Melatonin for non-respiratory sleep disorders in typically developing children (Protocol)


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Melatonin for non-respiratory sleep disorders in typically developing children

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of melatonin for non-respiratory sleep disorders in typically developing children, with regard to improvement in sleep initiation, sleep maintenance and sleep scheduling, when compared with placebo, other medication for sleep disorders, psychological/behavioural therapy, light therapy or no treatment.
BACKGROUND

Human beings spend approximately one-third of their lifetime sleeping (Keith 2008). As one of the most fundamental processes of life, sleep has attracted a great deal of attention from ancient philosophers to present day biomedical researchers. A sleep disorder exists when a lower quality of sleep results in impaired functioning or excessive sleepiness. Sleep disorders directly affect cognitive performance, including executive functioning such as abstract reasoning, goal-directed behaviour, and creative processing (Dewald 2010). Approximately one quarter of all children experience some type of sleep problem during childhood (Owens 2008). Sleep is crucial for children’s learning, memory processes and school performance. Problems with initiating and maintaining sleep are common in children and can be seen as an indicator of poor sleep quality (Dewald 2010). The management of sleep disorders in paediatrics is challenging. Since the beginning of the 1970s, considerable research has been done in paediatric sleep medicine, and this has grown steadily over the past two decades (Marcus 2006). However, the international scientific establishment engaged in the study of basic, clinical and population pharmacology in children is extremely limited (MacLeod 2007).

Melatonin is a neurohormone that regulates day-night circadian rhythm. Melatonin concentration differs at different stages of life (Zhadnova 2005). 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 and treatment strategies warrants an evaluation of the therapeutic outcomes of the neurohormone melatonin in different age groups.

Description of the condition

Sleep can be defined as an active, repetitive and reversible state of perceptual disengagement from, and unresponsiveness to, the environment (Carskadon 2005). The term ‘sleep disorders’ is used as a generic term that applies to various components of sleep that can become disrupted, for example, delayed phase syndrome, sleeplessness, excessive sleepiness, night-time episodes of disturbed behaviour and/or persistent early morning awakenings (Carr 2007). Non-respiratory sleep disorders in children without underlying medical or neurodevelopmental conditions are common. Although sleep-disordered breathing may be the common reason for referral, almost 25% of these children may have a second sleep disorder associated with equally important clinical morbidity (Owens 1998). Some of the common non-respiratory sleep problems in such children include insufficient sleep, bedtime resistance, sleep-walking, delayed sleep phase, behaviour insomnia of childhood and narcolepsy (Moore 2006). In many children, initial bedtime resistance may lead to delayed sleep phase causing insufficient sleep. Non-respiratory sleep disorders in typically developing children without underlying medical or psychiatric disorders are often overlooked and under-managed. Sleep disorders can adversely impact almost all aspects of a child’s functioning, with significant distress to caregivers (Meltzer 2006). Poor sleep quality, insufficient sleep and sleepiness are significantly associated with poorer school performance. 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 (Sadegh 2003). Other adverse health outcomes include deleterious effects on the cardiovascular, immune and numerous metabolic systems (Smaldone 2007). Glucose metabolism, obesity and endocrine function are also impaired and accidental injuries increased.

How the intervention might work

One of the commonest causes of sleep problems in children without comorbid conditions is an irregular sleep schedule. A late sleep onset in the night secondary to bedtime resistance or difficulty in settling with daytime drowsiness is often observed and there is a measurable delay in sleep phase. As timing of sleep plays an important role in sleep problems in typically developing children, melatonin supplementation may help to regulate the day-night biological rhythm. 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). Most studies have evaluated the effect of melatonin in fast-release preparation, which is mainly effective for sleep induction and delayed sleep onset. Recently, controlled-release formulations of melatonin have been studied for sleep maintenance (Giannotti 2006). Restored sleep in children helps them to be healthier and calmer, and more predictable, co-operative and playful, which reduces the burden of care for their families. Thus increased recogni-
tion and treatment of sleep disorders will positively affect a child's well-being and have significant effects on parental function as well.

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

Sleep problems can have a significant adverse impact on children's development and yet there is a lack of research into how to manage them in children without underlying comorbidities. Melatonin as a medication varies widely in its availability and use. In some countries, it is only available as a food supplementation without regulation; in others, it is not available for use in children at all and families may resort to buying through the internet to avail themselves of its benefits. Clinicians are cautious to prescribe melatonin in children without underlying comorbidities due to lack of evidence. Although melatonin has been used in children with neurodevelopmental disorders and visual impairment, efficacy of exogenous melatonin in the management of sleep disorders in typically developing children is not known. Hence there is a need to evaluate the efficacy and safety of exogenous melatonin in typically developing children.

