Melatonin for non-respiratory sleep disorders in visually impaired children (Review)

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Melatonin for non-respiratory sleep disorders in visually impaired children

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ABSTRACT

Background
Exogenous melatonin helps in regulating the circadian rhythm and is widely used for the management of sleep disorders in visually impaired children.

Objectives
The aim of the review was to assess melatonin therapy for treatment of non-respiratory sleep disorders in visually impaired children, with regard to improvement in sleep habit, sleep scheduling and sleep maintenance, when compared with placebo or no treatment.

Search strategy
We searched the following databases between February 2011 and July 2011: the Cochrane Central Register of Controlled Trials (CENTRAL) 2011(1) searched on 4th February 2011; MEDLINE (1950 to June Week 3, 2011) searched on 20th June 2011; EMBASE (1980 to June Week 4, 2011) searched on 7th July 2011; CINAHL (1937 to 21 September 2011); the metaRegister of Controlled Trials (this includes ClinicalTrial.gov) searched 20 July 2011, and reference lists of papers identified after initial screening.

Selection criteria
We planned to include randomized controlled trials (RCTs) and quasi-RCTs, including cross-over studies. Treatment would be exogenous melatonin. Control groups could be placebo, other medication for sleep disorders or no treatment. Outcomes sought were improved sleep with regard to timing and duration, quality of life and adverse events.

Data collection and analysis
Three review authors independently assessed trials for inclusion in the review.
Main results

We did not find any studies fulfilling the inclusion criteria, therefore no outcome data are reported.

We identified nine studies after initial screening and, after further evaluation, we excluded these. The excluded studies involved a total of 163 individuals aged two years to 18 years. We excluded studies for three main reasons: they were non-randomized or case series studies, they were studies of people over 18 years of age or even where the study was randomised, the study population was mixed and results pertaining to the visually impaired cohort could not be independently evaluated. No significant adverse effects of melatonin were reported in these excluded studies.

Authors’ conclusions

There is currently no high quality data to support or refute the use of melatonin for sleep disorders in visually impaired children. Placebo-controlled trials examining important clinical outcomes such as sleep quality, sleep latency, duration of sleep and night-time awakenings are needed. As the numbers of children meeting study inclusion criteria are likely to be low at individual sites, multicentre collaboration between developmental paediatricians, sleep physicians and other health care professionals is essential to achieve sufficient sample size for controlled studies. Such collaboration would help facilitate local recruitment at multiple sites, with study oversight being provided by paediatricians with expertise in sleep disorders. Participation of collaborators with experience in evidence-based practice research is also desirable due to the lack of protocols on melatonin therapy in the target population.
the largest day versus night variation (Reiter 1998). Young children are reported to have the highest circulating melatonin levels but this pattern begins to decline during puberty. The lack of data regarding melatonin rhythmicity highlight the need to evaluate the published studies under different age groups and the therapeutic effect of melatonin. By adulthood, most individuals maintain a circadian melatonin cycle; however, the amplitude of the nocturnal melatonin peak varies widely; for example, circulating concentrations in the elderly are significantly lower than in young adults.

Description of the condition

Sleep disorders are one of the most common causes for parents or caregivers of visually impaired children to seek medical attention for them. Sleep deprivation can have adverse neurological and psychological effects. Sleepiness may also result in neurocognitive performance deficits, lack of verbal creativity, poor abstract reasoning, impaired motor skills, decreased attention and vigilance, and memory impairment. Other adverse health outcomes include deleterious effects on the cardiovascular system, immune system and numerous metabolic systems (Smaldone 2007). Glucose metabolism, obesity and endocrine function are also impaired and accidental injuries increase. Adolescents may be at increased risk of sleep disturbances and inadequate sleep. Distress to the family and caregivers is one of the major adverse impacts (Meltzer 2006). Restored sleep in children helps them to be healthier and calmer, co-operative and playful; this in turn improves family functioning as the burden of care is reduced for the caregivers.

The prevalence of sleep disorders in visually impaired children is as high as 80% (Sadah 2000). Sleep disorders can include delayed phase syndrome, sleeplessness, excessive sleepiness, nighttime episodes of disturbed behaviour and persistent early morning awakenings (Carr 2007).

One of the mechanisms by which sleep disorders arise in visually impaired individuals is thought to be the inability of the circadian clock to respond correctly to external light and dark signals. Visual impairment diminishes the ability of individuals to perceive and interpret cues for synchronising their sleep with the environment (Sajith 2007). This may be due to ocular conditions or to damage to the posterior visual pathways and visual cortex. The latter form is referred to as cortical visual impairment and has become well recognised in recent years (Jan 2006).

The therapeutic management of sleep disorders in children with visual impairment is challenging. A recent consensus statement on the pharmacological management of insomnia in children and adolescents concluded that studies on safety and efficacy are urgently needed (Mindell 2006). Current pharmacotherapeutic options do not provide an optimal balance between tolerability and efficacy, especially in the area of sleep maintenance and long-term use (Rosenberg 2006).

