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TABLE OF CONTENTS

[Intervention Review]

Pharmacotherapies for sleep disturbances in dementia

Jenny McCleery[1], Ann L Sharpley[2]

[1]Oxford Health NHS Foundation Trust, Banbury, UK. [2]Department of Psychiatry, Oxford University, Oxford, UK

Contact: Jenny McCleery, jenny.mccleery@oxfordhealth.nhs.uk.

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ABSTRACT

Background

Sleep disturbances, including reduced nocturnal sleep time, sleep fragmentation, nocturnal wandering, and daytime sleepiness are common clinical problems in dementia, and are associated with significant carer distress, increased healthcare costs, and institutionalisation. Although non-drug interventions are recommended as the first-line approach to managing these problems, drug treatment is often sought and used. However, there is significant uncertainty about the efficacy and adverse effects of the various hypnotic drugs in this clinically vulnerable population.

Objectives

To assess the effects, including common adverse effects, of any drug treatment versus placebo for sleep disorders in people with dementia.

Search methods

We searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group's Specialized Register, on 19 February 2020, using the terms: sleep, insomnia, circadian, hypersomnia, parasomnia, somnolence, rest-activity, and sundowning.

Selection criteria

We included randomised controlled trials (RCTs) that compared a drug with placebo, and that had the primary aim of improving sleep in people with dementia who had an identified sleep disturbance at baseline.

Data collection and analysis

Two review authors independently extracted data on study design, risk of bias, and results. We used the mean difference (MD) or risk ratio (RR) with 95% confidence intervals (CI) as the measures of treatment effect, and where possible, synthesised results using a fixed-effect model. Key outcomes to be included in our summary tables were chosen with the help of a panel of carers. We used GRADE methods to rate the certainty of the evidence.

Main results

We found nine eligible RCTs investigating: melatonin (5 studies, n = 222, five studies, but only two yielded data on our primary sleep outcomes suitable for meta-analysis), the sedative antidepressant trazodone (1 study, n = 30), the melatonin-receptor agonist ramelteon (1 study, n = 74, no peer-reviewed publication), and the orexin antagonists suvorexant and lemborexant (2 studies, n = 323).

Participants in the trazodone study and most participants in the melatonin studies had moderate-to-severe dementia due to Alzheimer's disease (AD); those in the ramelteon study and the orexin antagonist studies had mild-to-moderate AD. Participants had a variety of common sleep problems at baseline. Primary sleep outcomes were measured using actigraphy or polysomnography. In one study, melatonin treatment was combined with light therapy. Only four studies systematically assessed adverse effects. Overall, we considered the studies to be at low or unclear risk of bias.

We found low-certainty evidence that melatonin doses up to 10 mg may have little or no effect on any major sleep outcome over eight to 10 weeks in people with AD and sleep disturbances. We could synthesise data for two of our primary sleep outcomes: total nocturnal sleep time (TNST) (MD 10.68 minutes, 95% CI −16.22 to 37.59; 2 studies, n = 184), and the ratio of day-time to night-time sleep (MD −0.13, 95% CI −0.29 to 0.03; 2 studies; n = 184). From single studies, we found no evidence of an effect of melatonin on sleep efficiency, time awake after sleep onset, number of night-time awakenings, or mean duration of sleep bouts. There were no serious adverse effects of melatonin reported.

We found low-certainty evidence that trazodone 50 mg for two weeks may improve TNST (MD 42.46 minutes, 95% CI 0.9 to 84.0; 1 study, n = 30), and sleep efficiency (MD 8.53%, 95% CI 1.9 to 15.1; 1 study, n = 30) in people with moderate-to-severe AD. The effect on time awake after sleep onset was uncertain due to very serious imprecision (MD −20.41 minutes, 95% CI −60.4 to 19.6; 1 study, n = 30). There may be little or no effect on number of night-time awakenings (MD −3.71, 95% CI −8.2 to 0.8; 1 study, n = 30) or time asleep in the day (MD 5.12 minutes, 95% CI −28.2 to 38.4). There were no serious adverse effects of trazodone reported.

The small (n = 74), phase 2 trial investigating ramelteon 8 mg was reported only in summary form on the sponsor's website. We considered the certainty of the evidence to be low. There was no evidence of any important effect of ramelteon on any nocturnal sleep outcomes. There were no serious adverse effects.

We found moderate-certainty evidence that an orexin antagonist taken for four weeks by people with mild-to-moderate AD probably increases TNST (MD 28.2 minutes, 95% CI 11.1 to 45.3; 1 study, n = 274) and decreases time awake after sleep onset (MD −15.7 minutes, 95% CI −28.1 to −3.3: 1 study, n = 274) but has little or no effect on number of awakenings (MD 0.0, 95% CI −0.5 to 0.5; 1 study, n = 274). It may be associated with a small increase in sleep efficiency (MD 4.26%, 95% CI 1.26 to 7.26; 2 studies, n = 312), has no clear effect on sleep latency (MD −12.1 minutes, 95% CI −25.9 to 1.7; 1 study, n = 274), and may have little or no effect on the mean duration of sleep bouts (MD −2.42 minutes, 95% CI −5.53 to 0.7; 1 study, n = 38). Adverse events were probably no more common among participants taking orexin antagonists than those taking placebo (RR 1.29, 95% CI 0.83 to 1.99; 2 studies, n = 323).

Authors' conclusions

We discovered a distinct lack of evidence to guide decisions about drug treatment of sleep problems in dementia. In particular, we found no RCTs of many widely prescribed drugs, including the benzodiazepine and non-benzodiazepine hypnotics, although there is considerable uncertainty about the balance of benefits and risks for these common treatments. We found no evidence for beneficial effects of melatonin (up to 10 mg) or a melatonin receptor agonist. There was evidence of some beneficial effects on sleep outcomes from trazodone and orexin antagonists and no evidence of harmful effects in these small trials, although larger trials in a broader range of participants are needed to allow more definitive conclusions to be reached. Systematic assessment of adverse effects in future trials is essential.

PLAIN LANGUAGE SUMMARY

Medicines for sleep problems in dementia

Background

People with dementia frequently experience sleep disturbances. These can include reduced sleep at night, frequent wakening, wandering at night, and sleeping excessively during the day.

These behaviours cause a lot of stress to carers, and may be associated with earlier admission to institutional care for people with dementia. They can also be difficult for care-home staff to manage.

Non-drug approaches to treatment should be tried first, However, these may not help and medicines are often used. Since the source of the sleep problems may be changes in the brain caused by dementia, it is not clear whether normal sleeping tablets are effective for people with dementia, and there are worries that the medicines could cause significant side effects (harms).

The purpose of this review

In this updated Cochrane review, we tried to identify the benefits and common harms of any medicine used to treat sleep problems in people with dementia.

Findings of this review

We searched up to February 2020 for well-designed trials that compared any medicine used for treating sleep problems in people with dementia with a fake medicine (placebo). We consulted a panel of carers to help us identify the most important outcomes to look for in the trials.

We found nine trials (649 participants) investigating four types of medicine: melatonin (five trials), trazodone (one trial), ramelteon (one trial), and orexin antagonists (two trials). Participants in all the trials had dementia due to Alzheimer's disease. The ramelteon trial, one melatonin trial, and both orexin antagonist trials were commercially funded. Overall, the evidence was moderate or low quality, meaning that further research is likely to affect the results.

Participants in the trazodone trial and most of those in the melatonin trials had moderate-to-severe dementia, while those in the ramelteon and orexin antagonist trials had mild-to-moderate dementia.

The five melatonin trials included 253 participants. We found no evidence that melatonin improved sleep in people with dementia due to Alzheimer's disease. The ramelteon trial had 74 participants. The limited information available did not provide any evidence that ramelteon was better than placebo. There were no serious harms for either medicine.

The trazodone trial had only 30 participants. It showed that a low dose of the sedative antidepressant trazodone, 50 mg, given at night for two weeks, may increase the total time spent asleep each night (an average of 43 minutes more in the trial) and may improve sleep efficiency (the percentage of time in bed spent sleeping). It may have slightly reduced the time spent awake at night after first falling asleep, but we could not be sure of this effect. It did not reduce the number of times the participants woke up at night. There were no serious harms reported.

The two orexin antagonist trials had 323 participants. We found evidence that an orexin antagonist probably has some beneficial effects on sleep. On average, participants in the trials slept 28 minutes longer at night and spent 15 minutes less time awake after first falling asleep. There was also a small increase in sleep efficiency, but no evidence of an effect on the number of times participants woke up. Side effects were no more common in participants taking the drugs than in those taking placebo.

The drugs that appeared to have beneficial effects on sleep did not seem to worsen participants' thinking skills, but these trials did not assess participants' quality of life, or look in any detail at outcomes for carers.

Shortcomings of this review

Although we searched for them, we were unable to find any trials of other sleeping medications that are commonly prescribed to people with dementia. All participants had dementia due to Alzheimer's disease, although sleep problems are also common in other forms of dementia. No trials assessed how long participants spent asleep without interruption, a high priority outcome to our panel of carers. Only four trials measured side effects systematically.

We concluded that there are significant gaps in the evidence needed to guide decisions about medicines for sleeping problems in dementia. More trials are required to inform medical practice. It is essential that trials include careful assessment of side effects.

SUMMARY OF FINDINGS

Summary of findings 1. Melatonin compared to placebo for sleep disturbances in dementia

Melatonin compared to placebo for sleep disturbances in dementia

Patient or population: sleep disturbances in dementia

Setting: –

Intervention: melatonin

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with melatonin				
Total nocturnal sleep time assessed with: actigraphy follow-up: range 8–10 weeks	The mean total nocturnal sleep time was 397 minutes	**MD 10.68 minutes higher** (16.22 lower to 37.59 higher)	—	184 (2 RCTs)	⊕⊕⊖⊖ **Low** [a,b]	Melatonin may result in little to no difference in total nocturnal sleep time.
Consolidated sleep time	—	—	—	—	—	Not measured.
Number of nocturnal awakenings assessed with: actigraphy follow-up: 8 weeks	The mean number of nocturnal awakenings was 34	**MD 6.0 more** (2.65 fewer to 14.65 more)	—	33 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	Melatonin may result in little to no difference in the number of nocturnal awakenings.
Reporting ≥ 1 adverse event assessed with: spontaneous patient/carer report follow-up: 8 weeks	**Study population**		**RR 1.07** (0.86 to 1.33)	151 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	—
	70 per 100	75 per 100 (60 to 93)				
Cognitive function assessed with: MMSE, change from baseline follow-up: range 8–24 weeks	The mean cognitive function was 14.3	**MD 0.09 higher** (0.85 lower to 1.03 higher)	—	162 (2 RCTs)	⊕⊕⊖⊖ **Low** [b,c,d]	Minimum clinically important difference is uncertain but has been estimated at 1.4 points in moderate to severe AD (Howard 2011).
Quality of life	—		—	—	—	Not reported.

Carer burden assessed with: Zarit Burden Interview follow-up: 8 weeks	The mean carer burden was 32.1	**MD 6.2 lower** (19.8 lower to 7.4 higher)	—	31 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	Melatonin may result in little to no difference in carer burden.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AD: Alzheimer's disease; **CI:** confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded due to imprecision: confidence interval included no effect and a difference likely to be of clinical importance.
[b]Downgraded due to imprecision: data from a single small study.
[c]One study had high risk of bias but result not downgraded because it contributed very few participants.
[d]Downgraded due to inconsistency.

Summary of findings 2. Trazodone compared to placebo for sleep disturbances in dementia

Trazodone compared to placebo for sleep disturbances in dementia

Patient or population: sleep disturbances in dementia

Setting: –

Intervention: trazodone

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with trazodone				
Total nocturnal sleep time assessed with: actigraphy follow-up: 2 weeks	The mean total nocturnal sleep	**MD 42.5 minutes more**	—	30 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	Trazodone may increase total nocturnal sleep time.

	time was 281.9 minutes	(0.9 more to 84 more)				
Consolidated nocturnal sleep time	—	—	—	—	—	Not measured.
Number of nocturnal awakenings assessed with: actigraphy follow-up: 2 weeks	The mean number of nocturnal awakenings was 26	**MD 3.7 fewer** (8.2 fewer to 0.8 more)	—	30 (1 RCT)	⊕⊕⊖⊖ **Low** [a,c]	Trazodone may have little or no effect on the number of nocturnal awakenings.
Reporting ≥ 1 adverse event assessed with: spontaneous patient/carer report follow-up: 2 weeks	**Study population**		**RR 0.67** (0.23 to 1.89)	30 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	Trazodone may result in little to no difference in reporting ≥ 1 adverse event. All adverse events were described as mild.
	40 per 100	27 per 100 (9 to 76)				
Cognitive function assessed with: MMSE Scale from: 0 (worse) to 30 follow-up: 2 weeks	The mean cognitive function was 10.5 MMSE points	**MD 0.1 MMSE points higher** (0.9 lower to 1.1 higher)	—	30 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	Trazodone probably results in little to no difference in cognitive function. Minimum clinically important difference was uncertain, but has been estimated at 1.4 points in moderate-to-severe AD (Howard 2011).
Quality of life	—		—	—	—	Not measured.
Carer burden, well-being or quality of life	—		—	—	—	Not measured.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AD: Alzheimer's disease; **CI:** confidence interval; **MMSE:** Mini-Mental State Examination; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded due to imprecision: data from a single small study.
[b]Downgraded due to imprecision: confidence interval included no effect and effect likely to be of clinical importance.
[c]Downgraded due to imprecision: confidence interval included an important decrease and a small increase.

Summary of findings 3. Orexin antagonists compared to placebo for sleep disturbances in dementia

Orexin antagonists compared to placebo for sleep disturbances in dementia

Patient or population: sleep disturbances in dementia

Setting: any

Intervention: orexin antagonists

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with orexin antagonists				
Change from baseline in total nocturnal sleep time assessed with: polysomnography follow-up: 4 weeks	The mean change from baseline in total nocturnal sleep time was 45.2 minutes	**MD 28.2 minutes more** (11.1 more to 45.3 more)	—	274 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	Orexin antagonist probably resulted in a greater increase than placebo in total nocturnal sleep time.
Consolidated sleep time	—		—	—	—	Not measured.
Change from baseline in ratio of number of nocturnal awakenings to total sleep time × 100 assessed with: polysomnography follow-up: 4 weeks	The mean change from baseline in the ratio of nocturnal awakenings was –0.9	**MD 0** (0.5 fewer to 0.5 more)	—	274 (1 RCT)	⊕⊕⊕⊖ **Moderate** [b]	The number of nocturnal awakenings was scaled to the total nocturnal sleep time. Orexin antagonist probably resulted in little or no difference in the ratio of number of awakenings to time spent asleep.
Reporting ≥ 1 adverse event follow-up: 4 weeks	**Study population**		**RR 1.29** (0.83 to 1.99)	323 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [c]	Orexin antagonists probably result in little to no difference in reporting ≥ 1 adverse event.
	174 per 1000	225 per 1000 (145 to 347)				
Change from baseline in cognitive function assessed with: MMSE Scale: 0–30 (better) follow-up: 4 weeks	The mean change from baseline in cognitive function was 0.9 MMSE points	**MD 0 MMSE points** (0.5 lower to 0.5 higher)	—	274 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	Orexin antagonist probably results in little to no difference in change from baseline in cognitive function (MMSE increased slightly in both groups). Results adjusted for baseline values.

Quality of life	—		—	—	—	—
Change from baseline in carer distress assessed with: carer distress item of Sleep Disorders Inventory Scale: 0–5 (worse) follow-up: 4 weeks	The mean change from baseline in carer distress was –0.5	**MD 0.1 more** (0.1 fewer to 0.2 more)	—	274 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	Orexin antagonist probably results in little to no difference in change from baseline in carer distress (carer distress decreased slightly in both groups).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **MMSE:** Mini-Mental State Examination; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded due to imprecision: data from a single study.
[b]Downgraded due to imprecision: data from a single study; confidence interval included a trivial effect and a probably important effect.
[c]Downgraded due to imprecision: confidence interval included no effect and a clinically significant increase in the intervention group.

