A systematic review of the effectiveness of oral melatonin for adults (18 to 65 years) with delayed sleep phase syndrome and adults (18 to 65 years) with primary insomnia

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CRD summary
This review assessed melatonin for adults with delayed sleep phase syndrome (DSPS) or primary insomnia (PI). The authors concluded that there is limited support for its use in people with DSPS, and little evidence to support its use for PI. These conclusions reflect the included evidence, which was poorly reported, but it is not clear whether they are reliable.

Authors' objectives
To assess the effectiveness of oral melatonin in adults with delayed sleep phase syndrome (DSPS) or primary insomnia (PI).

Searching
MEDLINE, PsycINFO, the Cochrane Database of Systematic Reviews, and the Cochrane Controlled Trials Register were searched from start of indexing to April 2004; the search terms were reported. Three sleep and two physiology journals were handsearched and the references of relevant studies were checked.

Study selection
Eligible studies examined oral melatonin as a therapeutic agent for the treatment of patients with PI or DSPS. Studies of adults aged 18 to 65 years were eligible for inclusion. Studies of patients with organic causes of sleep problems, patients who were blind or visually impaired, those with a learning disability, and those with a deteriorating neurological condition or a co-morbid physical condition which could influence sleep, were excluded from the review. A wide range of study designs were eligible for inclusion: randomised controlled trials (RCTs), controlled clinical trials, controlled single-case designs, uncontrolled case series and uncontrolled single-case designs. The review outcomes appeared to be reductions in sleep onset latency and wake time after sleep onset. The included studies reported a range of sleep parameters, as well as adverse events. The included studies were double-blind placebo-controlled trials and uncontrolled case series. The diagnosis of sleep disorder was made by polysomnography or actigraphy; in some cases self-reports were also used. The dose of melatonin used was 5 mg in the majority of studies, although some lower doses were employed. Melatonin doses were taken variously throughout the evening or at fixed intervals before sleep. The majority of the patients were male and, where reported, the ages ranged from 14 to 61 years.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The validity of the studies was assessed using two different tools. The first (Cho and Bero's instrument) assessed factors including study design and blinding; the second (Mendelson) assessed sleep measures and the reporting of sleep parameters. Ratings of between 0 and 1 (highest quality) were used in both cases.

Two reviewers independently assessed the studies for validity, and any disagreements were resolved through consensus.

Data extraction
Effect sizes were calculated for the primary review outcomes. The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
A narrative synthesis was employed, although the authors stated that they had planned to conduct a meta-analysis, including an exploration of participant and design factors associated with sleep outcomes. The studies were grouped by the condition treated (DSPS or PI) and by study design (controlled trials or case series).
Results of the review
Twelve studies (n=225) were included in the review: 7 double-blind placebo-controlled trials and 5 uncontrolled case series.

The quality of the included studies ranged from 0.21 to 0.85 on Cho and Bero's scale, and from 0.21 to 0.74 on the sleep-specific scale.

DSPS (3 placebo-controlled trials, 5 case series).

One controlled trial showed a large effect size for the effect of melatonin on sleep onset (effect size +2.61). Two other controlled trials found results which favoured melatonin, with effect sizes of +1.77 (self-report) and +1.21 (actigraphy), respectively; however, there were methodological concerns with these trials. All the case series reported that melatonin was an effective treatment, often without clear definitions of efficacy or statistical support.

PI (4 placebo-controlled trials).

One trial reported a statistically significant (p<0.05) increase in daytime alertness and total sleep time in the melatonin group but not the placebo group; none of the other trials reported any statistically significant effects of melatonin treatment.

Few adverse events were reported; where found, these were headache, daytime tiredness and an unusual taste in the mouth.

Poor reporting of sleep parameters in the included studies meant that the planned meta-analysis was not conducted.

Authors' conclusions
There is limited support for the use of melatonin in adults with DSPS, although most of the evidence comes from uncontrolled studies. There is little evidence to support the use of melatonin in adults with PI.

CRD commentary
The review question and inclusion criteria were clear. The authors searched several databases and other relevant sources. However, they did not report a systematic search for unpublished studies, which might have increased the possibility that some relevant studies were not included in the review. The authors reported using methods designed to reduce bias and error in the assessment of study validity, but not in the study selection or data extraction processes. The validity assessment appeared to use appropriate criteria. The included studies were poorly reported and, in view of this, the authors' decision to adopt a narrative synthesis instead of a planned meta-analysis appears appropriate. The authors' cautious conclusions are an accurate reflection of the included evidence. However, the nature of this evidence, together with poor reporting of some aspects of the review methodology, mean it is not possible to be sure of their reliability.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further high-quality research is needed to assess melatonin for both DSPS and PI. Such studies should use waiting-list controls, report sleep parameters in full, use adequate sample sizes, and employ long-term follow-up. In the case of PI, work is also required to assess the therapeutic dose of melatonin.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.