Melatonin for non-respiratory sleep disorders in children with neurodevelopmental disorders (Protocol)


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Melatonin for non-respiratory sleep disorders in children with neurodevelopmental disorders

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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 role of melatonin for non-respiratory sleep disorders in children with neurodevelopmental disorders for improvement in sleep initiation, sleep maintenance and sleep scheduling when compared with either placebo, other medication for sleep disorders, psychological/behavioural treatment, light therapy or no treatment.
**BACKGROUND**

Sleep problems occur in approximately 80% of children with moderate to severe neurodevelopmental disorders, adversely affecting the quality of life for them and for their families. Neurodevelopmental disorders encompass a broad range of conditions that include congenital anomalies (Q00-Q99), diseases of the nervous system (G00-G89), mental and behavioural disorders (F00-F99) and neoplasms (C00-D48) (Little 2000). Specifically, sleep problems have been identified in children with Attention Deficit Hyperactivity Disorder, Rett syndrome, autism spectrum disorders, intellectual deficits, visual impairment, epilepsy and brain damage (Jan 2006). Sleep problems in children with these disorders warrant special attention for several reasons: their prevalence, severity, and their adverse impact upon carers. They represent one of the most common reasons parents or caregivers of children with neurodevelopmental problems seek medical attention.

Over the past decade, it has become apparent that circadian rhythm sleep disorder (CRSD) is the most common sleep difficulty in this population of children (Jan 2004). CRSD is characterised by disruption in the sleep-wake cycle. For example, neurological lesions may affect the endogenous circadian rhythm generating and entrainment (the alignment of the internal biological clock rhythm, including its phase and period, to external time cues, such as the natural dark-light cycle) circuitry at different levels in the brain (Jan 2006). Non-24-hour sleep-wake syndrome is characterized by progressive increase of sleep phase onset delay, paralleled by delays of melatonin secretion. It can be caused by lesions to the eyes and/or retinohypothalamic pathways. Destruction of the specialised group of retinal ganglion cells, which pass photic information to the suprachiasmatic nucleus (SCN), can result in 'free-running' sleep wake rhythm (Jan 2006), i.e. the circadian rhythm is not synchronised with external cues. Children with severe brain damage or those with specific neurological syndromes may have abnormal autonomic function resulting in disturbed circadian rhythm. When there is marked, acute or chronic widespread cerebral disturbance, the noradrenaline-mediated tonic control of melatonin secretion may be compromised and/or inappropriately timed. This disruption is associated with fragmented sleep maintenance, frequently with sleep phase onset delay and early morning wakening (Jan 2006).

Melatonin concentration differs at different stages of life (Zhadnova 2005). In utero, the foetus receives a circadian melatonin message from the maternal pineal gland through placental transfer. This helps to entrain the foetal circadian rhythm to the mother's own day-night cycle. Newborn babies lack melatonin secretion for the first three months of life, but a well-developed circadian melatonin cycle is seen in the one-year old infant. During childhood (age one to 10 years), the amplitude of the melatonin rhythm is generally believed to be greatest, with 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. Once adults, most individuals maintain a circadian melatonin cycle; however, the amplitude of the nocturnal melatonin peak varies widely. Circulating concentrations in the elderly are significantly lower than in young adults. Though used quite extensively, there is a distinct lack of data regarding the impact of exogenous melatonin on its endogenous rhythmicity. There is evidence to suggest that melatonin can both phase advance, entrain or delay a circadian rhythm, i.e. bring forward, set or delay the timing of an endogenous rhythm such as sleep (Lewy 1997; Skene 2003). It is therefore necessary to evaluate the therapeutic outcomes of the neurohormone melatonin in different age groups and in different neurodevelopmental disorders.

**Description of the condition**

The term 'sleep disorders' is used as a generic term for various components of sleep that can become disrupted, for example, delayed phase syndrome, sleeplessness, excessive sleepiness, nighttime episodes of disturbed behaviour and/or persistent early morning wakenings (Carr 2007). Neurodevelopmental disorders can encompass a broad range of conditions (Little 2000); for the purpose of this review, we will include the categories of congenital anomalies, diseases of the nervous system, and mental and behavioural disorders.