BACKGROUND

Description of the condition

Dementia is a syndrome of global cognitive decline, usually due to one or more neurodegenerative conditions in old age. The most frequent subtypes are dementia in Alzheimer's disease (AD), vascular dementia (VaD), and the related conditions of dementia with Lewy bodies (DLB) and dementia in Parkinson's disease (PDD) (Goodman 2017). The dementia syndrome is characterised by progressive impairment in multiple cognitive domains and in the ability to carry out the usual activities of daily life, so that people with dementia become increasingly dependent on others. Over the course of the illness, other behavioural and psychological symptoms occur very frequently (Lyketsos 2000). Common among these are apathy, anxiety, agitation, and sleep disturbances.

Common sleep problems in dementia are increased wakefulness and fragmented sleep at night, increased sleep latency (time taken to go to sleep), and increased daytime sleepiness. These are examples of circadian abnormalities – that is, abnormalities of 24-hour biological rhythms. In the two-process model of sleep regulation, the timing of sleep and wakefulness is controlled by homeostatic sleep pressure, which is the accumulating drive for sleep during time spent awake, and by the brain's circadian timekeeping system (Borbély 2016). Circadian misalignment with the desired sleep-wake schedule and low amplitude circadian rhythms lead to mistimed and poorly consolidated bouts of wakefulness and sleep. Sleep disorders in dementia may be due directly to neurodegeneration of the sleep-wake circuitry. Consequences of sleep disruption or institutional care, such as artificial light exposure at night, can also shift the timing of the circadian pacemaker, and further perpetuate abnormal circadian patterns.

The reported prevalence of sleep disorders in AD varies widely with the detection method and the range and severity of sleep disorders investigated, but prevalence rates as high as 66% have been reported (Guarnieri 2012). Alzheimer's pathology affects multiple brain systems important for regulation of the sleep-wake cycle, leading to a gradual deterioration of circadian rhythms as AD progresses (Li 2019). Increasingly, the literature on sleep and AD suggests a bidirectional relationship where not only does AD pathology disrupt sleep, but sleep disorders promote the development of AD pathology (Van Egroo 2019).

VaD is caused by a variety of cerebrovascular pathologies. It can be subdivided into cortical, subcortical, and mixed types. The overall prevalence of sleep disturbances in VaD may be somewhat higher than in AD (Guarnieri 2012). One large consecutive series of people with AD or VaD found the highest prevalence of sleep disturbance in the cortical VaD group (Fuh 2005).

Sleep disorders are especially prevalent in DLB and PDD (Bliwise 2011; Guarnieri 2012). In their large multicentre study, Bliwise 2011 found that the odds of nocturnal sleep disturbance on the Neuropsychiatric Inventory (NPI) was 2.93 times higher (95% confidence interval (CI) 2.22 to 3.86) in people with DLB compared to those with probable AD. In a more fine-grained analysis of the sleep problems of people with mild dementia, Rongve 2010 reported that, compared to people with AD, people with DLB or PDD had higher rates of all sleep disorders examined, including insomnia (AD 24%, DLB or PDD 47.2%), and excessive daytime sleepiness (AD 16.7%, DLB or PDD 40.6%). They also had higher rates of a variety of dyssomnias and parasomnias (rapid eye movement sleep behaviour disorder (REM-BD), periodic leg movements of sleep, restless legs syndrome (RLS), sleep-related leg cramps, and obstructive sleep apnoea).

Sleep problems in dementia result in significant carer distress, healthcare costs, and have been reported in some studies to be a significant factor in decisions to admit a person with dementia to institutional care (Afram 2014; Donaldson 1998; Gaugler 2000). In one study of behavioural and psychological symptoms in mid- and late-phase dementia due to AD, sleep disturbance was notable as the only symptom rated by carers as being among the most distressing to both people with dementia and the carers themselves (Hart 2003). Carer burden appears to relate more to some care recipient sleep disturbances than others, with the strongest effects seen for nocturnal awakenings, nocturnal wandering, and snoring, and a smaller effect of daytime sleepiness (Gehrman 2018).

Description of the intervention

Both pharmacotherapies (drugs) and non-pharmacological treatments have been used to alleviate sleep problems in people with dementia. Non-pharmacological treatment approaches are an attractive alternative to drug treatments because they may have fewer adverse effects. They are generally recommended in guidelines as the first approach to management (e.g. NICE 2018). Non-pharmacological interventions for sleep disorders in dementia are the subject of another Cochrane Review (in preparation, Wilfling 2015).

Drugs that have been used to manage sleep disorders in people with dementia include atypical antipsychotics, benzodiazepines, other GABAergic drugs (such as zolpidem, zopiclone, and zaleplon), melatonin, sedating antidepressants, and antihistamines.

Among the hypnotic agents, the most commonly used are the benzodiazepines and non-benzodiazepine hypnotics, which are also agonists at the benzodiazepine receptor (the Z-drugs). These have effects on sleep, but they are also associated with a considerable number of side effects, including daytime sleepiness, worsened insomnia after discontinuation (rebound insomnia), confusion, amnesia, and increased frequency of falling (Closser 1991; Cumming 2003). All are considered to carry risks of physical and psychological dependence.

Sedating antidepressants, particularly trazodone, and antihistamines are prescribed for sleep problems in people with dementia, but have significant potential for similar adverse effects (Coupland 2011; Oderda 2012). Some sedative antihistamines also have anticholinergic effects that may worsen cognition.

Antipsychotics with sedative effects, such as quetiapine or olanzapine, may also be given to people with dementia with disturbed sleep, especially if accompanied by agitated behaviour at night, but their use in dementia has been linked with serious adverse events including increased mortality (Schneider 2005; Schneider 2006), and they are not recommended except in situations of high risk. The anticholinergic effects of several these drugs may also lead to worsened cognition.

Melatonin and melatonin-receptor agonists, such as ramelteon, are used to treat insomnia in healthy people, and there has

been considerable interest in their use in people with dementia. Melatonin is categorised as a dietary supplement in the USA, but in Europe, a sustained-release form is licensed as a medicine for the short-term treatment (up to 13 weeks) of primary insomnia in adults aged 55 years and over, at a dose of 2 mg each night, although the evidence for efficacy is very modest (Papillon-Ferland 2019). Ramelteon has a license in the USA for the long-term treatment of sleep-onset insomnia.

Orexin antagonists are a novel class of hypnotic which block the action of orexins, endogenous neuropeptides that promote wakefulness and appear to be dysregulated (overexpressed) in AD (Liguori 2014). Currently, only two drugs of this class – suvorexant and lemborexant – have received regulatory approval for the treatment of insomnia. In older adults with insomnia, suvorexant is well-tolerated and effective, particularly for sleep maintenance insomnia with less effect on sleep-onset difficulties (Herring 2017).

How the intervention might work

Drugs that are used to treat sleep disturbances work in a variety of ways. The disease processes underlying sleep disturbances in dementia may render some of these more or less effective in people with dementia than in neurologically healthy people.

There is some evidence that sleep itself may contribute to keeping in step with the circadian pacemaker (Buxton 2000). Hence, interventions to improve sleep at night may also improve circadian timing and potentially minimise other circadian symptoms such as sundowning, which is a phenomenon of increased motor activity and agitation in the late afternoon or evening.

Why it is important to do this review

Sleep problems in people with dementia are common, and are associated with high burdens to carers and to healthcare and social support systems. However, consensus on the safest and most effective ways to manage them is lacking. The aim of this review was to identify and appraise evidence from randomised controlled trials (RCTs) of drug treatments for sleep problems in dementia to inform clinical practice and identify research needs. This version of the review updates the previous version published in 2016.

OBJECTIVES

To assess the effects, including common adverse effects, of any drug treatment versus placebo for sleep disorders in people with dementia.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised placebo-controlled trials, including cross-over trials. We excluded quasi-randomised trials from the review.

Types of participants

We included people who had both: dementia of any sub-type, diagnosed using any well-validated criteria, such as the Diagnostic and Statistical Manual (DSM) or International Classification of Disease (ICD) criteria current at the time of the study, and a sleep problem identified on the basis of subjective or objective measures.

We did not exclude participants on the basis of gender, age, or clinical setting (inpatient or outpatient). We included studies only if at least 80% of the participants had dementia. Sleep problems included any well-defined disturbances in the sleep process, such as difficulty initiating sleep, problems with sleep maintenance, and excessive daytime napping. We excluded studies in which participants had obstructive sleep apnoea syndrome, because this is treated primarily as a respiratory disorder.

Types of interventions

Active intervention: any drug primarily intended to improve participants' sleep.

Control intervention: placebo.

Studies including non-pharmacological interventions were acceptable if the drug and placebo groups were exposed to identical non-pharmacological interventions.

We excluded studies in which the intervention was a single dose given with the aim of assessing effects on sleep architecture.

Types of outcome measures

Where possible, outcomes were divided into short-term (following treatment of up to six weeks) and long-term (following treatment of more than six weeks).

Primary outcomes

- Any or all the following objective sleep outcomes measured with polysomnography or – more feasibly for people with dementia – actigraphy:
  - total nocturnal sleep time (TNST);
  - consolidated sleep time at night (i.e. longest period of uninterrupted sleep between nocturnal sleep onset and final awakening);
  - sleep efficiency (%; i.e. TNST/time in bed × 100);
  - nocturnal time awake (wakenings after sleep onset (WASO); after sleep onset and before final awakening);
  - number of nocturnal awakenings;
  - sleep latency;
  - ratio of daytime sleep to night-time sleep, or of night-time sleep to total sleep over 24 hours.
- Adverse events.

Secondary outcomes

- Carer ratings of patient's sleep using sleep diaries or validated observer scales.
- Cognition measured with any validated scale.
- Activities of daily living (ADLs) measured with any validated scale.
- Quality of life.
- Carer outcomes (well-being, quality of life, burden, sleep).

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group (CDCIG) Specialized Register in November 2011, and updated the searches in March 2013, May 2013 (a supplementary search with some additional search terms), March 2016, October 2018, and 19 February 2020. The search terms were: sleep, insomnia, circadian, hypersomnia, parasomnia, somnolence, rest-activity, and sundowning.

ALOIS is maintained by the CDCIG Information Specialist, and contains dementia and cognitive improvement studies identified from the following.

- Monthly searches of major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO, and LILACS.
- Monthly searches of trial registers: meta-Register of Controlled Trials; Umin Japan Trial Register; World Health Organization portal (which covers ClinicalTrials.gov, ISRCTN, Chinese Clinical Trials Register, German Clinical Trials Register, Iranian Registry of Clinical Trials, Netherlands National Trials Register, and others).
- Quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL).
- Six-monthly searches of grey literature sources: ISI Web of Knowledge with Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS, see 'About ALOIS' on the website (www.medicine.ox.ac.uk/alois/content/about-alois).

We ran additional separate searches in many of the above sources to ensure that the most up-to-date results were retrieved. The search strategy we used can be seen in Appendix 1.

Where necessary, we had abstracts translated into English. We did not require any full-text translations.

Searching other resources

Two review authors independently searched reference lists of selected studies to find possible additional articles.

Data collection and analysis

Selection of studies

Two review authors independently examined the abstracts of references identified in the search process. We retrieved the full texts of all studies that appeared to meet our inclusion criteria, those for which an abstract was not available, and those whose eligibility either of the review authors considered uncertain. We resolved disagreements by discussion. In some cases, we contacted study authors for further information to reach a final decision on inclusion.

Data extraction and management

Two review authors independently extracted the data from each study using data collection forms which had been assessed for usability in previous versions of this review. We resolved disagreements by discussion.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias in accordance with Cochrane's tool for assessing methodological quality and risk of bias (Higgins 2011). This tool assesses how the randomisation sequence was generated, how allocation was concealed, the integrity of blinding (participants, raters, and personnel), the completeness of outcome data, selective reporting, and other biases. Where there were inadequate details of randomisation and other characteristics of the trials provided, we contacted authors of the studies to obtain further information.

We assessed the risk of bias in each domain and categorised them as follows.

- Low risk of bias: plausible bias that is unlikely to seriously alter the results (categorised as 'low' in the 'Risk of bias' table).
- High risk of bias: plausible bias that seriously weakens confidence in the results (categorised as 'high' in the 'Risk of bias' table).
- Unclear risk of bias: plausible bias that raises some doubts about the results, or inadequate information with which to make a decision (categorised as 'unclear' in the risk of bias table).

If sequence generation was considered to be inadequate (high risk of bias), we considered the study to be quasi-randomised and excluded it from the review.

We discussed any disagreements until we reached consensus.

Measures of treatment effect

We used the mean difference (MD) to measure the size of the treatment effect for continuous outcomes when studies used the same scales and the standardised mean difference (SMD) when studies used different scales, and the risk ratio for dichotomous outcomes, with 95% confidence intervals (CI).

Unit of analysis issues

We included one cross-over study, but it was not possible to extract paired data. We discussed this study in a narrative format only.

There were three relevant treatment groups in one included study: one placebo group and two groups receiving different formulations of melatonin (immediate release and modified release). In this case, we entered the two active treatment groups in analyses as separate subgroups and divided the shared placebo group. We chose this method to allow an approximate investigation of heterogeneity due to the drug formulation.

One study included four groups receiving different doses of oral lemborexant. In this case, we pooled the two groups receiving doses within the licensed dose range into a single group to be included in our primary analyses. We reported separately the data for the other two doses (one below and one above the licensed dose range).

Dealing with missing data

We used intention-to-treat (ITT) data where these were available, reporting any imputation methods used in the primary studies. We used completers' data if these were all that were available.

Assessment of heterogeneity

We used visual inspection of forest plots and the I^2 statistic to assess heterogeneity.

Assessment of reporting biases

We found too few studies to allow assessment of possible publication bias.

Data synthesis

We grouped studies by drug group. For each drug group, we performed meta-analyses if we considered the studies to be sufficiently homogeneous, clinically and methodologically.

For the comparison of melatonin with placebo, one study presented data after eight weeks of treatment and one after 12 weeks (for some outcomes) and 24 weeks. When 12-week data were provided, we preferred to pool these with eight-week data from the other study. For the outcomes for which 12-week data were not reported, we used the end-of-study (24-week) data and pooled these with the eight-week data.

We used a fixed-effect model for all analyses.

Subgroup analysis and investigation of heterogeneity

Due to the small number of identified studies and low numbers of participants, there was little heterogeneity to be investigated. We found more than one study only for melatonin and orexin antagonists. We conducted subgroup analyses of immediate-release and slow-release (SR) melatonin formulations. Planned subgroup analyses based on treatment duration and drug dose were not indicated.

Sensitivity analysis

We conducted sensitivity analyses on the results for our primary sleep outcomes to assess the impact of the strategy we had adopted to deal with different formulations of melatonin within a study (see Unit of analysis issues above). In the sensitivity analyses, we used the alternative strategy of combining the two melatonin groups into a single group.

Carer involvement

For this update of the review, we sought the advice of carers in order to identify any important outcomes missing from previous versions of the review and to prioritise outcomes for inclusion in 'Summary of findings' tables. We recruited six people who identified themselves as having direct experience of caring for someone with sleep problems in the context of dementia through the Alzheimer's Society (UK); they participated in telephone focus groups and completed an online survey. As a result of this exercise, we added one additional sleep outcome (consolidated sleep) to our list of primary outcomes and expanded secondary carer outcomes to include carer sleep, well-being, and quality of life (in addition to carer burden).

Presentation of results: GRADE and 'Summary of findings' tables

We used GRADE methods to rate the certainty of the evidence (high, moderate, or low) that supported each effect estimate in the review (Guyatt 2011). This rating referred to our level of confidence that the estimate reflected the true effect, taking into account the risk of bias in the included studies, inconsistency between studies, imprecision in the effect estimate, indirectness in addressing our review question, and the risk of publication bias. We produced 'Summary of findings' tables for the comparisons of melatonin, trazodone, and orexin antagonists with placebo to show the effect estimate and the quantity and certainty of supporting evidence for the following outcomes, which were chosen in conjunction with the panel of carers:

- TNST;
- consolidated sleep time;
- number of nocturnal awakenings;
- adverse effects;
- cognitive function;
- quality of life;
- carer well-being or quality of life.

We had insufficient detail about the ramelteon trial to construct a 'Summary of findings' table.

RESULTS

Description of studies

Results of the search

After deduplication and first assessment of results of all the searches by the Information Specialist of the CDCIG, the review authors received 475 records for closer scrutiny. We reviewed full texts if at least one of two review authors thought that a study might meet the inclusion criteria on the basis of its abstract, or if an abstract was not available. If no full text was available (e.g. abstract in conference proceedings), we attempted to reach a decision on the basis of the abstract alone. In total, we examined 111 records, relating to 68 unique studies, in more detail.

