021 May 27>
Search date: 28th May 2021
Number of results retrieved: 1423
Search strategy:

Database: Embase <1974 to 2021 May 27>

1 exp insomnia/ (71967)
2 sleep disorder/ or hypersomnia/ (73502)
3 (sleep* adj5 (disorder* or dysfunction*)).tw. (53500)
4 (insomnia* or sleepless* or agrypnia* or hyposomnia* or dyssomnia*).tw. (40861)
5 or/1-4 (167514)
6 melatonin/ (36656)
7 (melatonin* or 73-31-4 or jl5dk93rcl or ki 1001 or ki1001 or jan 13004 or jan13004 or sp 13004 or sp13004 or acetyltryptamine* or methoxytryptamine* or Syncrodin* or VesPro* or Slenyto* or Circadin* or Melovine* or Melatonina*).tw. (32873)
8 6 or 7 (41088)
9 5 and 8 (5840)
10 (MEDLINE or pubmed).tw. (299537)
11 exp systematic review/ or systematic review.tw. (356045)
12 meta-analysis/ (216221)
13 intervention$.ti. (218201)
14 or/10-13 (741085)
15 random:.tw. (1667264)
16 placebo:.mp. (474734)
17 double-blind:.tw. (220184)
18 or/15-17 (1928376)
19 Clinical study/ (155490)
20 Case control study/ (172698)

21 Family study/ (25317)
22 Longitudinal study/ (155826)
23 Retrospective study/ (1079442)
24 comparative study/ (900348)
25 Prospective study/ (686767)
26 Randomized controlled trials/ (203664)
27 25 not 26 (679016)
28 Cohort analysis/ (710626)
29 cohort analy$.tw. (14622)
30 (Cohort adj (study or studies)).tw. (343734)
31 (Case control$ adj (study or studies)).tw. (147125)
32 (follow up adj (study or studies)).tw. (66162)
33 (observational adj (study or studies)).tw. (190994)
34 (epidemiologic$ adj (study or studies)).tw. (111177)
35 (cross sectional adj (study or studies)).tw. (251911)
36 case series.tw. (116189)
37 prospective.tw. (926257)
38 retrospective.tw. (983810)
39 or/19-24,27-38 (4409395)
40 14 or 18 or 39 (6284002)
41 9 and 40 (1926)
42 limit 41 to (books or chapter or conference abstract or conference paper or "conference review" or editorial or letter or note or tombstone) (411)
43 41 not 42 (1515)
44 limit 43 to english language (1433)
45 nonhuman/ not human/ (4805559)
46 44 not 45 (1423)

Database: PyscInfo

Platform: Ovid
Version: APA PsycInfo <1806 to May Week 3 2021>
Search date: 28th May 2021
Number of results retrieved: 254
Search strategy:

Database: APA PsycInfo <1806 to May Week 3 2021>
Search Strategy:
---
1 sleep wake disorders/ or hypersomnia/ or insomnia/ (15357)
2 (sleep* adj5 (disorder* or dysfunction*)).tw. (13640)
3 (insomnia* or sleepless* or agrypnia* or hyposomnia* or dyssomnia*).tw. (13969)
4 or/1-3 (27992)
5 melatonin/ (3552)
6 (melatonin* or 73-31-4 or jl5dk93rcl or ki 1001 or ki1001 or jan 13004 or jan13004 or sp 13004 or sp13004 or acetyltryptamine* or methoxytryptamine* or Syncrodin* or VesPro* or Slenyto* or Circadin* or Melovine* or Melatonina*).tw. (5046)

