Systematic review of melatonin treatment in children with neurodevelopmental disabilities and sleep impairment

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CRD summary
This well-conducted review found improvements in time to sleep onset in children with neurodevelopmental disabilities and sleep impairment who were taking melatonin compared with placebo. However, the evidence was based on three trials of just 35 children. The authors highlighted the need for further, adequately powered trials to more clearly determine potential benefits and risks.

Authors' objectives
To assess the evidence for the use of melatonin for sleep disturbance in children with neurological and developmental problems.

Searching
The Cochrane Developmental, Psychosocial and Learning Problems Group’s Specialised Register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE and Zetoc were searched to 2002 with no language restrictions; the search terms were given. Abstracts submitted to scientific meetings were also included. In addition, the reference lists of retrieved articles were checked for additional articles, an expert was contacted, and pharmaceutical companies producing melatonin were approached.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were eligible for inclusion in this review. All of the included trials were double-blind and of a crossover design, and two included a washout period.

Specific interventions included in the review
Trials of oral melatonin, used in any dose for any length of time when compared with placebo, were eligible for inclusion. Sustained-release formulations were excluded. The doses of melatonin ranged from 0.5 to 7.5 mg, and melatonin was either given at specified times or one hour before bedtime.

Participants included in the review
Trials of children up to 18 years of age with any type of neurological disorder or neurodevelopmental disability and associated sleep disturbance were eligible for inclusion. The trials included children with at least moderate learning disability and fragmented sleep; Rett syndrome (most of whom were receiving anti-epileptic medication) and poor-quality sleep; and moderate developmental disability and significant sleep problems.

Outcomes assessed in the review
To be eligible, the trials had to report at least one of the following outcomes: total sleep time, time to sleep onset (sleep latency), number of awakenings, parental view of effect and adverse events. The included studies used sleep diaries completed by carers, or wrist actigraphy, to monitor sleep-wake activity.

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were evaluated for inclusion in the review, or how many reviewers performed the selection.

Assessment of study quality
The validity criteria included: allocation concealment; blinding of the participants, carers and assessors; and
completeness of follow-up. The authors did not state how the papers were assessed for the review, or how many reviewers performed the validity assessment.

**Data extraction**
Data on the specified outcomes were extracted and rechecked twice. Where data were incomplete, authors were contacted for any missing or supplementary information.

**Methods of synthesis**
- **How were the studies combined?**
  The studies were combined in a narrative.

- **How were differences between studies investigated?**
  Differences between the studies, in terms of participants, intervention details and outcomes, were explored within the report.

**Results of the review**
Three randomised crossover trials, with a total of 35 participants, were included in the review.

Whilst methods of allocation concealment and blinding appeared to be satisfactory in the included studies, two of the three studies did not include measures to minimise selection and attrition bias.

Two studies reporting time to sleep onset showed significant decreases: from 32 minutes (standard error 8.6) with placebo to 19 minutes (standard error 5.3) with melatonin in one trial, and from 1.2 hours (standard deviation 1.2) with placebo to 0.7 hours (standard deviation 0.8) with melatonin in the other. There was no statistically significant effect of melatonin compared with placebo on the other outcomes of total sleep time, night-time awakenings and parental opinions. No clinically significant adverse effects were reported in the included trials, although severe mood swings were reported in one child taking melatonin.

**Authors' conclusions**
Melatonin may be effective in reducing sleep latency in this patient group, and the more severe the sleep disorder the more obvious the improvement may be. The available trials were small, potentially underpowered and of limited quality.

**CRD commentary**
The review question was clear with defined inclusion criteria for the participants, interventions, study design and outcomes. A range of resources were searched and attempts were made to locate unpublished and foreign language material. Publication bias was not assessed. A range of threats to validity was examined, and details of the studies which might have impacted on the results were described in the report. Although some details of the review process were unclear, overall this was a well-conducted review that highlighted the need for further primary research in this area.

**Implications of the review for practice and research**
- **Practice:** The authors stated that melatonin may be effective in reducing sleep latency and that it is well tolerated for short-term use.

- **Research:** The authors highlighted the need for a well-designed, adequately powered, multicentre, randomised placebo-controlled, double-blind crossover trial to determine any potential benefit of melatonin in this patient group. Such a trial should consider short- and long-term effects, including possible adverse effects on epilepsy and on endocrine function.
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