In 2013, we identified one conference abstract from reference lists, which appeared to refer to a small RCT eligible for inclusion (Tozawa 1998). This study was also referred to by one of its authors in a later paper (Mishima 2000). It was described as a double-blind RCT of exogenously administered melatonin, 6 mg daily for four weeks, in seven inpatients with Alzheimer's-type dementia and rest-activity rhythm disorder. It reported that melatonin was associated with a significant reduction in night-time, but not total, activity. We were unable to retrieve the conference abstract and found no evidence of a subsequent full publication. We identified a current address for one of the authors, but received no reply to a request for further information. Given the very small size of the trial and the low probability now of retrieving any data, we decided to classify it as an excluded trial.

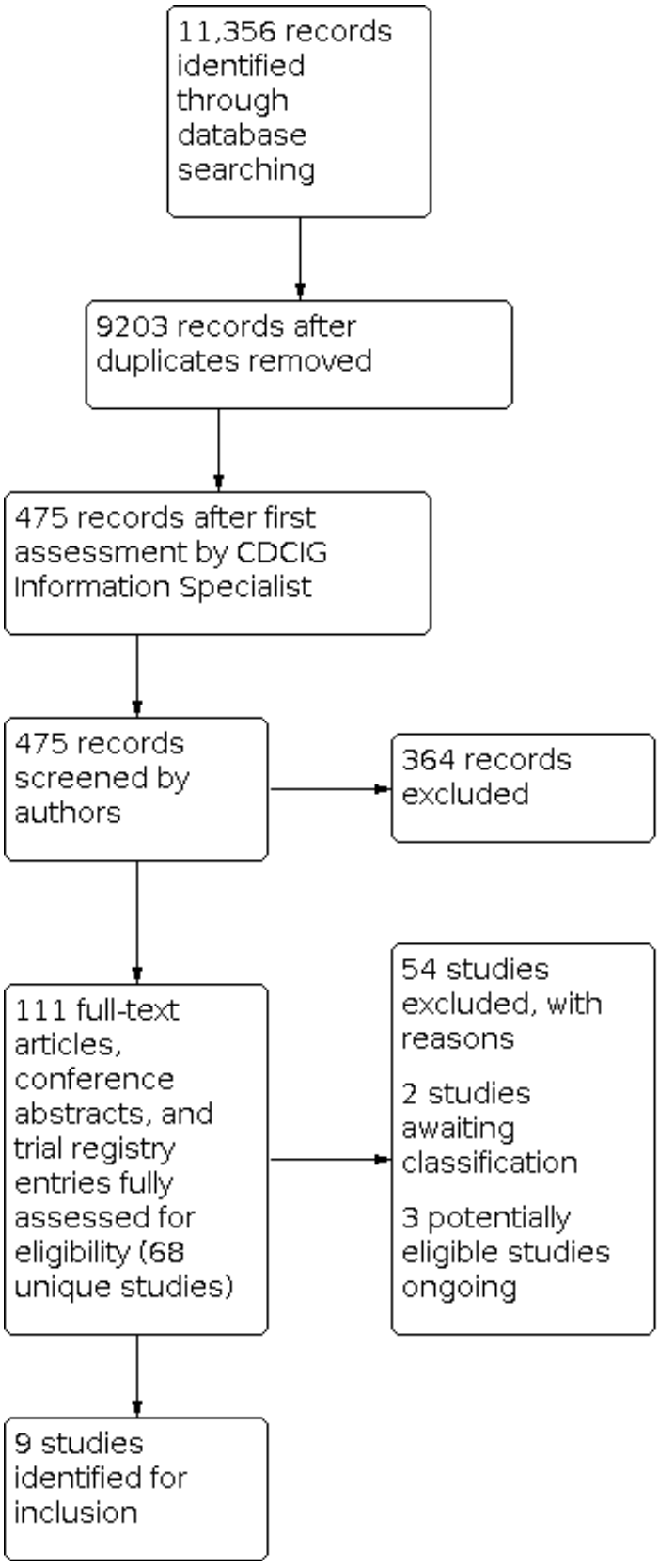
One possibly eligible trial of zolpidem was awaiting classification in 2016 due to insufficient information to be sure of eligibility and no available results (NCT00814502). The results of this trial (n = 17) have now been posted on ClinicalTrials.gov, but we remain uncertain of its eligibility (participants may not have been selected for baseline sleep problems) and we did not receive a reply to our request for information from the named contact; it is still classed as awaiting assessment. A second trial (intended n = 30) awaiting assessment is a trial of a herbal medicine, Ukgansan ga Jinpibanha, which is recorded in the Korean clinical trials register, CRIS, as having been completed in 2017 (KCT0002521). We were unable to locate any results or to make contact with the investigators.

We now include nine trials in the review. In 2013, we included three studies of melatonin (Dowling 2008; Serfaty 2002; Singer 2003), one study of trazodone (Camargos 2014), and one study of ramelteon, for which minimal data were available. In 2016, we included one additional study of melatonin (Wade 2014). In 2020, we included one further study of melatonin (Morales-Delgado 2018), and two studies of orexin antagonists (suvorexant (Herring 2020) and lemborexant (NCT03001557)).

We have also identified three ongoing studies. These are one study of Z-drugs in sleep disturbance in people with AD (NCT03075241); one study of gabapentin in people with AD and sleep disturbance due to RLS (NCT03082755); and one study of nelotanserin in people with PDD and REM-BD (NCT02708186).

The study selection process is summarised in Figure 1.

Figure 1. Study flow diagram. CDCIG: Cochrane Dementia and Cognitive Improvement Group.



Included studies

All studies are described in detail in the Characteristics of included studies table. All studies for which full information was available included participants similar to people seen in clinical practice with dementia ranging from mild to severe. Sleep-related inclusion criteria varied between studies, but all included participants with night-time behaviours that were associated with disturbance or distress to carers, including frequent wakening, nocturnal agitation, wandering, wakening and thinking it was daytime, early wakening, and excessive daytime sleepiness. Three studies required participants to meet specified diagnostic criteria for sleep disorders. These were described by the triallists as DSM-5 insomnia (Herring 2020), "DSM-5 circadian cycle sleep disorder with insomnia" (Morales-Delgado 2018), and DSM-5 circadian rhythm sleep disorder (irregular sleep-wake type) (NCT03001557).

Studies of melatonin

Dowling 2008 compared melatonin 5 mg to placebo in a parallel-group design, with a treatment period of 10 weeks. The 33 participants had moderate-to-severe dementia and were resident in long-term care facilities. All participants also received bright light exposure for one hour in the morning. Sleep outcomes were measured using actigraphy for continuous periods of 108 hours at baseline and end of treatment.

Morales-Delgado 2018 was a parallel-group study comparing melatonin 5 mg with placebo over eight weeks in outpatients with mild-to-moderate dementia (subtype unspecified, but 'focal disease' which could account for the dementia was excluded by neuroimaging). They randomised 40 participants of whom 31 completed the study and were included in the analyses. There were no actigraphic sleep measures. The primary outcome was the Pittsburgh Sleep Quality Index (PSQI). Although the paper stated that this could be completed by the patient or the carer, we decided to include it under our secondary outcome of carer-rated sleep, with exclusion in a sensitivity analysis.

Serfaty 2002 used a cross-over design to compare melatonin SR 6 mg with placebo. Treatment was two weeks for each treatment period with a one-week washout. The study randomised 44 participants, but reported results only on the 25 who completed the study. They were similar to Dowling 2008's participants, with the majority being resident in long-term care facilities. They measured sleep outcomes using actigraphy, but only at night, for three nights at the end of each treatment and washout period.

Singer 2003 was the largest study, reporting on 151 participants. There were three parallel groups receiving melatonin 10 mg, melatonin SR 2.5 mg, or placebo for eight weeks. Participants were broadly similar to those in the other two studies, although it was not clear how many were resident at home and how many in institutions. Participants wore actigraphs throughout the study, and outcomes were derived from a single actigraph record covering the entire eight weeks of treatment.

Wade 2014 was a parallel-group study comparing melatonin SR 2 mg with placebo over 24 weeks, in outpatients with mild-to-moderate AD. They randomised 73 participants, but only the 13 participants who met the study criteria for comorbid insomnia at baseline were relevant to this review. There were no actigraphic sleep outcomes reported, but we were able to extract data for some of our secondary outcomes.

Study of trazodone

Camargos 2014 compared trazodone 50 mg at night to placebo over two weeks in a parallel group study of 30 outpatients with moderate-to-severe dementia. Sleep outcomes were derived from an actigraph record of the whole treatment period.

Study of ramelteon

NCT00325728 was a phase 2, multicentred, parallel-group trial that randomised 74 participants with mild or moderate AD to eight weeks of treatment with either ramelteon 8 mg or placebo. The only account of the methods and results we could obtain was a clinical trial synopsis on the sponsor's website. Sleep outcomes were measured by actigraph at one, two, four, six, and eight weeks. The trial registry entry named the primary outcome as TNST; in the trial synopsis, the primary outcome was further specified as TNST at one week.

Studies of orexin antagonists

Herring 2020 was a multinational trial in which 285 participants with DSM-5 diagnoses of probable AD and insomnia were randomised to suvorexant 10 mg to 20 mg or placebo for four weeks. The starting dose of suvorexant was 10 mg, but it could be increased to 20 mg according to clinical response. The participants were unusually young; 29% were aged under 65 years. Most participants (79%) had mild dementia defined by a Mini-Mental State Examination (MMSE) in the range 21 to 26. Sleep outcomes were measured using both polysomnography and actigraphy, although at the time of writing only the polysomnographic results were available.

NCT03001557 was a phase 2, multinational, parallel-group trial in which 63 participants with mild-to-moderate AD according to National Institute on Aging Alzheimer's Association (NIA-AA) criteria and DSM-5 Circadian Rhythm Sleep Disorder (Irregular Sleep-Wake type) were randomised to placebo or to one of four doses of lemborexant (2.5 mg, 5 mg, 10 mg, or 15 mg) for four weeks. Data used in this review were taken from the study protocol and from ClinicalTrials.gov. Multiple 'primary' outcomes were specified. Sleep outcomes were measured using actigraphy at one, two, three, and four weeks.

Excluded studies

We excluded several RCTs because the participants, although having AD, were not selected for inclusion on the basis of a sleep problem at baseline, as would be the case for treatment of sleep disturbances in clinical practice. Some of these studies examined a wide range of neuropsychiatric outcomes, one of which was sleep, although several did have a primary aim of improving sleep (Asayama 2003; Gehrmann 2009; Magnus 1978; Valtonen 2005).

We excluded several older studies because the diagnostic status of the participants was not certain by modern standards; although they probably included some participants with AD, they also included participants with a variety of other types of dementia or functional psychiatric illnesses (Linnoila 1980a; Linnoila 1980b; Magnus 1978).

We excluded other studies on the basis of the study design (not RCTs).

Excluded studies, with reasons, are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

The risk of bias in the included studies was generally low, although there were areas of incomplete reporting, particularly for NCT00325728, for which the overall risk was unclear. We considered Wade 2014 at overall high risk of bias, primarily due to a high risk of selective reporting, but it contributed few data to the analyses. The assessments for each study are detailed in the Characteristics of included studies table, and the risk of bias across all included studies is summarised in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across included studies.

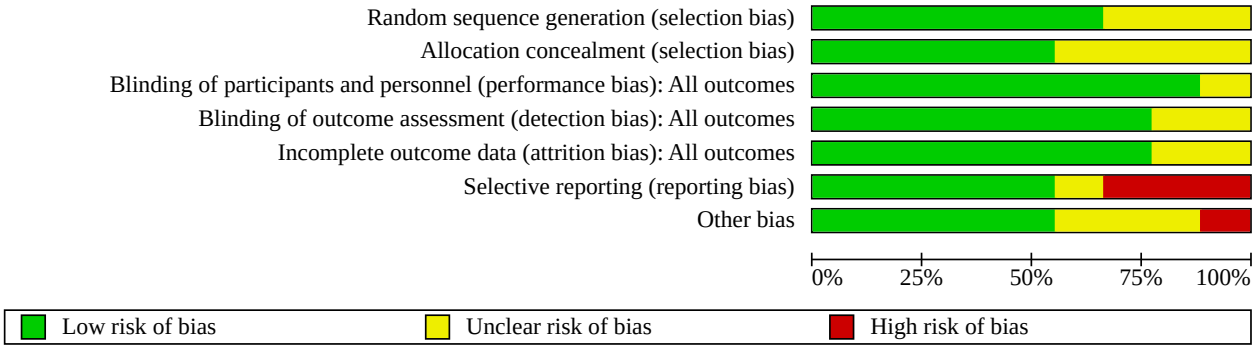
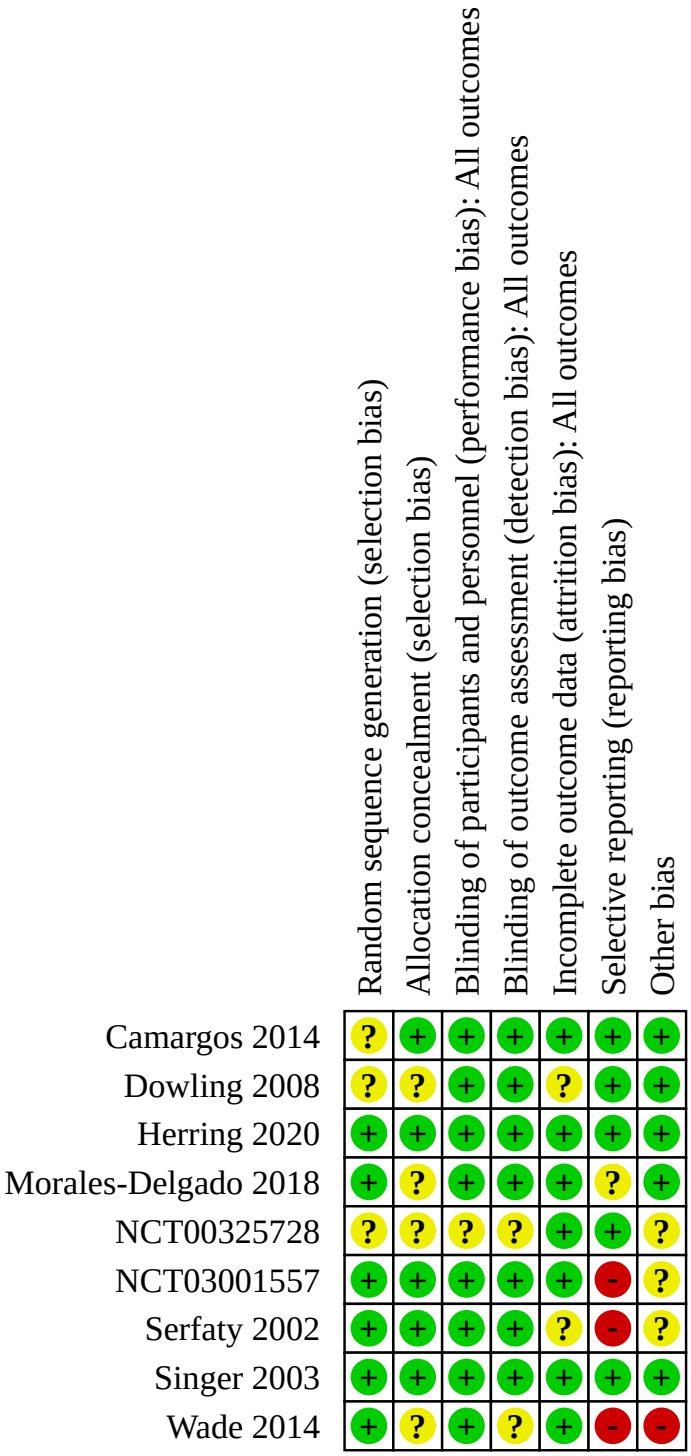


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Five studies were at unclear risk of selection bias due to a lack of methodological information. The method of sequence generation was incompletely reported for Dowling 2008 and Camargos 2014, although information obtained from the authors of the latter study clearly indicated adequate allocation concealment. Singer 2003 did not report details of the randomisation procedure either, but as a large, multicentred study with centralised randomisation, we judged that the risk of selection bias was likely to have been low. The report of NCT00325728 gave no details of the methods used for participant allocation. Wade 2014 and Morales-Delgado 2018 used adequate randomisation methods, but did not report how allocation concealment was assured. The other studies were at low risk of selection bias.