With so few pharmacotherapeutic options, melatonin has aroused widespread interest as a potential hypnotic and chronobiotic agent since the early 1990s (Sajith 2007). Melatonin products are regulated differently in several countries. In the USA, melatonin is classified as an ‘orphan drug’ by the Food and Drug Administration (FDA) (Buck 2003), is regarded as a dietary supplement under the Health and Education Acts and is generally recognised as safe. In Canada, melatonin is included in the Natural Health Products Directorate of Health Canada and is available for sale. In the European Union, melatonin is considered a medicine or hormone and is available only by prescription. In Australia, melatonin is an unregistered product under the therapeutic goods administration; however, it can be imported for use through prescription under the personal import scheme (Jansen 2006).

Description of the intervention

Melatonin, or N-acetyl-5-methoxytryptamine, is a small lipid-soluble indolamine molecule that is widely distributed in nature and highly conserved throughout evolution. Melatonin is the hormone of the pineal gland and has been found to have a remarkable array of functions that unequivocally link it to neurological and behavioural disorders. Endogenous nocturnal production of melatonin and its relation with physiological changes associated with the nocturnal period has led to it being named as the ‘chemical expression of darkness’ (Reiter 1991) or the ‘hormone of darkness’ (Utiger 1992).

How the intervention might work

The onset of melatonin secretion coincides with the increase in nocturnal sleepiness. It has been suggested that the circadian rhythm of melatonin secretion, with high levels at night and low levels during the day, is reflective of the general mechanism by which sleep is regulated in humans (Dijk 1997). Through its sleep-promoting and circadian phase-shifting effects, melatonin is an important neurohormone involved in the physiological mechanisms regulating the sleep-wakefulness rhythm (Arendt 2005). In a proportion of the blind population, circadian rhythms (the melatonin system) do not synchronise with the environment and instead free-run, usually with a period length of more than 24 hours. Non-24-hour sleep-wake syndrome is characterised by a progressive delay in sleep-phase onset. Melatonin treatment can entrain (please define) the circadian system in visually impaired people with abnormal circadian rhythm when treatment is initiated at an appropriate time (Lockley 1997; Lockley 2000). In addition, melatonin is able to stabilise sleep-wake timing. In a study by Lockley 1997, a high proportion (77%) of registered blind people with no perception of light had abnormal circadian rhythm that was assessed by the pattern of melatonin production. The study concluded that blind individuals with no perception of light...
have a higher incidence of circadian rhythm disorders than subjects with light perception. As a hypnotic and chronobiotic facilitator, melatonin is used for the treatment of age-related insomnia and circadian rhythm sleep disorders that include delayed sleep-phase syndrome, non-24-hour sleep disorder, jet lag and shift work (Pandi-Perumal 2007). Dose and time of melatonin administration is crucial. Paediatric groups have been little studied in terms of their circadian melatonin cycle. Prepubertal children may respond at a different dose range compared to children at the pubertal stage, hence evaluation of the effect of melatonin on children in different age ranges, with different types of sleep problems and different degrees of visual impairment is important.

**Why it is important to do this review**

Due to inconclusive information, there is lack of recommended pharmacotherapeutic options for sleep disorders in visually impaired children. A few small-scale studies (Jan 1994; Espezel 1996; Jan 2000; Dodge 2001; Copolla 2004) and case reports (Palm 1991; Cavallo 2002) have generated interest in the potential role of melatonin in sleep-wake cycle disorder in visually impaired children. However, lack of sufficient data to assess the potential effect with respect to time of administration and therapeutically dose range limits the development of protocols, and the availability of different melatonin formulations needs to be studied with respect to clinical efficacy and compliance. There is uncertain evidence on the relationship between the type of visual impairment and circadian rhythm sleep disorders and hence it is important to evaluate the type of visual impairment in these groups from a neurological viewpoint. Numerous small-scale studies have been published that examine the chronobiotic, sedative and hypothermic properties of melatonin in children with sleep disorders, but there has been no systematic review of the efficacy and safety of this drug in the management of sleep disorders in the target population of visually impaired children. This review seeks to address this evidence gap.

**OBJECTIVES**

To assess the effects of melatonin for non-respiratory sleep disorders in visually impaired children, with regard to improvement in sleep habit, sleep scheduling and sleep maintenance, when compared with placebo, other medication or no treatment.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

Randomised and quasi-randomised trials, including cross-over studies. Quasi-randomised trials are trials where a method of allocating participants to different forms of care is not truly random; for example, allocation by date of birth, day of the week, medical record number, month of the year or the order in which participants are included in the study (alternation).

**Types of participants**

Children aged three months to 18 years (age ranges: three months to one year, one to five years, five to 10 years, 11 years or more) with visual impairment and a sleep disorder defined as a disorder of initiating, maintaining or scheduling sleep. For the purposes of the review, visual impairment is defined as loss of vision due to ocular conditions or due to damage of the posterior visual pathways and visual cortex. Visual impairment may be cortical, retinal or mixed.