Knowledge of the management of sleep problems in children with neurodevelopmental disorders is mostly dependent on empirical practice. The varying nature of the underlying pathophysiology, along with different kinds of sleep disorder and scarcity of pharmacotherapeutic options, leads to widespread use of preparations lacking supportive evidence. A recent consensus statement on the pharmacological management of insomnia in children and adolescents concluded that studies on the safety and efficacy of these treatments are urgently needed (Mindell 2006). With the exception of melatonin, there are very few published studies on pharmacotherapy of sleep disorders in the target group. Melatonin therapy in sleep disorders with underlying neurodevelopmental anomalies shows a 70% to 90% response rate. These children frequently have CRSD, which is associated with abnormally-timed or inadequate melatonin secretion and thus presumably is sensitive to the rhythm-entraining (synchronizing) effects of exogenous melatonin (Skene 1996). Non-CRSD, which is not accompanied by abnormal melatonin secretion, is less sensitive to exogenous melatonin therapy (Jan 2006). Melatonin has been subject to numerous studies in children with neurodevelopmental disorders but very few of them have been randomised controlled trials. These studies evaluated melatonin therapy in children with tuberous sclerosis, Rett syndrome, intellectual disability, epilepsy and developmental disabilities. Neurological disability was the focus for the selection of participants in these studies and they had a variety of different sleep disorders. As not all sleep problems respond to melatonin therapy, there is a need to evaluate the results of the trials for a valid recommendation.
Description of the intervention

Melatonin, or N-acetyl-5-methoxytryptamine, is a small lipid-soluble indoleamine molecule released as a hormone from the pineal gland. It has been found to have a remarkable array of functions that unequivocally link it to neurological and behavioural disorders. The endogenous nocturnal production of melatonin and its relationship to physiological changes associated with the nocturnal period has led to it being named 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 timing of 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). By 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). As a hypnotic and a substance that affects the biological clock (chronobiotic), melatonin is being used for the treatment of age-related insomnia, and CRSD that include delayed sleep phase syndrome, non-24-hour sleep-wake syndrome, 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 pubertal stage children. It is important to evaluate the effect of melatonin on children in different age ranges, with different types of sleep problems and with different types of neurodevelopmental disorders.

Why it is important to do this review

The incidence of sleep disorders is high in children with underlying neurodevelopmental abnormalities and a recommended pharmacotherapeutic option for them is lacking. 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, decreased vigilance, and memory impairment, and children with neurodevelopmental disorders are highly susceptible as they may have underlying neurological complications that make their own contribution to neurocognitive performance deficits. Other adverse health outcomes include deleterious effects on the cardiovascular, immune and numerous metabolic systems (Smaldone 2007). Glucose metabolism, obesity and endocrine function are impaired. There is an increase in accidental injuries. Adolescents may be at increased risk for sleep disturbances and inadequate sleep. Distress to the family and caregivers is one of the major adverse impacts (Meltzer 2006). Poor sleep quality, insufficient sleep and sleepiness are significantly associated with poor school performance. Restored sleep in children helps them to be healthier, calmer, more predictable, co-operative and playful. The burden of care is reduced for their families (Jan 2006). 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 children with neurodevelopmental disorders. This review seeks to address the gap.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies
Randomised controlled trials, including cross-over studies and quasi-randomised 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
Children aged three months to 18 years with a neurodevelopmental disorder and a sleep disorder. For the purposes of the review, we will define a sleep disorder as a disorder of initiating, maintaining or scheduling of sleep. Neurodevelopmental disorder will encompass a broad range of conditions that include congenital anomalies, diseases of the nervous system, and mental and behavioural disorders. Children with visual impairment will be excluded.

Types of interventions
Melatonin supplement (all doses, formulations, routes and duration) compared with placebo, other medication for sleep disorders, psychological/behavioural treatment, light therapy or no treatment.
Types of outcome measures

Primary outcomes
1. Improved timing of sleep.
2. Improved 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.