Blinding

There was no information on blinding for NCT00325728. Wade 2014 took measures to blind participants and personnel, but did not mention the blinding of outcome assessors, so we judged risk of bias here to be unclear. There appeared to have been adequate measures taken to blind participants, personnel, and outcome assessors in the other studies, although only Serfaty 2002 reported any assessment of the success of blinding. Our primary sleep outcomes were measured with actigraphy or polysomnography, which is highly objective, thus reducing the potential for performance and detection bias.

Incomplete outcome data

Dowling 2008 failed mention dropouts and reported only on participants completing the study. Serfaty 2002 provided completers' data only, having had a very high dropout rate of 43% after randomisation, albeit for reasons that were not clearly related to group allocation (predominantly poor tolerance of actigraphy). We judged there was some potential for attrition bias in these two studies. Camargos 2014 and Singer 2003 reported fully on participant flow; both studies lost some participants due to technical difficulties with actigraphy, but we judged the risk of attrition bias to be low. The report of NCT00325728 described attrition by group, giving reasons, and we judged it to have a low risk of attrition bias. Wade 2014 lost only one participant from each treatment group in their insomnia subpopulation; we judged this at low risk of attrition bias. Herring 2020 included all randomised participants in the safety analyses, but in the efficacy analyses 7/142 (4.9%) participants were excluded from the suvorexant group and 4/143 from the placebo group, mainly because of missing data after participant withdrawal. We considered this a low rate of attrition and a low risk of bias. NCT03001557 excluded one participant who had been randomised 'inadvertently' and did not receive treatment; the other 62 participants all completed the trial and contributed data, giving a low risk of attrition bias.

Selective reporting

Serfaty 2002 reported sleep outcomes that differed from those listed in the study methods, and we judged it at high risk of bias for this item. We found trial registry entries in ClinicalTrials.gov and in the European clinical trial registry that we considered highly likely to refer to the study reported as Wade 2014, although there were differences between both trial registry entries and the published data, including differences in the number and location of sites, and in primary and secondary outcomes. Wade 2014 reported data on a subgroup with insomnia at baseline; although we included this subgroup as relevant to the review, it was not clear that the insomnia threshold had been defined prospectively. Wade 2014 measured quality of life, but the data were not reported beyond a statement of no significant difference. We considered this study at high risk of reporting bias. A trial registry entry for Morales-Delgado 2018 was posted on 28 February 2017, after the study was completed. This entry listed only two outcomes although additional outcomes were reported in the paper, and no protocol was available. We considered this study to have an unclear risk of selective reporting. For NCT03001557, we relied on the trial protocol and the entry in ClinicalTrials.gov. Several outcomes listed in the protocol were not listed as outcomes in the trial registry and were not reported on the ClinicalTrials.gov website so we considered there to be a high risk of bias in this domain, based on the currently available data. As far as we could determine, the other studies reported on all their planned outcomes.

Other potential sources of bias

We identified no other major sources of bias. Herring 2020, NCT00325728, NCT03001557, and Wade 2014 were commercially sponsored.

Effects of interventions

See: **Summary of findings 1** Melatonin compared to placebo for sleep disturbances in dementia; **Summary of findings 2** Trazodone compared to placebo for sleep disturbances in dementia; **Summary of findings 3** Orexin antagonists compared to placebo for sleep disturbances in dementia

Melatonin

We were unable to extract the intended data from Serfaty 2002, as data were presented as medians and interquartile ranges (IQR). The study had a cross-over design, and while the authors reported using an analysis that took account of this, the analysis method was not specified in any detail. Paired data were not presented. No data were presented for several outcomes. The authors reported no significant effect of treatment on total time asleep, number of awakenings, or sleep efficiency. Without presenting any data, they also reported no significant effect of treatment on carers' visual analogue scale (VAS) ratings of participants' sleep quality, or on MMSE scores. They stated that there were no adverse effects of treatment, but this was not listed as an outcome, and they provided no details on how the information was gathered.

We judged Dowling 2008, Morales-Delgado 2018, Singer 2003, and Wade 2014 to be sufficiently similar to justify the synthesis of data, despite some methodological differences, notably the concurrent morning bright light treatment in Dowling 2008, and the differences in melatonin dose. Morales-Delgado 2018 and Wade 2014 did not report any of our primary sleep outcomes because they did not measure sleep objectively (using actigraphy or polysomnography).

We were able to perform meta-analyses for two actigraphic sleep outcomes. We found that there may be little or no effect of melatonin on TNST (MD 10.68 minutes, 95% CI −16.22 to 37.59; 2 studies, n = 184; Analysis 1.1; Figure 4), or on the ratio of daytime sleep to night-time sleep (MD −0.13, 95% CI −0.29 to 0.03; 2 studies, n = 184; Analysis 1.6; Figure 5). Heterogeneity was low (I^2 = 0% for both analyses), and inspection of the forest plots did not suggest any difference between the immediate-release and SR melatonin

formulations. We considered this evidence to be of low certainty, downgraded due to very serious imprecision.

Figure 4. Forest plot of comparison: 1 Melatonin versus placebo, outcome: 1.1 total night-time sleep time (minutes).

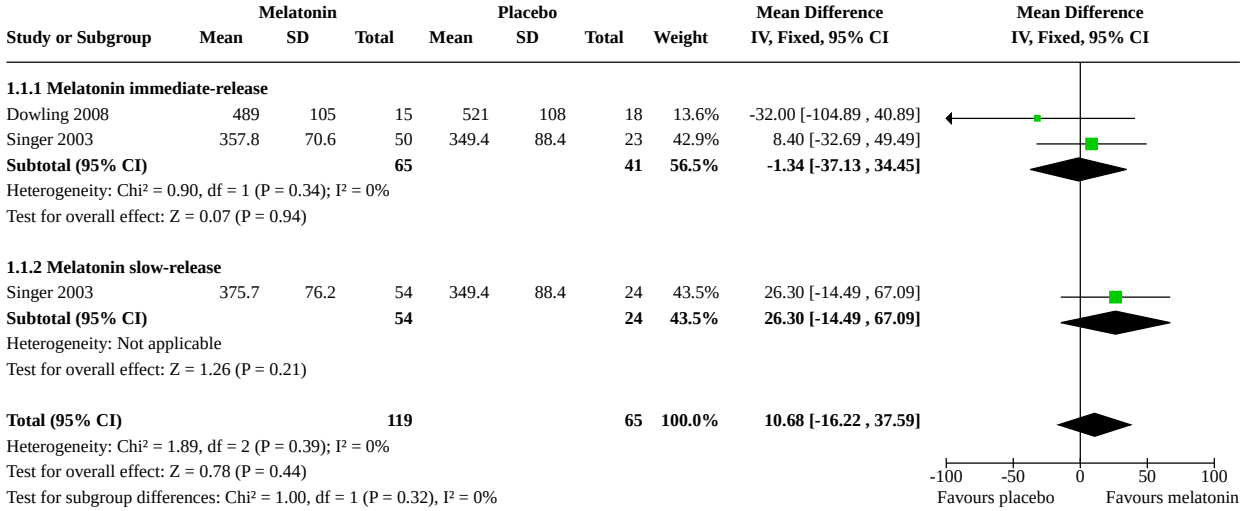
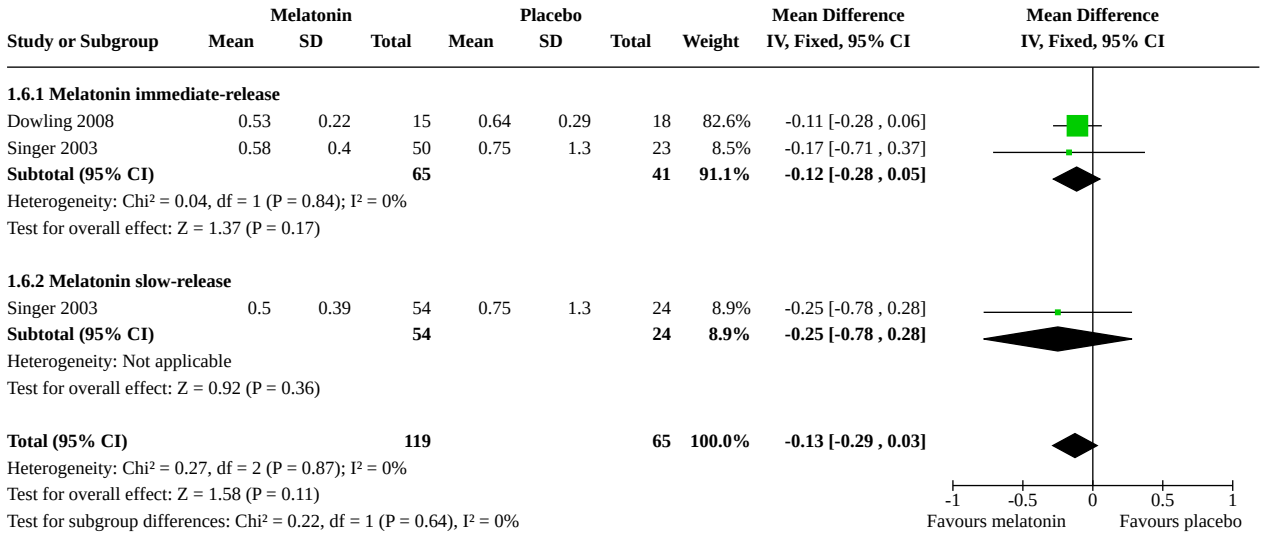


Figure 5. Forest plot of comparison: 1 Melatonin versus placebo, outcome: 1.5 ratio of daytime sleep to night-time sleep.



One of the two studies reported our other primary sleep outcomes. There may be little or no effect of melatonin on sleep efficiency (MD –0.01%, 95% CI –0.04 to 0.03; 1 study, n = 151; Analysis 1.2), nocturnal time awake after sleep onset (MD 9.08 minutes, 95% CI –7.51 to 25.66; 1 study, n = 151; Analysis 1.3), or number of night-time awakenings (MD 6.00, 95% CI –2.65 to 14.65; 1 study, n = 33; Analysis 1.4). Although neither study reported consolidated sleep time, which was a sleep outcome considered a priority by our advisory group of carers, Dowling 2008 reported the mean duration of sleep bouts, which we considered bore sufficient relation to consolidated sleep time for us to report it. There may be little or no effect of melatonin on the mean duration of nocturnal sleep bouts (MD –2.00 minutes, 95% CI –8.27 to 4.27; 1 study, n = 33; Analysis 1.5). We considered the evidence supporting all these results to be of low certainty, downgraded due to imprecision (wide CIs and small numbers of participants). Neither study measured sleep latency.

Two studies reported adverse effects (Singer 2003; Wade 2014), although Wade 2014 reported adverse event data for the whole trial population, not for the insomnia subgroup, so we did not use these data (for consistency with our exclusion of other trials that did not meet our inclusion criterion of sleep problems at baseline). There was low-certainty evidence, downgraded due to imprecision, that melatonin and placebo groups did not differ in the number of adverse event reports per person (MD 0.20, 95% CI –0.72 to 1.12; 1 study, n = 151; Analysis 2.1), in the severity of adverse events (3-

point scale from 1 = mild to 3 = severe; MD 0.10, 95% CI −0.06 to 0.26; 1 study, n = 151; Analysis 2.2), or in the likelihood of reporting any adverse event (74% in the melatonin group versus 69% in the placebo group; RR 1.07, 95% CI 0.86 to 1.33; 1 study, n = 151; Analysis 2.3). Morales-Delgado 2018 reported only that "the treatment was well-tolerated in all cases," and that no serious adverse events occurred during the trial, although they also reported that one participant in the placebo group died.

Morales-Delgado 2018, Singer 2003, and Wade 2014 reported our secondary outcome of carer-rated sleep quality. Singer 2003 used a 5-point rating of sleep quality; Morales-Delgado 2018 and Wade 2014 used the PSQI. Morales-Delgado 2018 stated that this could be completed by the patient or the carer, but we decided to include the data and consider this as a potential source of heterogeneity. Wade 2014 reported outcomes after 12 and 24 weeks; we preferred to pool the 12-week data with the eight-week data reported by Morales-Delgado 2018 and Singer 2003. In this analysis, a higher score equated to better sleep. We found moderate-certainty evidence, downgraded for imprecision, that melatonin probably has little or no effect on carer-rated sleep quality (SMD −0.02, 95% CI −0.32 to 0.28; 3 studies, n = 195; Analysis 1.7). Heterogeneity in this meta-analysis was low (I^2 = 15%). We imputed the standard deviation (SD) of the change from baseline for Morales-Delgado 2018, assuming a correlation of 0.8 between baseline and final scores. A sensitivity analysis with the conservative assumption of no correlation between baseline and final scores had minimal effect on the result.

Three studies reported cognition (Morales-Delgado 2018; Singer 2003; Wade 2014). All three trials assessed cognition using the MMSE, but Morales-Delgado 2018 reported data as medians with IQRs so we were unable to include this study in the meta-analysis. Singer 2003 and Wade 2014 also assessed cognition with the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog). Wade 2014 reported cognitive data from the 24-week time point only; we pooled these data with the eight-week data from Singer 2003. We found that there may be little or no effect of melatonin on cognition assessed with change from baseline in either MMSE (MD 0.09, 95% CI −0.85 to 1.03; 2 studies, n = 162; Analysis 1.8) or ADAS-cog (MD −1.03, 95% CI −2.70 to 0.65; 2 studies, n = 162; Analysis 1.9). The effect estimates were reasonably precise, but there were few participants, and for MMSE, there was inconsistency between the two included trials (I^2 = 69%), so we considered this evidence to be of low certainty. The median MMSE score reported by Morales-Delgado 2018 at the end of treatment was 17 (IQR 9) in both groups, supporting the absence of an effect.

Three studies reported performance of ADL using the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale (Singer 2003) and Lawton's Instrumental Activities of Daily Living Scale (IADL) scale (Morales-Delgado 2018; Wade 2014). In order to pool the data from Morales-Delgado 2018 with the other studies, we imputed the SD of the change from baseline (assuming r = 0.8, and then r = 0 in a sensitivity analysis). In this analysis, a higher score equated to better functioning. We found moderate-certainty evidence, downgraded for imprecision, that melatonin probably has little or no effect on performance of ADLs at the end of treatment (SMD −0.04, 95% CI −0.34 to 0.26; 3 studies, n = 195; Analysis 1.10; minimal change in sensitivity analysis).

One study measured patients' quality of life (Wade 2014), but did not report the data; the paper stated that there was no significant difference between treatment groups.

One study assessed carer burden using the Zarit Burden Interview (Morales-Delgado 2018). We found low-certainty evidence, downgraded for very serious concern about imprecision, that there may be little or no effect of melatonin on carers' feelings of burden (MD −6.20, 95% CI −19.81 to 7.41; 1 study, n = 31; Analysis 1.11). Wade 2014 measured carers' sleep with the Sleep Disorders Inventory (SDI); data were not reported but the text indicated that there was no significant difference between groups

Our sensitivity analysis in which the two active treatment groups in Singer 2003 were combined to form a single group had no effect on the results for our primary sleep outcomes (not shown).

Trazodone

Camargos 2014 presented results as the MD (with 95% CI) between trazodone and placebo groups post-treatment, adjusted for baseline values using an analysis of covariance (ANCOVA). We considered the evidence related to all the sleep outcomes of low certainty, downgraded due to very serious imprecision (wide CIs and a very small number of participants, n = 30). We found evidence that trazodone may increase TNST (MD 42.46 minutes, 95% CI 0.9 to 84.0) and sleep efficiency (MD 8.53%, 95% CI 1.9 to 15.1). There may be a decrease in the time spent awake after sleep onset, but this result was very imprecise and also compatible with an increase in time awake (MD −20.41 minutes, 95% CI −60.4 to 19.6). There may be little or no effect on the number of nocturnal awakenings (MD −3.71, 95% CI −8.2 to 0.8), the amount of time spent asleep during the day (MD 5.12 minutes, 95% CI −28.2 to 38.4), or the number of daytime naps (MD 0.84, 95% CI −2.6 to 4.3).

Data on adverse events were collected by spontaneous report only; 4/15 participants in the trazodone group and 6/15 in the placebo group reported an adverse event; all were mild.