**Types of interventions**

Melatonin supplementation (all doses, formulations, routes and durations) compared with placebo, other medication for sleep disorders or no treatment.

**Types of outcome measures**

**Primary outcomes**

Improved sleep with respect to the following.
1. Sleep duration.
2. Timing of sleep.
3. Quality of sleep.

**Secondary outcomes**

1. Adverse events.
2. Quality of life.

We planned to evaluate primary and secondary outcomes through subjective and objective means that could include polysomnography, actigraphy, sleep diaries or health-related quality of life questionnaires/interviews, as used by the studies.

**Search methods for identification of studies**

**Electronic searches**

We identified relevant trials through electronic searches of the following databases.
Cochrane Central Register of Controlled Trials (CENTRAL) 2011(1) (part of the Cochrane Library), searched 4 February 2011
MEDLINE (1950 to current), searched 20 June 2011
EMBASE (1980 to current), searched 7 July 2011
CINAHL (from 1937 to current), searched 21 September 2011
metaRegister of Controlled Trials (this includes ClinicalTrials.gov), searched 20 July 2011

The search strategies for each database are in Appendix 1.

Search strategies
It should be noted that we searched for 'melatonin' only as a database indexing term and not as a free text term. We will add 'melatonin' as a free text term when we update the review.

Searching other resources
We consulted references cited in identified trials and review articles for any additional trials.

Data collection and analysis
Please see Appendix 2 for details of the methods we had planned but were unable to use as there were no included studies. We will use these methods in any update of this review.

Selection of studies
Two authors independently assessed studies for inclusion by reviewing the full text of published report and we resolved differences in opinion through discussion. Provision was made for arbitration by a third co-author.

RESULTS

Description of studies
See: Characteristics of excluded studies.
The search strategy identified 127 potentially relevant references, which were assessed against the study criteria (Figure 1). We excluded 118 of these papers based on information in the title or abstract. The remaining nine papers were retrieved for more detailed evaluation. We subsequently excluded all of these nine studies (see Characteristics of included studies). Hence no trials are included in this review.
Figure 1. Study flow diagram: process of excluding studies

127 records identified through database searching and handsearching reference lists of retrieved citations

Records screened based on titles and abstracts

118 excluded on basis of information provided in title and abstract only

9 evaluated in detail

9 full-text articles excluded. See 'Characteristics of excluded studies' section

No studies to be included
Results of the search
In all, we identified 127 citations (Figure 1) but none met the inclusion criteria for our review.

Included studies
There are no trials included in this review.

Excluded studies
Nine studies were retrieved for detailed evaluation. We excluded studies from the review for one or more of the following reasons:

- It was not a randomised or quasi-randomised controlled trial;
- the study population of (visually impaired) was over 18 years; or
- although randomised, the study population was mixed and results pertaining to the visually impaired cohort could not be independently evaluated.

See also Characteristics of excluded studies.

Risk of bias in included studies
We did not find any study that met the inclusion criteria of the review.

Effects of interventions
We did not find any study that met the inclusion criteria of the review.

DISCUSSION
We did not find any study that met our inclusion criteria. The search yielded nine studies that we looked at in depth and then excluded: two randomised studies; five case series; a single "N of 1" study consisting of six individual patient trials, and a single non-randomised retrospective study.

The two studies that used a randomised, double-blind, placebo-controlled, cross-over approach, contained populations extending beyond visual impairment (Dodge 2001; Coppola 2004). The visually impaired component of the study groups was too small for independent data extraction and analysis, constituting only four of 20 participants (20%) (Dodge 2001) and four of 25 participants (16%) (Coppola 2004). In Dodge 2001, better outcomes were reported for participants receiving melatonin, though this was based on a comparison to baseline within subjects rather than against placebo. In Coppola 2004, the only outcome parameter reaching statistical significance was sleep latency. Both studies faced a number of additional methodological limitations, such as an overall small sample size, lack of comparison with regard to treatment outcome, presence of baseline differences, inadequate information regarding effect sizes and no reporting of confidence intervals. Further details of these studies are in the section Characteristics of excluded studies.

Collectively, the remaining seven studies included 171 children with visual impairment. We do not know what proportion of these children gained benefit from melatonin intervention, and yet all but the "N of 1" series, which had only three visually impaired children (Camfield 1996), concluded that melatonin is an effective agent for improving the sleep parameters of pattern and latency and improving health-related quality of life. Importantly, parameters measured were not consistent across these studies; and the strength of this evidence insufficient to draw conclusions for policy or practice.