7 5 or 6 (5100)
8 4 and 7 (905)
9 (MEDLINE or pubmed).tw. (25869)
10 systematic review.tw. (32374)
11 systematic review.pt. (0)
12 meta-analysis.pt. (0)
13 intervention$.ti. (75975)
14 or/9-13 (117615)
15 randomized controlled trial.pt. (0)
16 randomi?ed.mp. (90784)
17 placebo.mp. (41606)
18 or/15-17 (116220)
19 Observational Study as Topic/ (0)
20 Observational Study/ (0)
21 Epidemiologic Studies/ (0)
22 exp Case-Control Studies/ (0)
23 exp Cohort Studies/ (0)
24 Cross-Sectional Studies/ (0)
25 Comparative Study.pt. (0)
26 case control$.tw. (11858)
27 case series.tw. (4269)
28 (cohort adj (study or studies)).tw. (23759)
29 cohort analy$.tw. (969)
30 (follow up adj (study or studies)).tw. (13343)
31 (observational adj (study or studies)).tw. (11407)
32 longitudinal.tw. (124997)
33 prospective.tw. (63548)
34 retrospective.tw. (37950)
35 cross sectional.tw. (86298)
36 or/19-35 (317223)
37 14 or 18 or 36 (510972)
38 8 and 37 (254)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley
Version:
CDSR –Issue 5 of 12, May 2021
CENTRAL – Issue 4 of 12, April 2021
Search date: 28th May 2021
Number of results retrieved: CDSR 12 ; CENTRAL 438.

ID Search Hits
#1 MeSH descriptor: [Sleep Initiation and Maintenance Disorders] explode all trees 2524
#2 MeSH descriptor: [Sleep Wake Disorders] this term only 1754
#3 MeSH descriptor: [Dyssomnias] explode all trees 6887
#4 (sleep* near/5 (disorder* or dysfunction*)):ti,ab,kw 12436

#5 (insomnia* or sleepless* or agrypnia* or hyposomnia* or dyssomnia*):ti,ab,kw 11627
#6 #1 or #2 or #3 or #4 or #5 23557
#7 MeSH descriptor: [Melatonin] this term only 1225
#8 (melatonin* or "73-31-4" or jl5dk93rcl or "ki 1001" or ki1001 or "jan 13004" or jan13004 or "sp 13004" or sp13004 or acetyltryptamine* or methoxytryptamine* or Syncrodin* or VesPro* or Slenyto* or Circadin* or Melovine* or Melatonina*):ti,ab,kw 2976
#9 #7 or #8 2976
#10 #6 and #9 827
#11 "conference":pt or (clinicaltrials or trialsearch):so 543843
#12 #10 not #11 452

Database: HTA database

Platform: Wiley
Version: Up to 2015
Search date: 28th May 2021
Number of results retrieved: 25
Search strategy:

1 MeSH DESCRIPTOR Sleep Initiation and Maintenance Disorders EXPLODE ALL TREES 104 Delete
2 MeSH DESCRIPTOR sleep wake disorders 66 Delete
3 MeSH DESCRIPTOR dyssomnias EXPLODE ALL TREES 407 Delete
4 ((sleep* near5 (disorder* or dysfunction*))) 261 Delete
5 (insomnia* or sleepless* or agrypnia* or hyposomnia* or dyssomnia*) 234 Delete
6 #1 OR #2 OR #3 OR #4 OR #5 645 Delete
7 MeSH DESCRIPTOR Melatonin 30 Delete
8 (melatonin* or 73-31-4 or jl5dk93rcl or ki 1001 or ki1001 or jan 13004 or jan13004 or sp 13004 or sp13004 or acetyltryptamine* or methoxytryptamine* or Syncrodin* or VesPro* or Slenyto* or Circadin* or Melovine* or Melatonina*) 55 Delete
9 #7 OR #8 55 Delete
10 #6 AND #9 25 Delete

Database: INAHTA database

Platform: INAHTA website
Version: 28th May 2021
Search date: 28th May 2021
Number of results retrieved: 8
Search strategy:

(melatonin* or 73-31-4 or jl5dk93rcl or ki 1001 or ki1001 or jan 13004 or jan13004 or sp 13004 or sp13004 or acetyltryptamine* or methoxytryptamine* or Syncrodin* or

VesPro* or Slenyto* or Circadin* or Melovine* or Melatonina*) and (sleep* or insomnia* or agrypnia* or hyposomnia* or dyssomnia*)

Trials registry search strategies

Clinicaltrials.gov

Search date: 28 May 2021
Number of results retrieved: 11
Search strategy:

melatonin | Insomnia | Phase 3

Clinicaltrialsregister.eu

Search date: 28 May 2021
Number of results retrieved: 11
Search strategy:

melatonin and Insomnia (only phase 3 trials selected)