The study included several of our secondary outcomes. Carers of 10/15 trazodone-treated participants and 9/15 placebo-treated participants rated the participant's sleep as better, or much better. There was no evidence of a difference between groups in ADL performance on the Katz Index (MD 0.5, 95% CI −0.8 to 1.8; low-certainty evidence), or on any of a variety of cognitive measures, including the MMSE (MD 0.1, 95% CI −0.9 to 1.1; moderate-certainty evidence). The study did not report quality of life and carer burden.

Ramelteon

The sponsor's clinical trial synopsis for NCT00325728 gave most results in brief narrative form. The synopsis named the primary outcome as TNST at one week, despite the study duration being eight weeks. In all other included studies, the primary outcome was reported at the end of the treatment period. Therefore, we sought data from both the one-week and eight-week time points. Results were derived from an ANCOVA model with effects for treatment, pooled centre and baseline disease severity (mild or moderate), and with baseline as a covariate. The trial synopsis reported no significant difference between groups for the primary outcome of TNST at week one (MD 18.2 minutes, 95% CI −7.8 to 44.3). There was also no significant difference between groups after one week in the percentage of participants whose night-time sleep time increased by 30 minutes or more, in time awake after sleep onset, in sleep

efficiency, or in the number of daytime naps. Daytime total sleep time was significantly higher in the ramelteon group after one week (MD 43.1 (standard error (SE) 16.19) minutes; P = 0.010), although this was not seen at later time points. The ramelteon group also had a significantly higher ratio of daytime to night-time sleep at weeks one (P = 0.014), four (P = 0.019), and eight (P = 0.029), or early termination. No other sleep outcomes differed significantly between groups at week eight. The exploratory (non-sleep) outcomes appeared to have been assessed at weeks four and eight only. Among these, the only significant group difference in efficacy was a lower NPI disinhibition score at week eight or early termination in the ramelteon group (MD −0.9 (SE 0.44); P = 0.039); the authors of the report did not consider the results to be clinically significant.

Adverse events that were considered possibly, probably, or definitely related to the study drug occurred in 21/74 participants, with a similar incidence in placebo and ramelteon treatment groups (29.0% with ramelteon versus 27.9% with placebo). Four participants in the placebo group experienced at least one serious adverse event; there were no such events in the ramelteon group. There were no deaths.

In general terms, the evidence related to ramelteon was of low certainty. It was from a single trial with no peer-reviewed publication; the sponsor's report lacked important details on trial methods and results.

Orexin antagonists

Two included studies investigated orexin antagonists. We pooled data at the four-week (end of trial) time point from all participants in the intervention group in Herring 2020, who received suvorexant 10 mg to 20 mg, with the combined groups of participants receiving lemborexant 5 mg and 10 mg from NCT03001557. These are the recommended dose ranges for these drugs for treatment of insomnia in adults. The data from Herring 2020 were least square MDs in change-from-baseline scores, adjusted for baseline characteristics. In order to combine the two groups from NCT03001557, we used unadjusted change-from-baseline data. Because the studies used different outcomes, the only one of our primary sleep outcomes for which we could conduct a meta-analysis was sleep efficiency. Again, although no studies had reported consolidated sleep time, which was the sleep parameter favoured by our advisory group of carers, NCT03001557 reported the mean duration of sleep bouts, which we considered bore sufficient relation to consolidated sleep time for us to report it.

We found the following evidence for our primary sleep outcomes, where all results were changes from baseline:

- moderate-certainty evidence from one study that an orexin antagonist (suvorexant 10 mg to 20 mg) is probably associated with an increase in TNST (MD 28.2 minutes, 95% CI 11.1 to 45.3; n = 274; Analysis 4.1; downgraded for imprecision);
- low-certainty evidence from one study that an orexin antagonist (lemborexant 5 mg or 10 mg) may have little or no effect on the mean duration of sleep bouts (MD −2.42 minutes, 95% CI −5.53 to 0.7; n = 38; Analysis 4.2; downgraded for very serious concern about imprecision);
- moderate-certainty evidence from one study that an orexin antagonist (suvorexant 10 mg to 20 mg) is probably associated with a decrease in nocturnal time awake after sleep onset (MD −15.7 minutes, 95% CI −28.1 to −3.3; n = 274; Analysis 4.4; downgraded for imprecision);
- low-certainty evidence from two studies that orexin antagonists may be associated with a small increase in sleep efficiency (MD 4.26%, 95% CI 1.26 to 7.26; n = 312; Analysis 4.3). There was substantial heterogeneity associated with this result (I^2 = 59%), which was downgraded for imprecision and inconsistency;
- moderate-certainty evidence from one study that an orexin antagonist (suvorexant 10 mg to 20 mg) probably has little or no effect on the number of nocturnal awakenings (MD 0.0, 95% CI −0.5 to 0.5; n = 274; Analysis 4.5);
- low-certainty evidence from one study that an orexin antagonist (suvorexant 10 mg to 20 mg) may be associated with a small reduction in sleep latency although the result was imprecise and also compatible with little or no effect (MD −12.1 minutes, 95% CI −25.9 to 1.7; n = 274; Analysis 4.6).

Both trials reported the number of participants experiencing at least one adverse event. We found that adverse events were probably no more common among participants taking orexin antagonists than those taking placebo (RR 1.29, 95% CI 0.83 to 1.99; 2 studies, n = 323; Analysis 5.1). Herring 2020 reported one serious adverse event in the trial (a fall with fracture in the suvorexant group). NCT03001557 reported no serious adverse events.

We were able to pool data from both studies on changes from baseline in carers' ratings of participants' sleep using the SDI (range 0 to 12 where 12 is worst). We found moderate-certainty evidence that orexin antagonists had little or no effect on carer ratings of participants' sleep (MD −0.09, 95% CI −0.19 to 0.01; 2 studies, n = 312; Analysis 4.7).

We found moderate-certainty evidence from one study that an orexin antagonist (suvorexant 10 mg to 20 mg) probably has little or no effect on cognitive function measured with the MMSE (MD 0.0, 95% CI −0.5 to 0.5; n = 274; Analysis 4.8).

Neither study assessed performance of ADLs or quality of life.

Herring 2020 reported a number of carer outcomes. There was no evidence of an effect of suvorexant treatment for the participant on carers' ratings of their own sleep quality assessed on a single-item sleep quality scale (MD 0.2, 95% CI −0.2 to 0.7; 1 study, n = 274) or on carer distress scored as part of the SDI (range 0 to 5, where 5 is more distressed) (MD −0.1, 95% CI −0.2 to 0.1; 1 study, n = 274).

Although we chose lemborexant doses within the recommended dose range of 5 mg to 10 mg for treatment of insomnia in adults to include in meta-analyses and to report in the 'Summary of findings' table, we also extracted data on our primary outcomes for the lower dose (2.5 mg) and the higher dose (15 mg) investigated in NCT03001557. We found no evidence of an effect of either dose on sleep efficiency, mean duration of sleep bouts, or number of participants experiencing one or more adverse events, but all groups were very small (11 or 12 participants) and all results very imprecise; this is low-certainty evidence.

DISCUSSION

Summary of main results

We found no evidence from four RCTs, reporting data on 222 participants, that melatonin had either beneficial or harmful effects

on any major sleep outcome in people with sleep disorders with moderate-to-severe dementia due to AD. There were no serious adverse events reported in the trials.

One RCT of trazodone (30 participants) found that trazodone 50 mg at night may improve TNST and sleep efficiency in people with moderate-to-severe AD and disturbed sleep. It did not find evidence of an effect on daytime sleep, or on cognition or ADL. There were no serious adverse events.

One phase 2 trial of ramelteon (74 participants), reported in summary form on the sponsor's website, found no clear evidence of benefit or harm from ramelteon, used for the treatment of sleep disturbances in people with mild-to-moderate AD. There was some evidence, reported briefly, to suggest more daytime sedation in the ramelteon group. There were no serious adverse events among participants taking ramelteon.

Two studies of orexin antagonists, which included 323 participants with mild-to-moderate AD and either insomnia or irregular sleep-wake disorder, found some beneficial effects. Orexin antagonists probably lead to an increase in nocturnal sleep time and a reduction in the time awake after sleep onset, but not to a reduced number of awakenings. They may also be associated with an increase in sleep efficiency and reduced sleep latency. However, they may have little or no effect on the mean duration of a sleep bout and probably have no effect on carers' perception of participants' sleep quality. We found no evidence that the effects come at the expense of an excess of adverse events or impaired cognitive function.

Overall completeness and applicability of evidence

Although the number of trials of medications for sleep disorders in dementia is slowly increasing, important evidence to help guide treatment choices is still lacking. All the data was on participants with AD (other than in the small study, Morales-Delgado 2018, which did not specify dementia subtype) although sleep problems may be even more common in people with VaD and, especially, DLB or PDD.

We found adequately reported data from RCTs for trazodone, melatonin, and the novel orexin antagonists suvorexant and lemborexant. Trazodone is a drug in common clinical use for this indication, but the one study of trazodone was very small (30 participants), so its results must be regarded as preliminary. Of the five published trials of melatonin, only two yielded data on our primary sleep outcomes suitable for meta-analysis. A sixth RCT of melatonin was probably conducted, but we were unable to locate any data (Tozawa 1998). This trial purportedly found a beneficial effect of melatonin, but given its very small size (seven participants), it was unlikely to have had a substantial impact on our results.

No peer-reviewed data were available from a commercially sponsored trial of ramelteon that had been completed, and we found no other RCTs of melatonin agonists in people with dementia.

This update of our review includes data on a new class of hypnotic, the orexin antagonists. Two commercially sponsored trials investigated the effects of suvorexant and lemborexant, the latter being a phase 2, dose-finding study.

We found no RCTs of other drugs that are widely prescribed for sleep problems in dementia, including the benzodiazepine and non-benzodiazepine hypnotics, although there is considerable uncertainty about the balance of benefits and risks associated with these common treatments. One small trial of Z-drugs in ongoing (NCT03075241).

One of the included trials studied melatonin in combination with morning bright light; although heterogeneity between studies was low, on the basis of the small amount of included data, we could not confidently exclude any differential effects of melatonin in combination with light therapy. The doses of melatonin used in these studies were at or above the dose licensed for healthy elderly people in Europe, but were nevertheless low in comparison to doses of melatonin and melatonin analogues that have been used or studied in other populations (without dementia). We found no evidence relating to high-dose melatonin treatment in people with dementia, but it is possible that effects could be different. Several different mechanisms are likely to cause sleep disturbances in dementia, some of which may relate to circadian misalignment, and achieving the full chronobiotic effect of melatonin in these circumstances may take up to several months. Therefore, it is possible that some patients might respond to longer periods of treatment with melatonin. Until patients can be well-characterised on the basis of the mechanisms underlying their sleep disorders, differential effects on different subgroups cannot be excluded.

The sleep outcomes studied varied between studies. It was notable that our panel of carers afforded the highest priority to uninterrupted sleep at night; their two highest priority sleep outcomes were the number of nocturnal awakenings and consolidated nocturnal sleep time, which was not measured in any of the studies. This may go some way to explaining why, even where beneficial effects on some sleep outcomes were found, this was not necessarily reflected in any perception of improved sleep quality on the part of carers. The sleep of carers themselves was measured by self-report in only two studies.

Small RCTs are limited in their ability to detect adverse effects of treatment, but they can provide important evidence on common adverse events. One of the included trials made no mention of adverse effects of treatment, and three others failed to report adverse events in any detail. This was a gap in the evidence, given the potential for all sedative drugs to cause significant adverse events in people with dementia.

Quality of the evidence

Seven of the included studies measured sleep outcomes objectively. Six of these used actigraphy and one used polysomnography. Although polysomnography is considered the gold standard in sleep studies, its use in this patient group is challenging and it is perhaps not surprising that the study in which it was used had a very high proportion of participants with mild dementia. However, there is evidence of a good correlation between actigraphy and polysomnography measures in people with dementia (Ancoli-Israel 1997).

No study was at overall high risk of selection, performance, or detection bias. There were significant problems with attrition in two studies, largely reflecting poor tolerance of actigraphy among participants with AD and technical difficulties with the procedures. We judged three studies at high risk of selective

reporting bias because of discrepancies between planned and reported outcomes, which may affect the overall body of evidence. We did not consider the results of this review to be at significant risk from bias in the included trials.

Overall, we considered the certainty of evidence for trazodone to be low for almost all outcomes due to imprecision (wide CIs and data from one small study). We rated the evidence for melatonin at low certainty for all outcomes, again downgraded due to imprecision; although there were several trials, many outcomes were reported in only one trial, the numbers of participants were low, and the CIs were wide. For orexin antagonists, the certainty of evidence was moderate or low for all outcomes. Almost all outcomes were reported by only one trial and there was inconsistency between trials for the only objective sleep outcome that we could include in a meta-analysis. Other than for the MMSE, where estimates of a minimum clinically important difference have been published (e.g. Howard 2011), we had to base our judgements about precision, in part, on what we considered were likely to be clinically important differences.

Potential biases in the review process

We identified no potential biases in the review process.

Agreements and disagreements with other studies or reviews

Cardinali 2010 included a non-systematic review of studies of melatonin in people with AD, covering case reports and non-randomised studies as well as RCTs. The authors identified two RCTs with sleep outcomes, which we excluded because participants were not selected for a sleep problem at baseline. Following a narrative synthesis, they found the evidence for efficacy to be inconclusive.

Xu 2015 conducted a systematic review and meta-analysis of RCTs of melatonin in people with dementia, examining sleep efficiency, total sleep time, and cognitive outcomes. The authors included seven RCTs. We excluded three of these because participants had not been identified as having a sleep disorder at baseline (Asayama 2003; Gehrmann 2009; Riemersma-van der Lek 2008); a fourth study included by Xu had no primary aim to improve sleep (Gao 2009), and Xu and colleagues were able to extract only a cognitive outcome. In contrast to our findings, these authors reported marginal improvement in sleep efficiency and an increase in total sleep time on melatonin. However, we considered that there were important methodological errors in their review, including a unit of analysis error which led to excessive weight being given to the 'positive' results of Singer 2003.

AUTHORS' CONCLUSIONS

Implications for practice

The implications of this review for practice are limited by the scope of the primary evidence. The studies reviewed suggest that melatonin is unlikely to be of benefit to people with moderate-to-severe dementia due to Alzheimer's disease (AD) and sleep problems. There is some evidence that a low dose (50 mg) of trazodone improves sleep in people with moderate-to-severe dementia due to AD, although a larger trial is needed to be able to draw a more definitive conclusion on the balance of risks and benefits. There is also evidence that orexin antagonists probably improve some aspects of sleep in people with mild-to-moderate AD. However, until further evidence emerges, this and other hypnotic drugs should be used with particular caution in people with AD or other dementias if non-pharmacological treatment approaches have been unsuccessful, with careful assessment of the risks (of treatment and of no treatment), efficacy, and adverse effects in individuals.

Implications for research

There are many questions about drug treatment for sleep disorders in dementia still to be answered. Research is needed into a wider range of dementia-related sleep disorders and dementia subtypes beyond AD. Promising results in the literature for trazodone and orexin antagonists require replication and extension to a broader range of participants.

We consider that there is still a need for studies of other drugs that are in common clinical use. There is a risk that evidence will accumulate for novel, patented medications before the efficacy and harms of cheap and widely available hypnotic drugs in this population are understood. Pragmatic trials in clinical settings that employ sequential strategies in line with clinical guidelines (e.g. recruiting only people who have not responded to a non-pharmacological intervention) would be valuable.

The field of sleep research in dementia would benefit greatly from consensus on patient- and carer-important outcomes. From our own small-scale carer consultation exercise, there is evidence that research is not necessarily addressing the outcomes considered most important by carers. It is vitally important that trials include systematic assessment of adverse events.

