COCHRANE CORNER

Pharmacotherapies for sleep disturbances in Alzheimer's disease

Jenny McCleery, Daniel A. Cohen & Ann L. Sharpley

†This review is an abridged version of a Cochrane Review previously published in the *Cochrane Database of Systematic Reviews*, 2014, Mar 21, Issue 3: CD009178 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

We thank the Cochrane Review Group for their support in publishing these reviews.

See commentary on pp. 219–221, this issue.

Background

Sleep disturbances, including reduced nocturnal sleep time, sleep fragmentation, nocturnal wandering and daytime sleepiness are common clinical problems in dementia due to Alzheimer's disease, and are associated with significant caregiver distress, increased healthcare costs and institutionalisation. Drug treatment is often sought to alleviate these problems, but there is significant uncertainty about the efficacy and adverse effects of the various hypnotic drugs in this vulnerable population.

Objectives

To assess the effects, including common adverse effects, of any drug treatment versus placebo for sleep disorders in people with Alzheimer's disease through identification and analysis of all relevant randomised controlled trials (RCTs).

Search methods

We searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group's specialised register, on 31 March 2013 using the terms: sleep, insomnia, circadian, hypersomnia, parasomnia, somnolence, rest-activity, sundowning.

Selection criteria

We included RCTs that compared a drug with placebo and that had the primary aim of improving sleep in people with Alzheimer's disease who had an identified sleep disturbance at baseline. Trials could also include non-pharmacological interventions as long as both drug and placebo groups had the same exposure to them.

Data collection and analysis

Two authors working independently extracted data on study design, risk of bias and results from the included study reports. Additional information was obtained from study authors where necessary. We used the mean difference as the measure of treatment effect and, where possible, synthesised results using a fixed-effect model.

Main results

We found RCTs eligible for inclusion for three drugs: melatonin (209 participants, three studies, but only two yielded data suitable for meta-analysis), trazodone (30 participants, one study) and ramelteon (74 participants, one study, no peer-reviewed publication, very limited information available).

The melatonin and trazodone studies were of people with moderate to severe Alzheimer's disease; the ramelteon study was of people with mild to moderate Alzheimer's disease. In all studies participants had a variety of common sleep problems. All primary sleep outcomes were measured using actigraphy. In one study of melatonin, drug treatment was combined with morning bright light therapy. Only two studies made a systematic assessment of adverse effects. Overall, the published studies were at low risk of bias, although there were areas of incomplete reporting and some problems with participant attrition, related largely to poor tolerance of actigraphy and technical difficulties. The risk of bias in the ramelteon study was unclear owing to incomplete reporting.

We found no evidence that melatonin, either immediate- or slow-release, improved any major sleep outcome in patients with Alzheimer's disease. We were able to synthesise data for two sleep outcomes: total nocturnal sleep time (MD 10.68 minutes, 95% CI −16.22 to 37.59, two studies), and the ratio of daytime sleep to night-time sleep (MD −0.13, 95% CI −0.29 to 0.03, two studies). Other outcomes were reported in single studies. We found no difference between intervention and control groups for sleep efficiency, time awake after sleep onset or number of night-time awakenings, nor in cognition or performance of activities of daily living (ADLs). No serious adverse effects of melatonin were reported in the included studies.

Trazodone 50 mg administered at night for 2 weeks significantly improved total nocturnal sleep time (MD 42.46 minutes, 95% CI 0.9 to 84.0, one study) and sleep efficiency (MD 8.53, 95% CI 1.9 to 15.1, one study), but there was no clear evidence of any effect on the amount of time spent awake after sleep onset (MD −20.41, 95% CI −60.4 to 19.6, one study) or the number of nocturnal awakenings (MD −3.71, 95% CI −8.2 to 0.8, one study). No effect was seen on daytime sleep, nor on cognition or ADLs. No serious adverse effects were reported.

Results from a phase 2 trial investigating ramelteon 8 mg administered at night were available in summary form in a sponsor's synopsis. Ramelteon had no effect on total nocturnal sleep time at 1 week (primary outcome) or 8 weeks (end of treatment). The synopsis reported few significant differences from placebo for any sleep, behavioural or cognitive outcomes; none were likely to be of clinical significance. There were no serious adverse effects of ramelteon.

Authors' conclusions

We discovered a distinct lack of evidence to help guide drug treatment of sleep problems in Alzheimer's disease. In particular, we found no RCTs of many drugs that are widely prescribed for sleep problems in Alzheimer's disease, including the benzodiazepine and non-benzodiazepine hypnotics, although there is considerable uncertainty about the balance of benefits and risks associated with these common treatments. From the studies we identified for this review, we found no evidence that melatonin is beneficial to Alzheimer's disease patients with moderate to severe dementia and sleep problems. There is some evidence to support the use of a low dose (50 mg) of trazodone, although a larger trial is needed to allow a more definitive conclusion to be reached on the balance of risks and benefits. There was no evidence of any effect of ramelteon on sleep in patients with mild to moderate dementia due to Alzheimer's disease. This is an area with a high need for pragmatic trials, particularly of those drugs that are in common clinical use for sleep problems in Alzheimer's disease. Systematic assessment of adverse effects is essential.

Assessed as up to date: 31 Mar 2013

https://doi.org/10.1192/apt.21.4.218 Published online by Cambridge University Press