This systematic review identified potentially relevant studies of melatonin for the management of sleep disorders in visually impaired children. Empirical inference across these studies found melatonin to be effective, with improvement in sleep pattern, sleep latency and health-related quality of life. There were also no significant adverse drug reactions. However, the majority were case series and lacked a control group, so did not provide good quality evidence supporting the efficacy of melatonin in our target population. While outcome measures were appropriate, they were subjective and inconsistently employed across all studies. Objective measures were generally lacking. A sleep diary, a subjective measure, was the most widely used; while only one study used the objective measures of actigraphy and endogenous/exogenous melatonin concentrations (Palm 1997). Ideally, researchers involved with specialised populations like visually impaired children would collaborate, at an international level, to provide a single support research mechanism, for example, with regards to financial, information technology, clinical trial monitoring services, so eligible patients can be enrolled in standardised interventions with consistent outcome measures.

Potential biases in the review process
None.

AUTHORS’ CONCLUSIONS
Implications for practice

Despite empirical inference across the excluded studies finding melatonin to be effective, with improvement in sleep pattern, sleep latency and health related quality of life, and without any significant adverse effects, due to the lack of high quality evidence, the role of melatonin in the management of sleep disorders in visually impaired children is unclear.

Implications for research

High quality randomised placebo-controlled trials using clinically important objective outcome measures such as actigraphy in addition to subjective measures are required. Consistency in objective outcome measures of sleep and circadian pattern is required to systematically evaluate and compare end points in clinical trials. Ideally, researchers involved with specialised populations like visually impaired children would collaborate, at an international level, to provide a single support research mechanism, for example, with regards to financial, information technology, clinical trial monitoring services, so eligible patients can be enrolled in standardised interventions with consistent outcome measures.

As the numbers of children meeting study inclusion criteria are likely to be low at individual sites, multicentre collaboration of developmental paediatricians, sleep physicians and other health care professionals is essential to achieve sufficient sample size for controlled studies. Such collaboration can facilitate local recruitment at multiple sites, with study oversight by paediatricians with expertise in sleep disorders. Participation of collaborators with experience in evidence-based practice research is also desirable due to the lack of protocols on melatonin therapy in the target population. Basic science research is also required to build a compendia of typical circadian patterns in different cohorts of children with and without sleep disorders, with and without visual impairment, with and without developmental problems, and with and without intellectual disability (similar to those of electroencephalogram). This would provide a baseline for comparison when interventions such as melatonin are employed to phase-shift.

Acknowledgements

The Cochrane Developmental, Psychosocial and Learning Problems Group for timely instructions while drafting the review.

References

References to studies excluded from this review

Camfield 1996 [published data only]

Coppola 2004 [published data only]

Dodge 2001 [published data only]

Espezel 1996 [published data only]

Hung 1998 [published data only]

Jan 1994 [published data only]

Jan 2000 [published data only]

Palm 1997 [published data only]

Schmitt-Mechelke 1997 [published data only]

Additional references

Altman 1996

Arendt 2005
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Buck 2003

Carr 2007

Cavallo 2002

Copolla 2004

Dijk 1997

Egger 1997

Elbourne 2002

Fazzi 2008

Higgins 2008

Jan 2006

Jansen 2006

Lefebvre 2008

Lockley 1997

Lockley 2000

Meltzer 2006

Mindell 2006

Palm 1991

Pandi-Perumal 2007

Reiter 1991

Reiter 1998

Rosenberg 2006

Sadegh 2000
Sajith 2007

Sateia 2008

Smaldone 2007

Stores 1999

Utiger 1992

Wee 2004

Zhadnova 2005

* Indicates the major publication for the study
## Characteristics of studies

**Characteristics of excluded studies  [author-defined order]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 1994</td>
<td>Case series.</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Presents data in the form of case reports.</td>
</tr>
<tr>
<td></td>
<td>Study was done in a double-blind, randomized, cross-over manner; however, this is not reflected in the results with no information on the control response.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>N = 15; visually impaired = 9.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Melatonin 2mg, 2.5 mg, 5 mg.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Sleep charts recorded by caregivers assessing sleep duration; telephone follow-up with caregivers during the initial treatment period</td>
</tr>
<tr>
<td><strong>Author's conclusion</strong></td>
<td>The health, behavioural and social benefits of melatonin treatment were significant, and there were no adverse drug reactions.</td>
</tr>
<tr>
<td><strong>Risk of bias - Allocation concealment</strong></td>
<td>C = Inadequate</td>
</tr>
<tr>
<td>Camfield 1996</td>
<td>“N of 1” trials.</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>This was six “N of 1” trials conducted in a 10 week double-blind, randomized manner</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>N = 6; visually impaired = 3.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Melatonin 0.5 mg, 1 mg.</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>Placebo.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Sleep charts. Outcome measures include: a) the average number of hours asleep per 24 hours; b) the number of awakenings between 9pm and 7am per day; and c) number of nights with no arousals between 8pm and 7am</td>
</tr>
<tr>
<td><strong>Author's conclusion</strong></td>
<td>None of the three cases had a marked improvement in sleep pattern with melatonin</td>
</tr>
<tr>
<td><strong>Risk of bias - allocation concealment</strong></td>
<td>B = Uncertain</td>
</tr>
<tr>
<td>Espezel 1996</td>
<td>Case series, non-randomized.</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>A large case series with 100 patients - specific cohort of children with visual impairment</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>N = 100; visually impaired = 100.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Palm 1997
- **Description**: Case series, non-randomized.
- **Participants**: N = 8; visually impaired = 8.
- **Intervention**: Melatonin 0.5 mg - 4 mg.
- **Outcomes**: Sleep charts assessing sleep duration by the caregivers. Objective measures include actigraphy and measurement of serum/urine melatonin concentration by radioimmunoassay.
- **Author's conclusion**: Melatonin administration dramatically improved the non-24-hour sleep-wake cycle. The therapeutic effect was maintained between 1-6 years in 6 patients. One patient fell back into the earlier sleep pattern after 6 to 8 months, and another had increasing sleep disturbance because of reflux oesophagitis, although the improvement regarding the circadian component remained. No side effects were noted during the therapy.
- **Risk of bias - allocation concealment**: C = Inadequate.