Attention to consistency of trial design, actigraphy techniques, and reporting would aid further synthesis and interpretation of research in this area. Helpful suggestions regarding this are made by Camargos (Camargos 2013).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Camargos 2014

Study characteristics	
Methods	RCT, 2 parallel treatment groups
Participants	Number of participants: 36 randomised, data available for 30 Country: Brazil Setting: outpatients of a Geriatric Medical Centre Diagnosis: probable AD (NINCDS-ADRDA criteria)

Camargos 2014 *(Continued)*

	Sleep-related inclusion criteria: insomnia – complained of by patient or observed by carer; researcher judged the insomnia to be due to the dementia; the sleep disorder caused emotional distress to the carer (NPI ≥ 2) Gender: 20 women, 10 men Age: 81.0 (SD 7.5) years Severity of dementia: MMSE 11.2 (SD 6.2)
Interventions	Duration of treatment: 2 weeks Treatment group 1 (n = 15): trazodone 50 mg once daily Treatment group 2 (n = 15): placebo Route of administration: oral Time of administration: 10 p.m.
Outcomes	Single actigraph records were created for the 7- to 9-day screening/baseline and 2-week treatment periods Primary: • TNST • night-time waking after sleep onset • night-time number of awakenings • dTST • number of daytime naps (> 10 minutes) • night-time percent sleep (sleep efficiency) • gain of > 30 minutes in TNST Secondary: • cognitive function (MMSE, Paired Associate Learning Test forms I & II of Wechsler Memory Scale, Digit Span Test, Arithmetic, Letter-Number Sequencing, Digit Symbol-Coding, and Symbol Search of the WAIS-III • ADL (Katz Index of Independence in Activities of Daily Living) • tolerability and AEs (collected by spontaneous report) • subjective analysis of sleep improvement by carer
Notes	Adherence to treatment > 85% in all participants Non-commercial funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Online random number generator (www.random.org) was used by 1 investigator to produce random alphanumeric, 3-digit codes. These then were used by external pharmacist to label tablet bottles. Bottles were handed "in scrambled order" to clinical pharmacist to dispense.
Allocation concealment (selection bias)	Low risk	Allocation sequence known only to 1 investigator who took no further part in study, inaccessible to recruiting clinicians or clinical pharmacist.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both the medication pills and the equivalent placebos were received in bulk from the sole manufacturer of trazodone in Brazil (Apsen Laboratory®), and the placebos were prepared to be indistinguishable in appearance with

Camargos 2014 *(Continued)*

All outcomes		trazodone prepared as 50-mg pills. The bottles of trazodone or placebo had the same size." Quote: "All patients and geriatricians were blinded to the treatment assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All patients and geriatricians [outcome assessors] were blinded to the treatment assignment, and the final randomization list was not accessed until the clinical database was completed." Note: confirmed by author to mean after actigraphic analysis was completed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	After randomisation, 1 participant was excluded from each group for clinical reasons (heart failure secondary to noncompliance with other medication, episode of agitation leading to arm fracture), and 4 participants (3 trazodone, 1 placebo) due to technical failure of actigraphy. We judged these exclusions to be unlikely to lead to bias.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None identified.

Dowling 2008

Study characteristics	
Methods	RCT, 3 parallel treatment groups
Participants	Number of participants: 50 completed study (33 contributed data to this review) Country: USA Setting: 2 large long-term care facilities Diagnosis: probable AD (NINCDS-ADRDA criteria) Sleep-related inclusion criteria: rest-activity rhythm disruptions including insomnia, frequent nighttime awakenings, wandering at night, unusually early morning awakenings, sundowning, excessive daytime sleepiness. Gender: 43 women, 7 men Age: 86 (SD 8) years (range 60–100) Severity of dementia: MMSE 9.3 (SD 7.9), no significant difference between groups
Interventions	Duration of treatment: 10 weeks Treatment group 1 (n = 15): melatonin 5 mg in the evening combined with bright light exposure in the morning (light for 1 h, > 2500 lux, at gaze height, 5 days a week) Treatment group 2 (n = 18): lactose placebo in the evening combined with bright light exposure in the morning Route of administration: oral Time of administration: 5–6 p.m. (bedtime at 8 p.m.) Treatment group 3 (n = 17): usual light only, no drug or placebo (not included in review)

Dowling 2008 *(Continued)*

Outcomes	All outcomes measured using actigraphy over a 108-h monitoring period (Monday 8 p.m. to Saturday 8 a.m.) Outcome time points: baseline and end of treatment (10 weeks) Sleep/wake: Night-time outcomes • sleep time • number of awakenings • sleep bout duration • wake bout duration Daytime outcomes • sleep time • sleep bout duration • wake bout duration • number of sleep bouts • day total activity Subsidiary measures: Additional circadian outcomes were computed to quantify each participant's 24-h rest-activity rhythm, and this was then used to assess: • interdaily stability: the degree of resemblance between activity patterns of individual days • intradaily variability: the fragmentation of periods of rest and activity • L5: sequence of the 5 least-active hours in 24-h mean activity profile. Mean activity during L5 provides an indication of trough or nadir of the rhythm (i.e. regularity and restfulness of sleep periods) • M10: sequence of the 10 most-active hours in 24-h mean activity profile. Mean activity during M10 provides an indication of the peak of the rhythm (how active and regular the activity (wake) periods are) • amplitude: the difference between the most-active 10-h period and the least-active 5-h period in a mean 24-h pattern • relative amplitude: reflects the normalised difference between the most-active 10-h period and the least active 5-h period in a mean 24-h pattern
Notes	Placebo and melatonin groups did not differ significantly in bright light received No mention of AEs Non-commercial funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomly assigned to one of the three groups." Comment: no information on randomisation method provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The University of California, San Francisco Drug Product Services Laboratory provided melatonin (5 mg) and identically appearing lactose placebo capsules."

Dowling 2008 *(Continued)*

		Quote: "Study staff, nursing home staff, and subjects were all blinded to melatonin treatment group assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Study staff … were all blinded to melatonin treatment group assignment." Comment: outcomes were actigraphy data (objective).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Fifty subjects completed the study." Comment: no mention of how many participants were randomised, so unclear if there were any dropouts. Those completing the study were reported to have tolerated the procedures well. There was a target of 108 h of data at each time point. Valid data at baseline: mean 105 h (range 75–108); valid data at the end of intervention: mean 107 h (range 90–108); quote: "no significant differences between the groups."
Selective reporting (reporting bias)	Low risk	Results reported for all listed outcome measures.
Other bias	Low risk	None identified.

Herring 2020

Study characteristics	
Methods	RCT, 2 parallel treatment groups
Participants	Number of participants: 285 Country: 8 countries Setting: 35 centres, quote: "primarily memory clinics and contract research clinics with experience in neurology studies" Diagnosis: NIA-AA and DSM-5 clinical criteria for probable AD dementia Sleep-related inclusion criteria: DSM-5 criteria for insomnia, quote: "confirmed by a mean total sleep time (TST) of <6 hours over screening and (by) baseline sleep laboratory polysomnography (PSG) visits, with neither night >6.5 hours." Gender: 65% women Age: 71% ≥ 65 years Severity of dementia: 79% AD of mild severity (MMSE 21–26); 21% moderate severity (MMSE 12–20)
Interventions	Duration of treatment: 4 weeks (3-week screening period, 2-week single-blind placebo run-in, 4-week double-blind randomised treatment period). Treatment group 1 (n = 142): suvorexant 10 mg once a day. Quote: "At the week 2 clinic visit, this dose could be escalated, in a blinded fashion, to the maximum recommended dose of 20 mg (or matching placebo) if there was insufficient response as indicated by a Clinical Global Impression – Severity (CGI-S) for insomnia of mildly ill or worse and the tolerability of the current dose was acceptable in the investigator's judgment." Treatment group 2 (n = 143): matching placebo Route of administration: oral

Herring 2020 *(Continued)*

	Time of administration: 30 minutes before bedtime
Outcomes	Overnight PSG in a sleep laboratory for 8 h starting at participant's usual bedtime Outcome time points: baseline (7 days before randomisation) and at the end of the 4-week treatment period Primary: • TST Secondary: • WASO (amount of time awake during recording period after the first period of continuous sleep lasting ≥ 10 minutes) "Exploratory": • percentage of responders achieving an improvement in TST ≥ 50 minutes • TST and WASO by thirds of the night • sleep efficiency • latency to persistent sleep • number of arousals adjusted for TST • number of awakenings adjusted for TST • PSG sleep architecture (%TST in REM, N1, N2, N3, and REM sleep latency) • partner-rated assessments of the patient's sleep (daily e-diary including SQR) • total score on the SDI (weekly, trial-partner assessed), CGI-S, and partner-rated assessment of their own sleep quality and distress (SSQC) • NPI • MMSE • Digit Symbol Quote: "Actigraphy measures were also recorded via an activity/sleep watch worn by the patient and will be the subject of a separate report." Safety assessed by AE reports, laboratory analyses, electrocardiography, and physical examinations. Quote: "A guidance document listing adverse events pre-specified as events of clinical interest for which additional information was to be collected was provided to investigators."
Notes	Sponsored by MSD. Conflict of interest declarations: 8/9 authors are current or former employees of MSD, a subsidiary of Merck & Co., Inc. and own or owned stock options in Merck & Co., Inc. The 9th author has acted as a consultant for Merck & Co., Inc., Jazz, Eisai, and Ferring.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An interactive response system randomly assigned patients to suvorexant or placebo in a 1:1 ratio according to a computer-generated assignment schedule. Randomization was stratified according to dementia severity as indexed by screening MMSE score (moderate = 12–20, mild = 21–26), with the intention to enroll ≈30% of patients in the moderate stratum."
Allocation concealment (selection bias)	Low risk	Quote: "An interactive response system randomly assigned patients to suvorexant or placebo …"

Herring 2020 *(Continued)*

		From protocol: quote: "The Clinical Biostatistics department will generate the randomized allocation schedule(s) for trial medication assignment. Randomization will be implemented by an interactive voice response system (IVRS)."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All treatments were administered as identical-appearing tablets." Quote: "At the week 2 clinic visit, this dose could be escalated, in a blinded fashion, to the maximum recommended dose of 20 mg (or matching placebo) if there was insufficient response … The patient and caregiver were not told if the dose was increased." From protocol: quote: "5.2.3 Trial Blinding/Masking: The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Sleep stage scoring of the PSG recordings was performed for each 30 second epoch … by a certified sleep technician at a central sleep scoring laboratory." AEs: quote: "An independent committee blind to treatment assignment comprising three experts in neurology, psychiatry, and sleep, respectively, adjudicated all events of clinical interest." From protocol: quote: "5.2.3 Trial Blinding/Masking: The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The modified intent-to-treat approach was used for the primary and secondary efficacy endpoints, in which treated patients with both a baseline measurement and at least one post-randomization observation were included." Suvorexant: randomised n = 142; treated n = 142; discontinued n = 6 (participant withdrew n = 5, screen failure n = 1); completed trial n = 136; analysed efficacy n = 135, safety n = 142. Placebo: randomised n = 143; treated n = 143; discontinued n = 2 (participant withdrew n = 2); completed trial n = 141; analysed efficacy n = 139, safety n = 143. Quote: "The number of patients in the full-analysis-set for the primary endpoint of change from baseline in TST at week 4. In the suvorexant group, seven patients were excluded due to missing PSG data. In the placebo group, two patients were excluded due to missing PSG data and two patients were excluded due to Good Clinical Practice noncompliance issues at one site."
Selective reporting (reporting bias)	Low risk	Data on actigraphy outcomes not yet available although paper stated that these will be published elsewhere.
Other bias	Low risk	None identified.

Morales-Delgado 2018

Study characteristics	
Methods	RCT, 2 parallel treatment groups
Participants	Number of participants: 40 randomised, 31 completed study and included in analysis

Morales-Delgado 2018 *(Continued)*

	Country: Mexico Setting: single centre, outpatients of geriatric clinic Diagnosis: mild or moderate dementia (CDR, 1 and 2) Sleep-related inclusion criteria: DSM-5 circadian cycle sleep disorder with insomnia Gender: 24 women; 7 men Age: mean melatonin group 82.2 (SD 5.8) years; mean placebo group 83.1 (SD 7.4) years; range in whole study sample 66–93 years Severity of dementia: 11 in CDR stage 1; 20 in CDR stage 2
Interventions	Duration of intervention: 8 weeks Treatment group 1 (n = 16): melatonin 5 mg Treatment group 2 (n = 15): placebo Route of administration: oral Time of administration: 1–2 h before bedtime
Outcomes	Outcomes measured at baseline and 8 weeks Primary: • PSQI completed by participant or primary carer (also completed at weeks 2, 4, and 6) Secondary: • MMSE • ADL (Katz Index of Independence in Activities of Daily Living and Lawton IADL Scale) • ZBI • NPI • short-form (15-item) GDS • MNA
Notes	Authors declared no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Selection for a treatment group was determined by a computer-generated randomization list, in a 1:1 ratio using the randomized permuted block method."
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To prevent bias, matching placebo tablets, which were identical in appearance, taste and odor, were used. The treatment was double-blinded … The patients, carers and investigators were unaware of treatment assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The … investigators were unaware of treatment assignment." "Data were secured and analyzed per the preplanned statistical analysis plan."

Morales-Delgado 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow diagram available. Melatonin group: 21 randomised, 16 included in analysis (1 moved out of state, 4 changed mind). Placebo group: 19 randomised, 15 included in analysis (1 died, 3 changed mind). Quote: "Due to the small sample size and expected drop-out rate, we did not carry out an intention-to-treat analysis."
Selective reporting (reporting bias)	Unclear risk	Trial registry entry (posted 28 February 2017, after study completion) listed only 2 outcome measures (PSQI and Minimental test (*sic*)). Additional outcomes reported in paper. No protocol available.
Other bias	Low risk	None identified.

NCT00325728

Study characteristics	
Methods	RCT Stratified by severity of dementia (mild AD (MMSE 19–28) or moderate AD (MMSE 8–18))
Participants	Number of participants: 74 randomised, 66 completed study Country: USA (38 sites) Diagnosis: diagnosis of dementia of the Alzheimer's type (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Revised), or probable AD (NINCDS-ADRDA criteria) Sleep-related inclusion criteria: history of ≥ 2 sleep disorder behaviours occurring at least once weekly in the 2 weeks prior to the first screening visit and actigraphy evidence of a TNST < 7 h/night, based on ≥ 4/7 nights of complete actigraphy data collected over the single-blind, placebo run-in period Gender: 32 women, 42 men Age: mean 76 years (minimum for inclusion 55 years) Severity of dementia: mild or moderate, defined as MMSE 8–28, inclusive
Interventions	Duration of treatment: 8 weeks Treatment group 1: ramelteon (Rozerem) 8 mg once a day Treatment group 2: placebo Route of administration: oral Time of administration: at bedtime
Outcomes	Actigraphic data collected at 1, 2, 4, 6, and 8 weeks Primary outcome: • mean TNST as determined by actigraphy (further specified in trial synopsis as TNST at 1 week) Secondary outcomes: • night-time wake time after sleep onset • number of night-time awakenings • dTST • ratio of daytime to night-time sleep

NCT00325728 *(Continued)*

- number of daytime naps
- sleep efficiency
- safety and tolerability via AEs, laboratory tests, physical examinations, vital signs, and ECGs

Exploratory:

- NPI
- MMSE
- CGGI
- ADCS-ADL
- SDI
- CAS
- CGI

Notes	Phase 2 study of efficacy, safety and tolerability. Study completed in 2007. Sponsor: Takeda Global Research & Development Center, Inc. No peer reviewed publications identified. ClinicalTrials.gov accessed on 21 April 2020. Record last updated 14 August 2017 – status: completed. No results posted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This was a double-blind, randomized, placebo-controlled, parallel-group, proof-of-concept study." Comment: no further information provided. 43/74 (58%) participants received placebo.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "This was a double-blind, randomized, placebo-controlled, parallel-group, proof-of-concept study." Comment: no further information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "This was a double-blind, randomized, placebo-controlled, parallel-group, proof-of-concept study." Comment: no further information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	8/74 (10.8%) participants discontinued prematurely (4 placebo, 4 ramelteon). Of these, 5 participants withdrew due to an AE (3 placebo, 2 ramelteon). 2 participants withdrew voluntarily, and 1 participant was terminated for other reasons. ITT and per-protocol analyses conducted.
Selective reporting (reporting bias)	Low risk	Although reporting of results in the clinical trial synopsis was cursory, mention was made of all planned outcomes.
Other bias	Unclear risk	Limited information available.

