Exogenous melatonin for sleep problems in individuals with intellectual disability: a meta-analysis

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CRD summary
The authors concluded that melatonin decreased sleep latency and the number of wakes per night and increased total sleep time in people with intellectual disabilities. These conclusions appeared supported by the evidence, but the limited search and incomplete reporting of review methods made it difficult to assess their reliability.

Authors' objectives
To evaluate the efficacy of melatonin for the treatment of sleep problems in people with intellectual disabilities.

Searching
MEDLINE, EMBASE and reference lists of identified studies were searched from 1990 to July 2008 for studies published in English. Search terms were reported.

Study selection
Randomised double-blind placebo-controlled trials that evaluated melatonin for the treatment of sleep problems in people with any type of diagnosis of intellectual disability were eligible for inclusion in meta-analyses. Studies had to report quantitative data for sleep latency, total sleep time or number of wakes per night.

The included studies evaluated different doses of melatonin; most used a fixed 5mg dose or a dose ranging from 2mg to 7.5mg depending on age or weight. Melatonin was administered at different times (mainly a fixed time between 6pm and 8pm or from 20 to 30 minutes before bedtime). Treatment duration ranged from one to four weeks. Most of the studies involved younger people aged 20 or under (range 1.1 to 20 years); in two studies participants' ages ranged from two to 28 or 78 years. Participants' diagnoses varied. Some studies included people with specific disorders, including Rett syndrome, tuberous sclerosis, autism spectrum disorder and Angelman syndrome. All studies used sleep diaries to assess outcomes; two studies also used actigraphic recordings. The review also assessed adverse effects.

The authors stated neither how papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed validity using the Downs and Black checklist. Inter-rater agreement was assessed.

Data extraction
For each study, mean differences with standard deviations (SD) were extracted or calculated for sleep latency, number of wakes per night and total sleep time. The authors did not state how many reviewers extracted data. Time measurements were converted from minutes to decimals.

Methods of synthesis
Pooled weighted mean differences (WMD) with 95% confidence intervals (CIs) were calculated using a random-effects model. Studies were weighted using the inverse variance method. Heterogeneity was examined using Galbraith plots and the T^2 statistic. Publication bias was assessed using funnel plots and tested using the adjusted rank correlation test.

Results of the review
Nine randomised controlled trials (RCTs) were included (n=183): seven crossover and two parallel-group RCTs. Crossover studies incorporated a one-week wash-out period between treatment periods. Sample size ranged from 6 to 51. Downs and Black quality scores ranged from 19 to 31 out of a maximum 32 (mean 25.28).

Compared to placebo, melatonin was associated with a statistically significant reduction in sleep latency (WMD -33.8
minutes, 95% CI -42.97 to -24.70, p<0.001; seven studies), a significantly reduced mean number of wakes per night (WMD -0.16, 95% CI -0.30 to 0.02, p=0.024; eight studies) and significantly increased total sleep time (WMD 0.83 hours, 95% CI 0.57 to 1.08, p<0.001; seven studies).

Funnel plots and statistical tests showed no evidence of publication bias. Galbraith plots apparently showed some evidence of statistical heterogeneity, but $T^2$ was zero.

**Adverse effects:** Four studies specified adverse effects. The authors stated that adverse effects were minor, with a similar incidence in melatonin and placebo phases.

**Authors’ conclusions**
Melatonin decreased sleep latency and the number of wakes per night and increased total sleep time in people with intellectual disabilities.

**CRD commentary**
The review question was clearly stated and inclusion criteria were appropriately defined. Limiting the search to English-language published studies identified in two databases plus references may have resulted in the omission of other relevant studies and raised the potential for publication and language biases. Methods were used to minimise reviewer errors and bias in the assessment of validity, but it was not clear whether similar steps were taken in study selection and data extraction. Only double-blind RCTs were included and validity was assessed, but only composite scores were presented which made it difficult to independently comment on the reliability of the evidence presented. Evidence came from short-term studies (a limitation that was acknowledged by the authors). Appropriate methods were used for the meta-analyses and heterogeneity was assessed. Assessment of the reliability of the conclusions was hindered by the limited search and incomplete reporting of review methods.

**Implications of the review for practice and research**
**Practice:** The authors stated that prescribing melatonin to people with sleep problems and intellectual disability may be useful provided the patient's biological clock (circadian rhythms) had been assessed.

**Research:** The authors stated that additional good-quality placebo-controlled RCTs were required to evaluate the optimal timing and dose of melatonin, circadian rhythm parameters and quality of life in patients with intellectual difficulties and their carers.

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