### Schmitt-Mechelke 1997
- **Description**: Case series, non-randomized.
- **Participants**: N = 36; visually impaired = 16.
- **Intervention**: Melatonin 2 mg - 10 mg.
- **Outcomes**: Sleep charts assessing sleep duration by the caregivers.
- **Author's conclusion**: Melatonin administration improved sleep pattern.
- **Risk of bias - allocation concealment**: C = Inadequate.

### Hung 1998
- **Description**: Retrospective non-randomized study.
- **Participants**: A retrospective data evaluation of use of melatonin in children with sleep disturbances previously resistant to behavioural modification or sedative therapy.
- **Risk of bias - allocation concealment**: C = Inadequate.
N = 37; visually impaired = 15.

**Intervention**
Melatonin 2 mg -10 mg.

**Outcomes**
Parental description of sleep pattern, completion of sleep charts and a global evaluation

**Author's conclusion**
Parents of 32 (86.48%) children reported beneficial response to melatonin usually within 1-2 weeks of starting treatment. Two of the 37 children experienced an increase in seizure frequency (despite improved sleep pattern). No other adverse effects were observed.

**Risk of bias - allocation concealment**
C= Inadequate.

---

**Jan 2000**
Non-randomized study.

**Description**
First study to examine effective doses of controlled-release (CR) melatonin in children with chronic sleep-wake cycle disorders

Initially, a randomized double-blinded cross-over design was used in 16 children, comparing the effectiveness of fast-release (FR) and CR melatonin. In the remainder of the patients, the CR melatonin was studied on a clinical basis and in a non-randomized way

**Participants**
N = 42; visually impaired = 20.

**Intervention**
Melatonin 2 mg - 12 mg.

**Outcomes**
Sleep charts and clinical follow-up.

**Author's conclusion**
FR melatonin was most effective when there was only delayed sleep onset, but CR formulations were more useful for sleep maintenance. Children appeared to require higher doses than adults

**Risk of bias - allocation concealment**
C= Inadequate.

---

**Dodge 2001**
Mixed population group. Results pertaining to the visually impaired cohort could not be independently evaluated

**Description**
Randomized, double-blind, placebo-controlled cross-over trial

Visually impaired group were not evaluated separately. Effectiveness and significance of melatonin therapy as compared to placebo is not clear

**Participants**
N = 25; visually impaired = 4.

**Intervention**
Melatonin 5mg.
Control
Placebo.

**Outcomes**
Sleep charts and clinical follow-up

**Author's conclusion**
Melatonin reduces sleep latency in children with developmental disabilities

**Risk of bias - allocation concealment**
B= Uncertain.
Continued

<table>
<thead>
<tr>
<th>Coppola 2004</th>
<th>Mixed population group. Results pertaining to the visually impaired cohort could not be independently evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Randomized, double-blind, placebo controlled cross-over trial</td>
</tr>
<tr>
<td></td>
<td>Visually impaired group were not evaluated separately.</td>
</tr>
<tr>
<td></td>
<td>Effectiveness and significance of melatonin therapy as compared to placebo is not clear</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>N = 20; visually impaired = 4.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Melatonin 3 mg -12 mg.</td>
</tr>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Placebo.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Sleep charts and clinical follow-up.</td>
</tr>
<tr>
<td><strong>Author's conclusion</strong></td>
<td>Melatonin is effective in young patients with mental disabilities and epileptic seizures in improving the wake-sleep disorders.</td>
</tr>
<tr>
<td><strong>Risk of bias - allocation concealment</strong></td>
<td>B= Uncertain.</td>
</tr>
</tbody>
</table>
DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search strategies

We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library 2011(1), which contains the Cochrane Developmental, Psychosocial Support and Learning Problem Group (CDPLPG) Register.