NCT03001557

Study characteristics	
Methods	RCT, 5 parallel treatment groups
Participants	Number of participants: 63 enrolled, 62 included in analysis (1 did not receive any treatment) Country: Japan, USA, UK Setting: 57 sites, nature of sites not reported Diagnosis: AD according to NIA-AA criteria Sleep-related inclusion criteria: DSM-5 circadian rhythm sleep disorder, irregular sleep-wake type; complaint by the participant or carer of difficulty sleeping during the night or excessive daytime sleepiness associated with multiple irregular sleep bouts during a 24-h period (or both); frequency of complaint of sleep and wake fragmentation ≥ 3 days per week; duration of complaint of sleep and wake fragmentation ≥ 3 months; during the screening period, mean actigraphy-derived sleep efficiency < 87.5% within the defined nocturnal sleep period and mean actigraphy-derived wake efficiency < 87.5% during the defined wake period; confirmation by actigraphy of a combination of sleep bouts > 10 minutes during the wake period plus wake bouts > 10 minutes during the sleep period, totalling ≥ 4 bouts per 24-h period, ≥ 3 days per week Gender: 37 women, 25 men Age: 74.5 (SD 6.9) years Severity of dementia: baseline MMSE 10–26 for inclusion
Interventions	Duration of treatment: 4 weeks Treatment group 1: lemborexant 2.5 mg once daily Treatment group 2: lemborexant 5 mg once daily Treatment group 3: lemborexant 10 mg once daily Treatment group 4: lemborexant 15 mg once daily Treatment group 5: placebo Route of administration: oral Time of administration: bedtime
Outcomes	Actigraphic data at baseline and at weeks 1, 2, 3, and 4 Sleep/wake: • sleep efficiency • sleep fragmentation index • mean duration of wake bouts • wake efficiency • wake fragmentation index • mean duration of sleep bouts • intradaily variability • interdaily stability • mean activity count over least active 5-h period • mean activity count during most active 10-h period • relative amplitude of rest-activity rhythm Other (at week 4):

NCT03001557 *(Continued)*

- number of participants with non-serious or serious AEs (up to 14 days after last study dose)
- number and percentage of participants in each category of the Alzheimer's Disease Cooperative Study – CGIC-ISWRD
- ADAS-cog
- NPI-10
- SDI
- EQ-5D-5L
- PSQI
- ZBI-short

Notes	Sponsored by Eisai, Inc. ClinicalTrials.gov record accessed 11 May 2020 Results taken from ClinicalTrials.gov Information on study design, including outcomes, taken from protocol (available on ClinicalTrials.gov)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From protocol: quote: "Approximately 60 subjects will be randomized to one of the following treatment arms: PBO [placebo], LEM2.5, LEM5, LEM10, or LEM15 [LEM = lemborexant], in an approximate 1:1:1:1:1 ratio, stratified by country. Randomization will be based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician."
Allocation concealment (selection bias)	Low risk	No information. Likely to be adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	From protocol: quote: "During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per standard operating procedure." From protocol: quote: "Identity of Investigational Products The sponsor will provide lemborexant tablets in strengths of 2.5 mg, 5 mg, 10 mg and lemborexant-matched placebo, identical in appearance." Quote: "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	From protocol: quote: "During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO [contract research organisation] and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per standard operating procedure." From protocol: quote: "Identity of Investigational Products The sponsor will provide lemborexant tablets in strengths of 2.5 mg, 5 mg, 10 mg and lemborexant-matched placebo, identical in appearance."

NCT03001557 *(Continued)*

		Quote: "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The full analysis set (FAS) included group of randomized participants who received at least 1 dose of randomized study drug and had at least 1 post-dose efficacy measurement. Participants who were evaluable for this measure at given time point were included for the assessment." Randomised n = 63 (1 participant was inadvertently randomised but did not receive any study drug) Placebo: randomised n = 12; treated n = 12; completed n = 12 Lemborexant 2.5 mg: randomised n = 12; treated n = 12; completed n = 12 Lemborexant 5 mg: randomised n = 14; treated n = 13; completed n = 13, not completed n = 1; randomised but not treated n = 1 Lemborexant 10 mg: randomised n = 13; treated n = 13; completed n = 13 Lemborexant 15 mg: randomised n = 12; treated n = 12; completed n = 12
Selective reporting (reporting bias)	High risk	No full paper published. Results taken from ClinicalTrials.gov. Several outcome measures listed in protocol not listed as outcomes in trial registry entry and results not reported on trial registry.
Other bias	Unclear risk	Limited information available.

Serfaty 2002

Study characteristics	
Methods	Randomised, 2-period cross-over design
Participants	Number of participants: 44 randomised, 25 completed study Country: UK Setting: 16 participants resident in nursing home, 4 in hospital, 5 at home (25 study completers) Diagnosis: dementia (DSM-IV criteria). 35/44 (80%) of those randomised and 21/25 (84%) of those completing the study had AD or mixed (AD + vascular dementia) pathology Sleep-related inclusion criteria: sleep disturbance identified by the main carer, defined as shouting, agitated behaviour, wandering, or a combination, on ≥ 2 nights/week Gender: 16 women, 9 men (25 study completers) Age: 84.2 (SD 7.6) years (25 study completers) Severity of dementia: MMSE 13.4 (SD 8.5) (25 study completers) Other information: 9/25 were regularly taking other sleep medication (stable for ≥ 4 weeks prior to trial entry)
Interventions	Duration of treatment: 1-week baseline period, then 2 treatment periods of 2 weeks, each followed by a 1-week washout period Treatment group 1: melatonin slow-release 6 mg Treatment group 2: placebo

Serfaty 2002 *(Continued)*

	Route of administration: oral Time of administration: at usual bedtime
Outcomes	Outcomes measured for 3 nights at each of: baseline, end of both treatment periods, and end of both washout periods. Outcome was the mean of the 3 measurements at each time point 'Main' outcomes (measured with wrist actigraphy): • sleep onset time • wakening • rest period • sleep efficiency 'Subsidiary' outcomes: • carers' daily diary recordings of bedtime, sleep onset time, estimated total sleep, wake time, and comments on sleep quality • Sleep Evaluation Questionnaire (VAS) • Likert scales to assess the quality and duration of sleep for participants and carers • cognitive function (MMSE)
Notes	Tablet count was used to assess compliance: 4.9% doses missed in first treatment period, 10.6% in second; no differences between placebo and melatonin groups. Paper reported "no adverse effects," but this was not a listed outcome and it was not clear how data were gathered. 308/352 participants who met inclusion criteria had to be excluded (207 due to absence of suitable carer, other reasons not given). Results were presented as medians and interquartile ranges. Analysis method was not described in any detail. Non-commercial funding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment order was random and determined individually by a computer-generated algorithm as soon as consent was obtained."
Allocation concealment (selection bias)	Low risk	Quote: "Treatment order was random and determined individually by a computer-generated algorithm as soon as consent was obtained."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both the pharmacist dispensing the trial medication and the researchers were blind to the treatment received. The code for treatment allocation was only broken once the trial was completed." Quote: "Melatonin and placebo were identical with respect to preparation and packaging." Blindness of participants, carers, and researchers was rated using a VAS. None of the participants could remember taking medication. Neither carers nor researchers could distinguish between treatments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both the pharmacist dispensing the trial medication and the researchers were blind to the treatment received. The code for treatment allocation was only broken once the trial was completed."

Serfaty 2002 *(Continued)*

		Quote: "Melatonin and placebo were identical with respect to preparation and packaging." Blindness of participants, carers, and researchers was rated using a VAS. None of the participants could remember taking medication. Neither carers nor researchers could distinguish between treatments. Main outcomes were actigraphic (objective).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10/44 randomised participants excluded from analysis because they had no actigraph data. Further 9 participants excluded due to insufficient actigraph data (n = 6), stroke (n = 1), or poor compliance with medication (n = 2). Results reported on only 25/44 randomised. (ITT analysis conducted on 34 participants, but not reported: "as this did not alter the results.") In main analysis, group median baseline scores used in 4 cases, and LOCF in 7 cases.
Selective reporting (reporting bias)	High risk	Sleep results reported (total time asleep, number of awakenings, and sleep efficiency) differed from those described in methods section. Compliance with diary sheets poor and data not analysed. Participants' sleep quality by VAS and cognitive function reported as "unchanged with melatonin," but no data presented. Carers' sleep not reported because only 5 participants lived with informal carer.
Other bias	Unclear risk	Authors reported conducting an analysis that excluded carry-over effects on sleep outcomes. Quote: "In order to detect carry-over effects the 'summed' scores for each participant were compared across the two groups (Mel [melatonin]/Plac [placebo] and Plac/Mel; Everitt 1994). No significant carry-over effects were observed."

Singer 2003

Study characteristics	
Methods	RCT, 3 parallel treatment groups
Participants	Number of participants: 157 randomised (data for ITT analysis available for only 151 due to technical difficulties with actigraphy) Country: USA Setting: recruited through 36 AD research centres. Broad recruitment strategy including long-term care facilities; number in institutional care not specified Diagnosis: probable AD (NINCDS-ADRDA) Sleep-related inclusion criteria: night-time sleep disturbance defined as mean < 7 h of total time immobile between 8 p.m. and 8 a.m. during the screening period of ≥ 1 week plus ≥ 2 episodes/week of night-time behaviours as reported by the carer on the SDI. SDI is derived from the NPI. The SDI items included difficulty falling asleep, getting up during the night (other than for toileting), night-time wandering, awakening the carer, awakening and thinking it is daytime, awakening too early, and excessive daytime sleeping Gender: 88 women, 69 men Age: mean 77.4 (SD 8.9) years Severity of dementia: MMSE mean 13.9 (SD 8.8), ADAS-cog mean 38.5 (SD 18.9)

Singer 2003 *(Continued)*

Interventions	Duration of treatment: 8 weeks (2- to 3-week screening and baseline period, 8-week treatment period, 2-week placebo washout period) Treatment group 1 (n = 54; 54 included in ITT analysis): melatonin SR 2.5 mg Treatment group 2 (n = 51; 51 included in ITT analysis): melatonin (immediate-release) 10 mg Treatment group 3 (n = 52; 47 included in ITT analysis): placebo All treatment groups: Route of administration: oral Time of administration: 1 h before habitual bedtime
Outcomes	Sleep outcomes all measured with actigraphy. Single actigraph records were created for the 2- to 3-week screening and baseline periods and 8-week treatment period Primary outcome: • TNST – TST (minutes) between 8 p.m. and 8 a.m., as calculated by the computerised algorithm Other actigraphic sleep outcomes: • dTST – TST (minutes) between 8 a.m. and 8 p.m., as calculated by the computerised algorithm • ratio of daytime to TNST • time awake after sleep onset – time awake (minutes) between 8 p.m. and 8 a.m. after sleep onset, until the final awakening • sleep efficiency – percentage of time asleep between 8 p.m. and 8 a.m. • gained > 30 minutes – percentage of participants with ≥ 30-minute increase in TNST Secondary outcomes: • cognitive function (MMSE and ADAS-cog) • ADL (ADCS-ADL Inventory) • neuropsychiatric symptoms (NPI and SDI) • depression (Hamilton Depression Rating Scale) • SQR – 5-point sleep-quality rating scale included in the Daily Sleep Diary that the primary carer completed every morning. Scores ranged from 1 (very poor night with no or little sleep) to 5 (outstanding night with no awakenings) • AEs
Notes	Other psychotropic or sleep medications were allowed if use was stable Non-commercial funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomly assigned (blocked by study site) in a double-blind fashion to 1 of 3 groups." Comment: randomised centrally. Likely to have been adequate.
Allocation concealment (selection bias)	Low risk	No details of process given, but centrally randomised, so effective allocation concealment highly likely.
Blinding of participants and personnel (performance bias)	Low risk	Stated to be double-blind.

Singer 2003 *(Continued)*

All outcomes		Quote: "Placebo and both melatonin preparations were supplied by Genzyme Limited (Boston, Mass) in identical capsules."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Actigraphic analysis conducted off site. Site staff conducting other assessments stated to be blinded. Quote: "Sealed code breakers were distributed to each site and recovered at the end of the trial. In no instance was it necessary to break the blind."
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 randomised participants excluded from sleep analyses due to technical difficulties with actigraphy. Group allocations not reported, but judged to be unlikely to introduce bias. 12 participants discontinued treatment but were included in ITT analysis, using an LOCF method. Group allocation of these participants also not reported.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	None identified.

Wade 2014

Study characteristics	
Methods	RCT, 2 parallel treatment groups
Participants	Number of participants: 73 people were randomised; 13 of these were in the subpopulation with comorbid insomnia at baseline and hence were relevant to this review. Country: 1 centre in UK; 4 centres in USA Setting: outpatients Diagnosis: AD (diagnostic criteria not specified) Sleep-related inclusion criteria: subset of participants had insomnia at baseline, defined as PSQI score ≥ 6 Gender: data available for whole study population only, 36 women, 37 men Age: data available for whole study population only, range 52–85 years Severity of dementia: data available for whole study population only, MMSE ≥ 15 for inclusion Other information: all participants were on stable doses of acetylcholinesterase inhibitor with or without memantine for 2 months prior to recruitment. Participants were instructed to spend 2 h a day in outdoor daylight.
Interventions	Duration of treatment: 2-week single-blind placebo run-in phase, 24-week double-blind randomised treatment phase, 2-week placebo run-out phase Treatment group 1: n = 7 from insomnia subpopulation: melatonin SR 2 mg, once daily, 1–2 h before bedtime Treatment group 2: n = 6 from insomnia subpopulation: placebo
Outcomes	• ADAS-cog • MMSE

Wade 2014 *(Continued)*

- IADL
- PSQI global and individual component scores
- Number and duration of mid-sleep awakenings by sleep diary
- CGI
- NPI
- WHO-5 Well-Being Index
- Carer's sleep using SDI
- AEs and SAEs by spontaneous report
- Vital signs, physical examination, and laboratory tests

Notes	Study funded by Neurim Pharmaceuticals. 4/8 authors were paid employees of Neurim Pharmaceuticals. The other 4 authors had acted as paid consultants to Neurim Pharmaceuticals. The study used the PSQI as a carer-reported sleep measure. No evidence was cited for its validity in this context.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Selection for treatment group was determined by a computer-generated randomization list in a 1:1 ratio using the randomized permuted blocks method." Comment: no stratification by baseline sleep score was used to identify insomnia subgroup.
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To prevent bias, matching placebo tablets, which were identical in appearance, taste and odor, were used. The treatment was double-blinded."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant lost from each group.
Selective reporting (reporting bias)	High risk	Relation of this report to NCT00940589 and to EUCTR2009-014388-38-GB was uncertain. It seems likely that these all refer to the same study, but we were unable to get confirmation of this from Neurim Pharmaceuticals. The trial registry entries and this report differ in several respects, including sites and outcome measures.
Other bias	High risk	Not clear that insomnia subgroup was defined prospectively; possible that the choice of cut-off on the PSQI could have been data-driven.

AD: Alzheimer's disease; ADAS-cog; Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living; ADL: activities of daily living; AE: adverse event; CAS: Caregiver Burden via the Caregiver Activity Survey; CDR: Clinical Dementia Rating; CGGI: Caregiver Global Impression; CGI: Clinical Global Impression; CGI-S: Clinical Global Impression – Severity; CGIC-ISWRD; Clinician's Global Impression of Change for Irregular Sleep-Wake Rhythm Disorder; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; dTST: daytime

total sleep time; ECG: electrocardiogram; EQ-5D-5L: 5-level EQ-5D, EuroQol quality of life instrument; GDS: Geriatric Depression Scale; h: hour(s); IADL: Instrumental Activities of Daily Living Scale; ITT: intention-to-treat; LOCF: last observation carried forward; MMSE: Mini-Mental State Examination; MNA: Mini Nutritional Assessment; n: number of participants; NIA-AA; National Institute on Aging-Alzheimer's Association; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NPI: Neuropsychiatric Inventory; PSG: polysomnography; PSQI: Pittsburgh Sleep Quality Index; RCT: randomised controlled trial; REM: rapid eye movement; SAE: serious adverse event; SD: standard deviation; SDI: Sleep Disorders Inventory; SQR: Sleep Quality Rating; TNST: total nocturnal sleep time; TST: total sleep time; VAS: visual analogue scale; WIAS-III: Wechsler Adult Intelligence Scale third edition; WASO: wakenings after sleep onset; WHO: World Health Organization; ZBI: Zarit Burden Inventory.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Asano 2013	Not an RCT.
Asayama 2003	Participants had no identified sleep problem at baseline.
Bergener 1968	Geriatric population with mixed diagnoses. No primary sleep aim. No identified sleep problem at baseline.
Bergonzi 1973	Not an RCT.
Blytt 2018	Participants had dementia and depression, but no specifically identified sleep problem at baseline.
Cardinali 2014	Not an RCT.
Cohen-Mansfield 2000	Not an RCT.
Cruz-Aguilar 2013	Not an RCT.
Eeles 2003	Not an RCT (group assignment by birth date).
Gehrmann 2009	Participants had no identified sleep problem at baseline.
Gillman 1997	Not an RCT.
Ginsburg 1976	Not an RCT (incomplete Latin square design). Uncertain diagnoses.
Hamuro 2018	Not an RCT (letter).
Haworth 2001	Trial register entry in 2001 for an investigator-led trial of melatonin planned for 2001 to 2002. Described in the trial register as "a pilot study." We found no evidence that this trial was ever completed and were unable to obtain any information from the author.
Howcroft 2005	Not an RCT.
Kittur 1999	Not an RCT.
Linnoila 1980a	Participants were 19 psychogeriatric inpatients, 7 of whom were identified as having 'senile dementia.'
Linnoila 1980b	Participants were 20 psychogeriatric inpatients, 10 of whom were identified as having 'senile dementia.'
Magnus 1978	Participants were 17 elderly people with unspecified organic dementia. No identified sleep problems at baseline.

