Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia: are there implications for delirium? A systematic review

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CRD summary
The review concluded that sundowning (exacerbation of delirium during the evening or night)/agitated behaviour improved with melatonin treatment in patients with dementia. The authors’ conclusions appear overly strong given the limitations of the evidence presented.

Authors’ objectives
To evaluate the effectiveness of melatonin treatment on circadian rhythm disturbances in patients with dementia.

Searching
PubMed, EMBASE, CINAHL and Cochrane Database of Systematic Reviews were searched from 1985 up to April 2009. Search terms were reported. Reference lists of relevant papers were scanned for further references. No language restrictions were applied. Authors were contacted for original papers, where necessary.

Study selection
Prospective studies that evaluated melatonin treatment for patients with dementia were included. Outcomes of interest were sundowning/agitated behaviour, sleep quality and daytime functioning. Studies that reported another intervention alongside melatonin, or where data were not discernable, were excluded.

The included trials compared melatonin (dosage 1.5mg to 10mg) versus placebo and had a treatment duration that ranged from 10 days to eight weeks; patients had a mean age that ranged from 77 to 84 years. Case series studies melatonin treatment duration ranged from three weeks to 35 months, with dosage ranging from 3mg to 9mg; participants had a mean age of 72 to 85 years. Patients lived at home, in nursing homes or in a geriatric ward of a hospital (where reported). Assessment tools for outcomes varied between studies.

The authors did not report how many reviewers selected studies for inclusion.

Assessment of study quality
The authors did not state that they formally assessed study quality.

Data extraction
Data were extracted independently for the relevant outcomes by three reviewers. Disagreements were resolved by discussion or referral to a fourth reviewer.

Methods of synthesis
The studies were combined in a narrative synthesis.

Results of the review
Nine studies (330 patients) were included in the review, comprising four randomised controlled trials (RCTs, 243 patients) and five case series (87 patients). Two RCTs were reported to be double-blind.

Significant improvements on sundowning/agitated behaviour were reported for melatonin compared with placebo (two RCTs); one RCT reported no improvement compared with placebo. All five case series reported improvements for sundowning/agitated behaviour.

There was mixed evidence for sleep quality from eight studies. Only one of four RCTs using actigraph measurement reported an improvement. One RCT using a sleep diary reported an improvement in sleep quality. Of five case series, one reported improvements in sleep quality using actigraph measurements and two reported improvements using assessment scales.
Of four studies assessing daytime functioning, one RCT reported an improvement using actigraph measurements, but three case series reported no improvements.

**Authors' conclusions**
Sundowning/agitated behaviour improved with melatonin treatment in patients with dementia.

**CRD commentary**
The review question was broadly defined and inclusion criteria reported. Several relevant sources were searched to 2009 with no language restriction. It was unclear whether attempts were made to locate unpublished studies. Methods to reduce reviewer error and bias were only used for data extraction.

Study quality was not assessed systematically, which made it difficult to determine the reliability of the evidence presented. Over half the studies were case series which were liable to multiple biases. A narrative synthesis appeared appropriate given the variability between the studies in dosage, treatment durations, assessment tools, patient setting, sample sizes and study designs. Details of the included patients were sparse. Results were based on statements by study authors, and some without corresponding levels of statistical significance, which made it difficult to verify the findings of the review.

The authors stated that, as no side effects were reported in the studies, it was reasonable to assume that melatonin was safe and well-tolerated at the dosages studied. However, this may be due to a lack of reporting in the original studies and the statement may not be reliable. The authors also offered some hypotheses on the effectiveness of melatonin on sundowning/agitated behaviour in patients with delirium, but these were not derived directly from the evidence in the included studies.

The authors' conclusions appear overly strong given the limitations of the evidence presented.

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

**Research:** The authors stated that further clinical research was needed to determine whether melatonin had an effect on circadian rhythm disturbances in patients with delirium, and to determine the optimum dosage.

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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.