We searched MEDLINE using the following keywords and MeSH terms in conjunction with the Cochrane highly sensitive search strategy to find randomized trials (Lefebvre 2008). The same strategy but without the RCT filter was used to search CENTRAL and adapted to search EMBASE and CINAHL.

MEDLINE

1. Melatonin/
2. adolescent/ or child/ or child, preschool/ or infant/
3. (baby or babies or infant$ or child$ or boy$ or girl$ or toddler$ or preschool$ or pre-school$ or pre-school$ or teen$ or schoolchild$ or adolescence or juvenil$).tw.
4. 2 or 3
5. Visually Impaired Persons/
6. exp Vision Disorders/
7. ((vision$ or visual$) adj3 (handicap$ or disabili$ or disabl$ or impair$ or disorder$)).tw.
8. blind$.tw.
9. 5 or 6 or 7 or 8
10. exp Sleep Disorders/
11. insomnia.tw.
12. (sleep adj3 (disorder$ or problem$ or pattern$)).tw.
13. (wakefulness or waking).tw.
14. 10 or 11 or 12 or 13
15. 1 and 4 and 9 and 14
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomized.ab.
19. placebo.ab.
20. drug therapy.fs.
21. randomly.ab.
22. trial.ab.
23. groups.ab.
24. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. humans.sh.
26. 24 and 25
27. 15 and 26

CENTRAL

1. MeSH descriptor Melatonin explode all trees
2. MeSH descriptor Adolescent, this term only
3. MeSH descriptor Child explode all trees
4. MeSH descriptor Infant, this term only
5. (bab$ OR infant$ OR child$ OR boy$ OR girl$ OR toddler$ OR preschool$ OR teen$ OR schoolchild$ OR adolescent$ OR juvenile$):ti,ab,kw
6. 2 or 3 or 4 or 5
7. MeSH descriptor Visually Impaired Persons, this term only
8. MeSH descriptor Vision Disorders explode tree 1
9. (vision* NEAR/3 handicap*:ti,ab,kw or (vision* NEAR/3 disabi*:ti,ab,kw or (vision* NEAR/3 impair*:ti,ab,kw or (vision* NEAR/3 disorder*:ti,ab,kw
10. (visual* NEAR/3 handicap*:ti,ab,kw OR (visual* NEAR/3 diabi*:ti,ab,kw OR (visual* NEAR/3 disabl*:ti,ab,kw OR (visual* NEAR/3 impair*:ti,ab,kw OR (visual* NEAR/3 disorder*:ti,ab,kw
11. blind*:ti,ab,kw
12. 7 or 8 or 9 or 10 or 11
13. MeSH descriptor Wakefulness, this term only
14. MeSH descriptor Sleep Disorders explode all trees
15. (sleep NEAR/3 disorder*:ti,ab,kw or (sleep NEAR/3 problem*:ti,ab,kw or (sleep NEAR/3 patterns*:ti,ab,kw
16. (waking):ti,ab,kw OR (insomni*):ti,ab,kw
17. 13 or 14 or 15 or 16 (search only Clinical trials)
18. 1 and 6 and 17

EMBASE
#1 'melatonin'/exp AND [embase]/lim
#2 'adolescent'/de OR 'preschool child'/exp OR 'child'/de OR 'infant'/de AND [embase]/lim
#3 'baby'/exp OR 'toddler'/de OR 'juvenile'/de
#4 'baby'/exp OR 'toddler'/exp OR 'juvenile'/exp AND [embase]/lim
#5 bab* OR infant* OR child* OR boy* OR girl* OR toddler* OR preschool* OR teen* OR schoolchild* OR adolescent* OR juvenile* AND [embase]/lim
#6 #2 OR #4 OR #5
#7 'visual disorder'/exp AND [embase]/lim
#8 (vision* OR visual*) NEAR/3 (handicap* OR disabi* OR impair* OR disorder*) AND [embase]/lim
#9 visually impaired persons'/exp OR 'visually impaired person' AND [embase]/lim
#10 'blindness'/exp AND [embase]/lim
#11 #7 OR #8 OR #9 OR #10
#12 'sleep disorder'/exp AND [embase]/lim
#13 'insomnia'/de AND [embase]/lim
#14 'wakefulness'/de AND [embase]/lim
#15 sleep NEAR/3 (disorder* OR problem* OR pattern*) AND [embase]/lim
#16 #12 OR #13 OR #14 OR #15
#17 #1 AND #6 AND #11 AND #16
#18 #1 AND #6 AND #11 AND #16 AND ('clinical study'/de OR 'clinical trial'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'human'/de OR 'major clinical study'/de OR 'randomized controlled trial'/de OR 'systematic review'/de)
#19 'melatonin'/mj AND [embase]/lim
#20 #6 AND #11 AND #16 AND #18 AND #19