**OBJECTIVES**

To assess the effects of melatonin for non-respiratory sleep disorders in typically developing children, with regard to improvement in sleep initiation, sleep maintenance and sleep scheduling, when compared with placebo, other medication for sleep disorders, psychological/behavioural therapy, light therapy or no treatment.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

Randomized controlled trials including cross-over studies and quasi-randomized trials in which participants were allocated to groups on the basis of a quasi-random process such as alternate hospital numbers or odd/even date of birth.

**Types of participants**

Typically developing children aged three months to 18 years with a sleep disorder. For the purpose of the review, typical development is defined as no identified delayed or abnormal development of neurological, genetic or metabolic origin. A sleep disorder is defined as a difficulty in initiating, maintaining or scheduling of sleep, excluding disrupted sleep induced by respiratory disorders.

**Types of interventions**

Melatonin supplementation (in all doses, formulations, routes and durations) compared with placebo, other medication for sleep disorders, psychological/behavioural therapy, light therapy or no treatment.

**Types of outcome measures**

**Primary outcomes**

1. Improved sleep - timing of sleep.
2. Improved sleep - sleep efficiency.
3. Adverse drug reaction.

**Secondary outcomes**

1. Quality of life.
2. Daytime behaviours (behaviours of interest that have been identified in relation to sleep disorders in this group would include i) hyperactivity, ii) measures of attention, iii) measures of emotional/mood states etc).
3. Other adverse events.
4. Family functioning.
5. Psychosocial impact, for example, depression.

We will evaluate timing of sleep, sleep efficiency and adverse drug reactions through subjective and objective means that could include actigraphy, polysomnography, sleep diaries, as used by the included studies. We will evaluate secondary outcomes like quality of life, daytime behaviour through subjective measures like Likert scales and/or validated measures like the Child Behaviour Checklist (Kramer 1992) or health-related quality of life questionnaires. We will take into consideration the study period and follow-up as described in the included studies.

We will include timing of sleep, sleep efficiency, adverse drug reaction and quality of life in the ‘Summary of findings’ table.
All the searches will include appropriate truncation and possible alternative spellings. Where appropriate, we will apply a trials search filter.

We will use the following search strategy to search MEDLINE:
1 Melatonin/
2 melatonin.tw.
3 1 or 2
4 exp Sleep Disorders/
5 (insomnia$ or in-somnia$).tw.
6 dyssomnia$.tw.
7 (parasomnia$ or para-somnia$).tw.
8 somnambulis$.tw.
9 (sleepwalk$ or sleep-walk$).tw.
10 nocturnal wander$.tw.
11 myoclonus.tw.
12 (sleep$ adj3 (depriv$ or disrupt$ or disorder$ or problem$ or pattern$ or schedul$)).tw.
13 (sleep$ or somnolen$) adj3 (initiat$ or maintain$ or excess$)).tw.
14 (hypersomnia$ or hyper-somnia$ or hypersomnolenc$ or hyper-somnolenc$).tw.
15 (wakeful$ or waking or sleep-wake$ or sleepless$).tw.
16 or/4-15
17 infant/
18 exp child/
19 adolescent/
20 (baby or babies or infant$ or child$ or boy$ or girl$ or toddler$ or preschool$ or pre-school$ or teen$ or schoolchild$ or adolescence$ or juvenile$).tw.
21 or/17-20
22 3 and 16 and 21
23 randomized controlled trial.pt.
24 controlled clinical trial.pt.
25 randomi#ed.ab.
26 placebo$.ab.
27 drug therapy.fs.
28 randomly.ab.
29 trial.ab.
30 groups.ab.
31 or/23-30
32 exp animals/ not humans.sh.
33 31 not 32
34 22 and 33

This will be modified, where necessary, to search the other databases listed. Where appropriate, we will apply a trials search filter.

**Data collection and analysis**

**Selection of studies**

Review author pairs will independently screen titles and abstracts identified in the search and indicate which reports should be retrieved. If there is insufficient information in the title and abstract to make such decisions, we will retrieve the full text. Two review authors will independently read full reports and determine whether these studies meet the inclusion criteria. Disagreements will be resolved within the team. We will document the principal reason for exclusion of each study that seems to meet the inclusion criteria but on closer inspection does not.