Appendix F: Excluded studies

Excluded studies

Study reference	Reason for exclusion
Anon (2008) Melatonin for secondary sleep disorders.	Full text paper not available.
Anon (2008) Melatonin for secondary sleep disorders. Lansdale, PA: HAYES, Inc.	Full text paper not available.
Baglioni, Chiara, Bostanova, Zarina, Bacaro, Valeria et al. (2020) A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials Evaluating the Evidence Base of Melatonin, Light Exposure, Exercise, and Complementary and Alternative Medicine for Patients with Insomnia Disorder. Journal of clinical medicine 9(6)	Does not contain a population of adults who are blind.
Besag, Frank M C, Vasey, Michael J, Lao, Kim S J et al. (2019) Adverse Events Associated with Melatonin for the Treatment of Primary or Secondary Sleep Disorders: A Systematic Review. CNS drugs 33(12): 1167-1186	Does not contain a population of adults who are blind
Brasure, Michelle, MacDonald, Roderick, Fuchs, Erika et al. (2015) Management of Insomnia Disorder. Comparative effectiveness review number 159. Agency for Healthcare research and Quality. No. 15(16)-EHC027-EF	Does not contain a population of adults who are blind
Buscemi, Nina, Vandermeer, Ben, Hooton, Nicola et al. (2006) Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. BMJ (Clinical research ed.) 332(7538): 385-93	Does not contain a population of adults who are blind
Chase, J E and Gidal, B E (1997) Melatonin: therapeutic use in sleep disorders. The Annals of pharmacotherapy 31(10): 1218-26	Does not contain a population of adults who are blind
Costello, Rebecca B, Lentino, Cynthia V, Boyd, Courtney C et al. (2014) The effectiveness of melatonin for promoting healthy sleep: a rapid evidence assessment of the literature. Nutrition journal 13: 106	Does not contain a population of adults who are blind
Fatemeh, Gholami, Sajjad, Moradi, Niloufar, Rasaei et al. (2021) Effect of melatonin supplementation on sleep quality: a systematic review and meta-analysis of randomized controlled trials. Journal of neurology	Does not contain a population of adults who are blind
Fischer, Stefan, Smolnik, Rudiger, Herms, Markus et al. (2003) Melatonin acutely improves the neuroendocrine architecture of sleep in blind individuals. The Journal of clinical endocrinology and metabolism 88(11): 5315-20	Study not prioritised (not the best available evidence).
Foley, Hope M. and Steel, Amie E. (2019) Adverse events associated with oral administration of melatonin: A critical systematic	Does not contain a population of adults who are blind

Study reference	Reason for exclusion
review of clinical evidence. Complementary Therapies in Medicine 42: 65-81	
Li, Tian, Jiang, Shuai, Han, Mengzhen et al. (2019) Exogenous melatonin as a treatment for secondary sleep disorders: A systematic review and meta-analysis. Frontiers in neuroendocrinology 52: 22-28	Does not contain a population of adults who are blind
Low, Tian Ling; Choo, Faith Nadine; Tan, Shian Ming (2020) The efficacy of melatonin and melatonin agonists in insomnia - An umbrella review. Journal of psychiatric research 121: 10-23	Does not contain a population of adults who are blind
Palagini, Laura, Manni, Raffaele, Aguglia, Eugenio et al. (2020) Expert Opinions and Consensus Recommendations for the Evaluation and Management of Insomnia in Clinical Practice: Joint Statements of Five Italian Scientific Societies. Frontiers in psychiatry 11: 558	Review article
Riemann, Dieter, Baglioni, Chiara, Bassetti, Claudio et al. (2017) European guideline for the diagnosis and treatment of insomnia. Journal of sleep research 26(6): 675-700	Review article
Sack, R L, Lewy, A J, Blood, M L et al. (1991) Melatonin administration to blind people: phase advances and entrainment. Journal of biological rhythms 6(3): 249-61	Study not prioritised (not the best available evidence).

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