CINAHL
S15 S1 and S4 and S13 and S14
S14 S5 or S6 or S7 or S8
S13 S9 or S10 or S11 or S12
S12 "insomnia"
S11 (sleep N3 disorder*) OR (sleep N3 problem*) or (sleep N3 pattern*)
S10 (MH "Insomnia")
S9 MH "Sleep Disorders"
S8 visual* N3 handicap* OR visual* N3 disabi* OR visual* N3 disabl* OR visual* N3 impair* OR visual* N3 disorder*
S7 vision* N3 handicap*OR vision* N3 disabi*OR vision* N3 disabl* OR vision* N3 impair* OR vision* N3 disorder*
S6 visually impaired person OR visually impaired persons
S5 MH "Vision Disorders" OR MH "Blindness"
S4 S2 or S3
S3 baby or babies or infant* or child* or boy* or girl* or toddler* or preschool* or schoolchild* or adolescent* or juvenile*
## Appendix 2. Table of unused methods

| Data extraction and management | Study methods:  
|                              | • Randomisation technique.  
|                              | • Method of allocation concealment.  
|                              | • Blinding method (for those giving the treatment, participants, outcome assessors).  
|                              | • Design (cross-over, cluster-randomisation, intention-to-treat etc.).  
|                              | Study methods:  
|                              | • Randomisation technique.  
|                              | • Method of allocation concealment.  
|                              | • Blinding method (for those giving the treatment, participants, outcome assessors).  
|                              | • Design (cross-over, cluster-randomisation, intention-to-treat etc.).  
|                              | Participants:  
|                              | • Inclusion/exclusion criteria.  
|                              | • Gender proportions.  
|                              | • Age range.  
|                              | • Diagnosis and criteria used.  
|                              | Interventions:  
|                              | • Type of intervention (melatonin versus placebo, other drug, no medication, light therapy, behavioural therapy).  
|                              | • Dose of melatonin.  
|                              | • Route of administration of melatonin.  
|                              | • Time of administration of melatonin.  
|                              | • Duration of melatonin treatment.  
|                              | • Type of control.  
|                              | • Assessment of compliance.  
|                              | Outcome and analysis:  
|                              | • Primary outcome used and associated data.  
|                              | • Secondary outcomes used and associated data.  
|                              | • Length of follow up.  

| Assessment of risk of bias in included studies | To assess the risk of bias for each individual study, two authors planned to use the Cochrane Collaboration tool for assessing risk of bias (Higgins 2008, section 8.5.1). We would have resolved any disagreement by consultation with a third author. We would have assessed the degree to which:  
|                                                 | • the allocation sequence was adequately generated (sequence generation);  
|                                                 | • the allocation was adequately concealed (allocation concealment);  
|                                                 | • knowledge of the allocated intervention was adequately prevented during the study (blinding);  
|                                                 | • incomplete outcome data were adequately addressed;  
|                                                 | • reports of the study were free of suggestion of selective outcome reporting; and  
|                                                 | • the study was apparently free of other problems that could put it at risk of bias. |
We did not find any study that met the review's inclusion criteria with respect to risk of bias, so meta-analysis was not possible in this present review. Should relevant RCTs be undertaken in the future, we recommend that the study design allow for assessment of the study using the Cochrane risk of bias assessment criteria, as stated above. Each of these criteria will be rated as low risk of bias, high risk of bias or unclear risk of bias where the risk of bias is uncertain or unknown.

For the nine trials excluded after detailed evaluation, we assessed allocation of RCTs based on randomisation concealment as follows (Higgins 2008):

- (A) Indicates adequate allocation concealment; for example, randomisation by third party or a priori using sealed envelopes.
- (B) Indicates uncertainty about the adequacy of allocation concealment; for example, where method of concealment is not reported.
- (C) Indicates allocation was inadequately concealed; for example, open random number lists or quasi-randomisation such as alternation, day of the week, case number.

**Measures of treatment effect**

We had no included studies so meta-analysis was not possible. Should relevant studies be identified in the future, we will conduct any meta-analysis according to the methods detailed below.

We will use Review Manager 5.1 to perform the statistical analysis. For dichotomous (binary data), we will use the relative risk (RR) with a 95% confidence interval (CI) to summarise the results for each study. We will use mean difference (MD) where the same outcome measure is reported in more than one study. We will use the standardised mean difference (SMD) where different outcome measures of the same construct are reported. We will report continuous data that are skewed in a separate table and will not calculate treatment effect sizes to minimise the risk of applying parametric statistics to data that depart significantly from normal distribution. We will define skewness as occurring when, for a scale or measure with positive values and a minimum value of zero, the mean is less than twice the standard deviation (Altman 1996).

**Unit of analysis issues**

Should relevant studies be identified in the future, any meta-analysis will be conducted according to the methods detailed below. Where trials have used clustered randomisation, we anticipate that study investigators would have presented their results after appropriately controlling for clustering effects (robust standard errors or hierarchical linear models). If it is unclear whether a cluster-randomised trial has used appropriate controls for clustering, we will contact the study investigators for further information. We will use the generic inverse variance method for cluster-randomised trials as well as cross-over trials (Elbourne 2002).