**Data extraction and management**

Two authors will extract data independently using a data extraction sheet. We will enter the data into Cochrane Collaboration’s Review Manager 5 software (RevMan 2008). If data are not available from the published trials we will contact the authors for further information.

We will extract the following data:

- Author, year of publication and location.
- Clinical setting (primary/secondary care/inpatient/outpatient/residential care).
- Ethics approval.
- Study methods
  - Randomisation technique.
  - Method of allocation concealment.
  - Blinding method (for those giving the treatment, participants, outcome assessors).
  - Design (cross-over, cluster-randomisation, etc).
- Participants
  - Inclusion/exclusion criteria.
  - Gender proportions.
  - Age range.
  - Diagnosis and criteria used.
  - Rates of drop-out/attrition.
  - Number randomized (or allocated).
- Interventions
  - Type of intervention (melatonin versus placebo, other drug, no medication, light therapy, behavioural therapy).
  - Dose of melatonin.
  - Formulation 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.

Primary outcome (timing of sleep, sleep efficiency and adverse drug reaction) has been measured by a variety of methods (timing of sleep, sleep efficiency and adverse drug reactions). Published evidence supports actigraphy as the most convenient and widely used objective method followed by polysomnography (Spruyt 2011). Sleep diaries present the most subjective evidence for monitoring sleep quality (Bates 2002). Therefore, primary outcome measures will be assessed in accordance with the following ranking of these techniques: 1. actigraphy, 2. polysomnography, 3. sleep diaries.

Assessment of risk of bias in included studies
To assess the risk of bias for each individual study, two authors will use the Cochrane Collaboration tool for assessing risk of bias (Higgins 2008, section 8.5.1). We will resolve any disagreement by consultation with a third author. We will assess 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); where relevant, blinding of both participants and blinding of outcome assessors will be addressed;
• 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 high risk of bias.

We will allocate each domain one of three possible categories for each of the included studies:
(A) high risk of bias;
(B) low risk of bias; or
(C) unclear or unknown risk of bias.

Other potential sources include: i) the possibility that the conduct of the study is affected by interim results (for example, recruiting additional participants from a subgroup showing more benefit); ii) there is pre-randomisation administration of an intervention that could enhance or diminish the effect of a subsequent randomisation intervention, etc.

Measures of treatment effect
We will calculate unadjusted treatment effects using the Review Manager 5 software (RevMan) where possible (RevMan 2008).

Dichotomous outcome data
We will calculate odds ratios (ORs) and 95% confidence intervals (CIs) for dichotomous outcomes. For meta-analyses of dichotomous outcomes that are included in ‘Summary of findings’ tables, we will express the results as absolute risks, using high and low observed risks among the control groups as reference points.

Continuous outcome data
We will calculate mean differences (if all studies use the same measurement scale) or standardised mean differences (SMDs) (if studies use different measurements scales) and 95% CIs for continuous outcome measures. If necessary, we will compute effect estimates from P values, t statistics, ANOVA tables or other statistics as appropriate. 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
Cluster-randomised trials
Where trials have used clustered randomisation, we anticipate that study investigators will have presented their results after appropriately controlling for clustering effects (robust standard errors or hierarchical linear models). We will contact authors for further information if this is unclear. If the clustering effect was not controlled for, we will request individual participant data to calculate an estimate of the intra-cluster correlation coefficient (ICC). If individual participant data are not available, we will obtain external estimates of the ICC from similar studies or available resources. Once established, we will use the ICC to re-analyse the trial data to obtain approximate correct analyses. We will then enter these data into RevMan (RevMan 2008) to analyse effect sizes and confidence intervals using the generic inverse variance method (Higgins 2008). If insufficient information is available to control for clustering in this way, we will enter data into RevMan using individuals as the unit of analysis. We will then perform sensitivity analyses to assess the potential bias that may have occurred as a result of the inadequately controlled clustered trials. We will also perform sensitivity analyses if the ICCs were obtained from external sources to assess the potential biasing of inadequately controlled cluster trials (Donner 2001).