Timing of sleep, sleep efficiency and adverse drug reactions will be evaluated by subjective and objective means that could include actigraphy, polysomnography, sleep diaries or sleep-related questionnaires (for example, Sleep Disturbance Scale for Children (Bruni 1996)), as used by the included studies. Secondary outcomes like quality of life and daytime behaviour will be evaluated through subjective measures like Likert scales and/or objective measures such as the Developmental Behaviour Checklist (Einfeld 1995). 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 reactions and quality of life in our ‘Summary of findings’ table.

Search methods for identification of studies

Electronic searches
We will identify relevant trials through electronic searches of the following databases.
- Cochrane Central Register of Controlled Trials (CENTRAL), part of The Cochrane Library
- MEDLINE
- EMBASE
- CINAHL
- metaRegister of Controlled Trials

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 schedule$)).tw.
13 ((sleep$ or somnolence$) adj3 (initiat$ or maintain$ or excess$)).tw.
14 (hypersomnia$ or hyper-somnia$ or hypersonolence$ or hyper-somnolence$).tw.
15 (wakful$ 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 adolescents$ 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

We will modify this, where necessary, to search the other databases listed. We will not apply any language or date restrictions. All the searches will include appropriate truncation and possible misspellings. Where appropriate, we will apply a trials search filter.

Searching other resources
We will check the reference lists of identified trials and relevant review articles for possible trials missed by the electronic searches.

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. We will resolve disagreements 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 Review Manager 5 (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 randomised (or allocated) to groups.

**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.

The primary outcome (improved sleep) is measured by a variety of methods (timing of sleep, sleep efficiency and adverse drug reaction). Published evidence supports actigraphy as the most widely used and convenient objective method followed by polysomnography (Natale 2009; Owens 2009). 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). Any disagreement will be resolved 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 Cochrane Collaboration's Review Manager (RevMan) software where possible (RevMan 2008).

#### Dichotomous outcome data

We will calculate odds ratios (ORs) and 95% confidence intervals (CIs). 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 (MDs) if all studies use the same measurement scale, or standardised mean differences (SMDs) if studies use different measurements scales and 95% CIs. 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 skewedness 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 cluster trials. We will also perform sensitivity analyses if the ICCs were obtained from external sources to assess the potential biasing effects 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, the original data will be requested from study authors or the value will be imputed. Correlation coefficients will be calculated 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. Where possible, we will use data from all original participants in meta-analyses and will 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 the random-effects model of meta-analysis when studies show comparability/lack of heterogeneity with respect to 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 of 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, the experimental diversity of the studies will be further examined 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 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 a 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. concomitant medication;
4. melatonin dose; and/or
5. type of neurodevelopmental disorders (for example, Attention Deficit Hyperactivity Disorder, Rett syndrome, autism spectrum disorders etc).

If these data are not available in the published articles, we will seek this information from the authors.

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 will restrict 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 above).

ACKNOWLEDGEMENTS

To the Cochrane review group for timely instructions.

REFERENCES

Additional references

Altman 1996

Arendt 2005

Bates 2002

Bruni 1996

Carr 2007

Dijk 1997

Donner 2001

Egger 1997

Einfeld 1995

Elbourne 2002

Follmann 1992

Higgins 2008

Jan 2004
Jan 2006

Lewy 1997

Little 2000

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.

Mindell 2006

Natale 2009

Owens 2009

Pandi-Perumal 2007

Reiter 1991

Reiter 1998

RevMan 2008

Skene 1996

Skene 2003

Smaldone 2007

Utiger 1992

Zhadanova 2005

* Indicates the major publication for the study
Roles and responsibilities

<table>
<thead>
<tr>
<th>TASK</th>
<th>WHO HAS AGREED TO UNDERTAKE THE TASK?</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 trials to include (2 people and 1 arbiter in the event of dispute)</td>
<td>Helen Heussler, Carolyn Dakin and David Pache</td>
</tr>
<tr>
<td>Extract data from trials (2 people)</td>
<td>Sohil Khan, Vicki Flenady</td>
</tr>
<tr>
<td>Enter data into Review Manager 5 (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, Ross Norris, Bruce Charles</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
SOURCES OF SUPPORT

Internal sources

• NIL, Not specified.

External sources

• NIL, Not specified.