**Dealing with missing data**

Missing data may consist of statistical data (for example, standard deviations for means), or raw follow-up data for participants who dropped out of a study. Should relevant studies be identified in the future, the study authors will be contacted in cases of missing data. Attrition will be explored as a possible source of heterogeneity and bias.
Assessment of heterogeneity

Should relevant studies be identified in the future, any meta-analysis will be conducted according to the following methods. We will assess consistency of results across studies by examining the I^2 statistic (Higgins 2008), a quantity which describes approximately the proportion of variation in point estimates that is due to heterogeneity rather than sampling error. We will assess heterogeneity by visual inspection of the outcomes tables and forest plots. We will assess the extent of between-trial differences and the consistency of results of meta-analysis by visual inspection of forest plots and the Chi^2 test for heterogeneity (where a significance level less than 0.10 will be interpreted as evidence of heterogeneity). In addition, we will employ a Chi^2 test of homogeneity to determine the strength of evidence that heterogeneity is genuine. Where statistical heterogeneity is found, we will look for an explanation. We will consider studies appropriate for meta-analysis when they show comparability/lack of heterogeneity in terms of participants, interventions, controls and outcomes.

Assessment of reporting biases

Should relevant studies be identified in the future, we will draw funnel plots (effect size against standard error) if a sufficient number of studies are found. Asymmetry of the plot may indicate publication bias, although it may also represent a true relationship between trial size and effect size. In case of such relationship, we will examine the clinical diversity of the studies further as a possible explanation (Egger 1997).

Data synthesis

Should relevant studies be identified in the future, we will undertake quantitative syntheses of data by using fixed- and random-effects models of meta-analysis. We will perform meta-analyses for studies with similar participants, interventions, comparators and outcome measures.

Subgroup analysis and investigation of heterogeneity

Should relevant studies be identified in the future, depending on the data reported and where heterogeneity is identified, we may perform the following subgroup analyses:
1. nature of sleep problem (initiating sleep, maintenance, sleep phase);
2. age (three months to one year, one to five years, five to 10 years, 11 years or more);
3. degree of visual impairment (type of visual impairment); and
4. concomitant medication.

Sensitivity analysis

Should relevant studies be identified in the future, we will perform sensitivity analyses as follows to explore whether the results of the review are robust and not affected by the decisions we make about inclusion
1. We will group studies qualitatively into low, moderate or high risk of bias and meta-analyses performed by group.
2. We will make comparisons between studies which use a cross-over design versus parallel-group design.
3. We will repeat the analysis using methods to handle the missing data, as suggested by Higgins et al (see above under 'Dealing with missing data').
WHAT’S NEW

Last assessed as up-to-date: 27 September 2011.

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<th>Event</th>
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<td>4 April 2011</td>
<td>Amended</td>
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HISTORY

Protocol first published: Issue 4, 2010
Review first published: Issue 11, 2011

CONTRIBUTIONS OF AUTHORS

<table>
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<th>Contributors</th>
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<tr>
<td>Draft the protocol</td>
<td>All</td>
</tr>
<tr>
<td>Develop a search strategy</td>
<td>Sohil Khan, Helen Heussler, Treasure McGuire, Vicki Flenady</td>
</tr>
<tr>
<td>Select which trials to include (two people + one arbiter in the event of dispute)</td>
<td>Helen Heussler, Carolyn Dakin, David Pache</td>
</tr>
<tr>
<td>Extract data from trials (two people)</td>
<td>Sohil Khan, Vicki Flenady</td>
</tr>
<tr>
<td>Enter data into RevMan (Cochrane software)</td>
<td>Sohil Khan</td>
</tr>
<tr>
<td>Carry out the analysis</td>
<td>Vicki Flenady, Treasure McGuire</td>
</tr>
<tr>
<td>Interpret the analysis</td>
<td>Helen Heussler, Carolyn Dakin, Vicki Flenady, David Pache, Bruce Charles, Ross Norris, David (Gus) Cooper</td>
</tr>
<tr>
<td>Draft the final review</td>
<td>All</td>
</tr>
<tr>
<td>Keep the review up to date</td>
<td>Sohil Khan</td>
</tr>
</tbody>
</table>
DECLARATIONS OF INTEREST

Sohil Khan - none known.
Helen Heussler - none known.
Treasure McGuire - none known.
Carolyn Dakin - none known.
David Pache - none known.
David Cooper - none known.
Ross Norris - none known.
Vicki Flenady - none known.
Bruce Charles - none known.

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Internal sources
- Mater Health Services, Brisbane, Australia.
- School of Pharmacy, The University of Queensland, Brisbane, Australia.

External sources
- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the nine trials that were excluded after detailed evaluation, we evaluated the assessment of allocation of RCTs based on randomisation concealment (Higgins 2008). It helped in determining the quality and potential for bias while we include those reasons in the Characteristics of excluded studies. Type of outcome measures are reduced (as suggested by the reviewer).