Cross-over trials
We will pool data from cross-over trials according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) and by Elbourne 2002. We will enter mean within-participants difference and standard error of the mean difference into RevMan using the generic inverse outcome type. Where the standard error of the mean difference is not reported, we will request the original data from study authors or impute the value. We will calculate correlation coefficients from studies where sufficient data is available and if these values are consistent they will be used to calculate the missing standard errors for other studies.
Dealing with missing data

We will assess missing data and drop-outs/attrition for each study. We will assess and report numbers, reasons and characteristics of drop-outs. We will contact authors for missing data. In meta-analysis we will use data from all original participants where possible and report when that is not the case. If missing data are not available in studies, we will conduct a sensitivity analysis to assess potential bias in the analysis. We will also discuss the extent to which the results might be biased by missing data. For missing continuous data, we will provide a qualitative summary along with the proportion of missing data. The standard deviation (SD) of the outcome measures should be reported for each group in each trial. If the data are not available, we will impute standard deviations using relevant data such as standard errors (SE) or correlation coefficients from other similar studies (Follmann 1992), but only after seeking statistical advice.

Assessment of heterogeneity

We will use a random-effects model when studies appropriate for meta-analysis show comparability/lack of heterogeneity in terms of participants, interventions, controls and outcomes. We will describe statistical heterogeneity by computing $I^2$ (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 visually inspect outcomes tables and forest plots to assess the extent of between-trial differences and consistency of meta-analysis results. In addition, we will employ a Chi $^2$ test for homogeneity to determine the strength of evidence that heterogeneity is genuine.

Assessment of reporting biases

We will assess the possibility of publication bias by constructing funnel plots to investigate any relationship between effect size and standard error. Such a relationship could be due to publication or related biases, or due to systematic differences between small and large studies. Where such a relationship is identified, we will further examine the experimental diversity of the studies as a possible explanation (Egger 1997).

Data synthesis

We will use random-effects meta-analysis due to clinical or methodological heterogeneity between studies sufficient to suggest treatment effects may differ between trials. If the trials examine the same intervention with same population and method, we may use fixed-effect inverse variance meta-analysis. If we identify substantial heterogeneity in a fixed-effect meta-analysis, we will note this and repeat the analysis using a random-effects method. We will assess the possible source(s) of heterogeneity using subgroup and sensitivity analysis. We will undertake separate analysis for different treatment comparisons.

Subgroup analysis and investigation of heterogeneity

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; more than one year to five years; more than five years to 10 years; 11 years or more);
3. melatonin dose.

Sensitivity analysis

We will conduct sensitivity analyses to determine whether findings are sensitive to restricting the analyses to studies judged to be at low risk of bias. In these analyses, we restrict the analysis to: (a) only studies with low risk of selection bias (associated with sequence generation or allocation concealment); (b) only studies with low risk of performance bias (associated with issues of blinding); (c) only studies with low risk of attrition bias (associated with completeness of data). In addition, we will assess the sensitivity of findings to any imputed data. We will repeat the analysis using methods to handle the missing data, as suggested by Higgins 2008 (see Dealing with missing data).

Acknowledgements

To the Cochrane review group for timely instructions.
Additional references

Altman 1996

Arendt 2005

Bates 2002

Carr 2007

Carlsadon 2005

Dewald 2010

Donner 2001

Dijk 1997

Donner 2001

Egger 1997

Elbourne 2002

Follmann 1992

Giannotti 2006

Higgins 2008

Keith 2008

Kramer 1992

MacLeod 2007

Marcus 2006
Marcus CL. And miles to go before we sleep. Sleep Medicine Reviews 2006;10:79–81.

Meltzer 2006
Meltzer LJ, Mindell JA. Impact of a child’s chronic illness on maternal sleep and daytime functioning. Archives of Internal Medicine 2006;166:1749–55.

Moore 2006

Owens 1998

Owens 2008

Reiter 1991

RevMan 2008

Sadeh 2003

Smaldone 2007
Smaldone A, Honig JC, Byrne MW. Sleepless in America: inadequate sleep and relationships to health and well being.

**Spruyt 2011**

**Utiger 1992**

**Zhadnova 2005**

* Indicates the major publication for the study

**HISTORY**

**CONTRIBUTIONS OF AUTHORS**

<table>
<thead>
<tr>
<th>Task</th>
<th>Contributors</th>
</tr>
</thead>
<tbody>
<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 trial to include (2 people and 1 arbiter in the event of dispute)</td>
<td>Helen Heussler, Carolyn Dakin and David Pace</td>
</tr>
<tr>
<td>Extract data from trials (2 people)</td>
<td>Sohil Khan, Vicki Flenady</td>
</tr>
<tr>
<td>Enter data into RevMan</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>
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</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>
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</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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