Study	Reason for exclusion
Mahlberg 2004	Not an RCT.
Markowitz 2003	No identified sleep problem at baseline. Aimed to assess effect of galantamine on sleep but no primary aim to improve sleep.
Meguro 2004	Not an RCT. Participants selected for wandering behaviour.
Mishima 1992	Not an RCT. Participants had multi-infarct dementia.
Moraes 2003	No identified sleep problems at baseline.
Moraes 2006	No identified sleep problems at baseline. (Patients excluded for severe sleep disturbance.)
NCT00035204	No primary aim to improve sleep. No placebo control (comparison of 2 cholinesterase inhibitors).
NCT00232570	Not an RCT.
NCT00480870	No identified sleep problems at baseline. No primary aim to improve sleep.
NCT00626210	Not an RCT.
NCT00706186	Study terminated July 2010. Withdrawn by investigator.
NCT00940589	No identified sleep problems at baseline.
NCT01548287	No identified sleep problems at baseline (confirmed by representative of sponsor).
NCT02258152	Participants had Parkinson's disease dementia but no specifically identified sleep problems at baseline. No primary sleep aim.
Petit 1993	No mention of randomised allocation. No identified sleep problems at baseline.
Riemersma-van der Lek 2008	No identified sleep problems at baseline.
Riley McCarten 1995	Not an RCT.
Ruths 2004	No identified sleep problems at baseline. Drug withdrawal study.
Schubert 1984	Not an RCT.
Scoralick 2017	Only 10/24 included participants were randomised; majority of control data were drawn from an earlier study.
Scripnikov 2007	No primary sleep aim. No identified sleep problems at baseline.
Shaw 1992	Participants were elderly psychiatric inpatients, < 50% had dementia.
Shinno 2008	Not an RCT.
Simon Padilla 2009	Not an RCT.
Singer 2007	Not an RCT.
Stahl 2004	No primary sleep aim investigated sleep-related adverse events in RCTs of galantamine).

Study	Reason for exclusion
Stemmelin 2013	No identified sleep problems at baseline.
Tozawa 1998	Identified from conference proceedings and other literature. Probably a small RCT (7 participants). Minimal information and no results obtainable.
UMIN000006251	Not an RCT.
UMIN000006388	Not an RCT.
UMIN000016374	No placebo control, compared hypnotic, antidepressant, and herbal medicine.
UMIN000022860	No placebo control.
Valtonen 2005	No identified sleep problems at baseline.
Walther 2011	Planned trial (Swissmedic 2007DR2217) was not completed. Only 2 participants could be randomised, published as case reports.
Yehuda 1996	No primary sleep aim. No identified sleep problems at baseline.

RCT: randomised controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

KCT0002521

Methods	RCT, 2-arm parallel group assignment, placebo-controlled, double-blind (participant, investigator)
Participants	Alzheimer's disease (DSM-IV), K-MMSE > 12 and < 26 Quote: "have some difficulty in sleep quality" Intended n = 30
Interventions	Ukgansan ga Jinpibanha 3 g 3 times/day or placebo; 4 weeks
Outcomes	Primary: sleep efficiency (WASO: Wake After Sleep Onset) *(sic)* Secondary: PSQI, ISI K-MMSE (Korean version of MMSE), K-IADL, ADAS-cog, NPI
Notes	CRIS accessed 22 April 2020 Record last updated 6 November 2017 – status: completed (30 September 2017), no results posted

NCT00814502

Methods	RCT, 2-arm parallel-group assignment, placebo-controlled, quadruple-blinded
Participants	Patients admitted to the Massachusetts General Psychiatric inpatient service Clinical diagnosis of Alzheimer's disease or vascular dementia, or both using DSM-IV criteria Intended n = 20, actual n = 17

NCT00814502 *(Continued)*

Interventions	Zolpidem CR 6.25 mg or placebo once daily at night; up to 3 weeks or to end of participant's hospital stay
Outcomes	Primary: sleep efficiency and total sleep time during down period Secondary: measures of aggression, psychosis, general clinical status, cognitive measures, mood symptoms, length of hospital stay, and percentage of participants who remained on zolpidem CR at end of study
Notes	ClincalTrials.gov accessed 22 April 2020 Record last updated 22 May 2017 – status: results posted Participants probably not selected for sleep problem at baseline. Further information sought from principal investigator but not received.

ADAS-cog: Alzheimer's Disease Assessment Scale – Cognitive Subscale; CR: controlled release; CRIS; Clinical Research Information Service; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ISI: Insomnia Severity Index; K-IADL: Korean Instrumental Activities of Daily Living; K-MMSE; Korean version of Mini-Mental State Examination; n: number of participants; NPI: Neuropsychiatric Inventory; PSQI: Pittsburgh Sleep Quality Index; RCT: randomised controlled trial; WASO: wakenings after sleep onset.

Characteristics of ongoing studies *[ordered by study ID]*

NCT02708186

Study name	Study evaluating nelotanserin for treatment of REM sleep behavior disorder in subjects with dementia (DLB or PDD)
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	ClinicalTrials.gov record accessed 11 May 2020 – no results published

NCT03075241

Study name	Z-Drugs for sleep disorders in Alzheimer's disease
Methods	RCT, 3-arm parallel group assignment,
Participants	n = 60; probable AD by NINCDS-ADRDA criteria, MMSE 0–26, defined sleep disturbance at baseline
Interventions	Zolpidem 10 mg Zopiclone 7.5 mg Placebo 1 daily at night; 14 days

NCT03075241 *(Continued)*

Outcomes	Primary: TNST Secondary: DTST; ratio daytime to night-time sleep; WASO; proportion of sleep time at night-time; proportion of participants with gain of ≥ 30 min in TST; sleep efficiency; number of awakenings
Starting date	October 2016
Contact information	Flávio Vieira, MD, MsC; 55 61 996304041; flaviovum@yahoo.com.br Einstein F Camargos MD, MsC; 55 61 99798345; einsteinfc@gmail.com
Notes	ClinicalTrials.gov record accessed 22 April 2020 Study entry last updated 6 February 2020 – status: recruiting Estimated study completion date December 2020

NCT03082755

Study name	Nighttime agitation and restless legs syndrome in people with Alzheimer's disease
Methods	RCT, 2-arm parallel assignment, placebo-controlled, double-blind
Participants	136 nursing home residents with night-time agitation, RLS, and moderate-to-severe AD
Interventions	Gabapentin enacarbil or placebo; 8 weeks
Outcomes	Primary: night-time agitation (CMAI – direct observation). Secondary: night-time agitation (CMAI-caregiver and mADCS-CGIC); sleep disturbance (direct observation and BIT-RL and actigraphy). Actigraphic measures to include TNST, WASO, sleep efficiency, sleep latency, awakenings); fall risk (GLORF); cognition (MMSE); adverse event checklist
Starting date	2017
Contact information	Janet D Morrison, PhD; 512-471-8061; jmorrison@mail.nur.utexas.edu
Notes	ClinicalTrials.gov record accessed 22 April 2020 Study entry last updated 25 October 2019 – status: recruiting Estimated primary completion date 31 March 2021

ADAS-cog: Alzheimer's Disease Assessment Scale – Cognitive Subscale; AD: Alzheimer's disease; BIT-RL: Behavioral Indicators Test – Restless Legs; CMAI: Cohen-Mansfield Agitation Inventory; CR: controlled release; DLB: dementia with Lewy bodies; dTST: daytime total sleep time; GLORF: Global Rating of Fall Risk; MMSE: Mini-Mental State Examination; mADCS-CGIC: Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; n: number of participants; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NPI: Neuropsychiatric Inventory; TNST: total nocturnal sleep time; PDD: dementia in Parkinson's disease; PSQI: Pittsburgh Sleep Quality Index; RCT: randomised controlled trial; REM: rapid eye movement; RLS: restless leg syndrome; SDI: Sleep Disorders Inventory; TNST: total nocturnal sleep time; TST: total sleep time; WASO: wakenings after sleep onset.

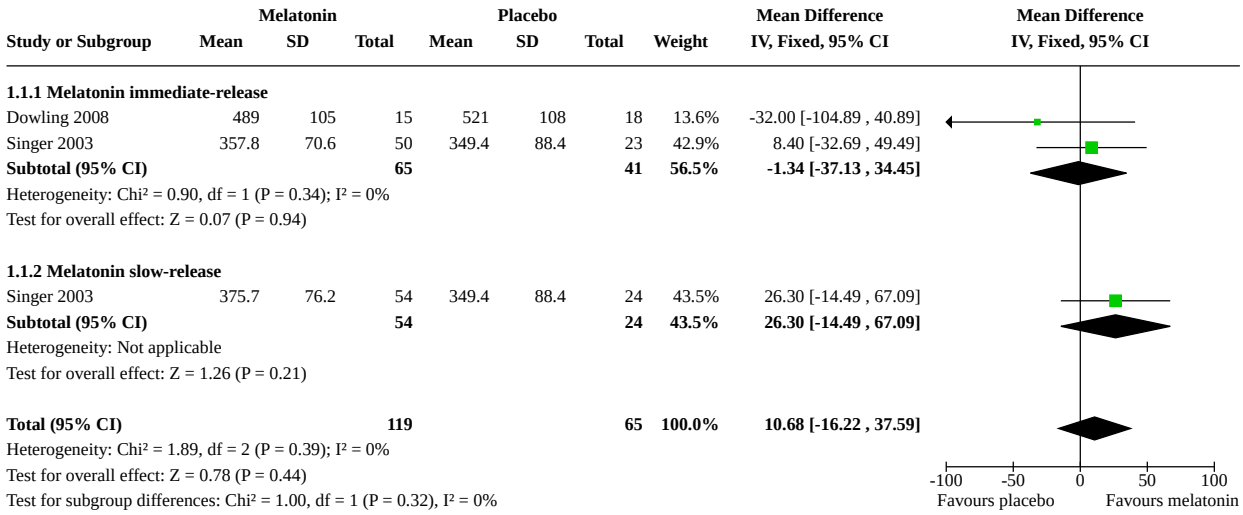
DATA AND ANALYSES

Comparison 1. Melatonin versus placebo: efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Total nocturnal sleep time (minutes)	2	184	Mean Difference (IV, Fixed, 95% CI)	10.68 [-16.22, 37.59]
1.1.1 Melatonin immediate-release	2	106	Mean Difference (IV, Fixed, 95% CI)	-1.34 [-37.13, 34.45]
1.1.2 Melatonin slow-release	1	78	Mean Difference (IV, Fixed, 95% CI)	26.30 [-14.49, 67.09]
1.2 Sleep efficiency	1	151	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.04, 0.03]
1.2.1 Melatonin immediate-release	1	73	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.06, 0.04]
1.2.2 Melatonin slow-release	1	78	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.05, 0.05]
1.3 Nocturnal time awake (minutes)	1	151	Mean Difference (IV, Fixed, 95% CI)	9.08 [-7.51, 25.66]
1.3.1 Melatonin immediate-release	1	73	Mean Difference (IV, Fixed, 95% CI)	10.80 [-11.90, 33.50]
1.3.2 Melatonin slow-release	1	78	Mean Difference (IV, Fixed, 95% CI)	7.10 [-17.20, 31.40]
1.4 Number of nocturnal awakenings	1	33	Mean Difference (IV, Fixed, 95% CI)	6.00 [-2.65, 14.65]
1.5 Mean duration of nocturnal sleep bouts (minutes)	1	33	Mean Difference (IV, Fixed, 95% CI)	-2.00 [-8.27, 4.27]
1.6 Ratio of daytime sleep to night-time sleep	2	184	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.29, 0.03]
1.6.1 Melatonin immediate-release	2	106	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.28, 0.05]
1.6.2 Melatonin slow-release	1	78	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.78, 0.28]
1.7 Carer-rated sleep quality, change from baseline	3	195	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.32, 0.28]
1.7.1 Melatonin immediate-release	2	104	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.65, 0.16]
1.7.2 Melatonin slow-release	2	91	Std. Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.19, 0.69]
1.8 MMSE, change from baseline	2	162	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.85, 1.03]

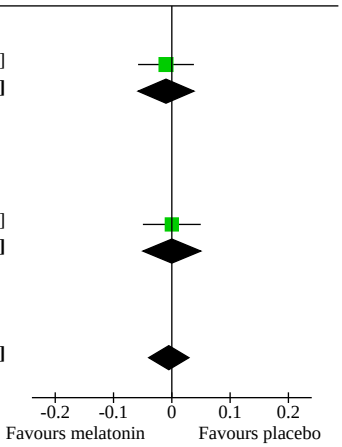
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8.1 Melatonin immediate-release	1	73	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-1.99, 0.91]
1.8.2 Melatonin slow-release	2	89	Mean Difference (IV, Fixed, 95% CI)	0.54 [-0.69, 1.76]
1.9 ADAS-cog, change from baseline	2	162	Mean Difference (IV, Fixed, 95% CI)	-1.03 [-2.70, 0.65]
1.9.1 Melatonin immediate-release	1	73	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-2.95, 2.09]
1.9.2 Melatonin slow-release	2	89	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-3.74, 0.74]
1.10 ADL, change from baseline	3	193	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.34, 0.26]
1.10.1 Melatonin immediate-release	2	104	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.45, 0.36]
1.10.2 Melatonin slow-release	2	89	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.48, 0.41]
1.11 Carer burden	1	31	Mean Difference (IV, Fixed, 95% CI)	-6.20 [-19.81, 7.41]

Analysis 1.1. Comparison 1: Melatonin versus placebo: efficacy, Outcome 1: Total nocturnal sleep time (minutes)



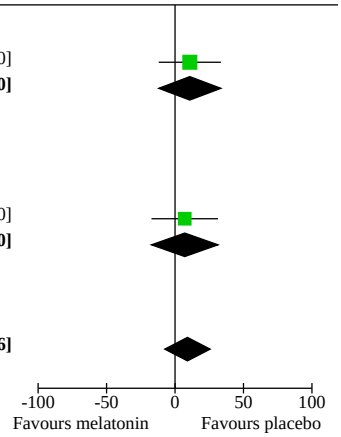
Analysis 1.2. Comparison 1: Melatonin versus placebo: efficacy, Outcome 2: Sleep efficiency

Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Melatonin immediate-release								
Singer 2003	0.68	0.09	50	0.69	0.1	23	51.8%	-0.01 [-0.06 , 0.04]
Subtotal (95% CI)			**50**			**23**	**51.8%**	**-0.01 [-0.06 , 0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.41 (P = 0.68)								
1.2.2 Melatonin slow-release								
Singer 2003	0.69	0.11	54	0.69	0.1	24	48.2%	0.00 [-0.05 , 0.05]
Subtotal (95% CI)			**54**			**24**	**48.2%**	**0.00 [-0.05 , 0.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**104**			**47**	**100.0%**	**-0.01 [-0.04 , 0.03]**
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%								
Test for overall effect: Z = 0.29 (P = 0.77)								
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%								



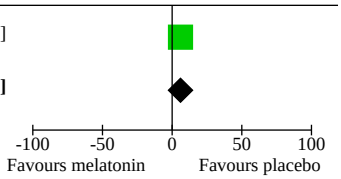
Analysis 1.3. Comparison 1: Melatonin versus placebo: efficacy, Outcome 3: Nocturnal time awake (minutes)

Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 Melatonin immediate-release								
Singer 2003	166.7	48	50	155.9	45	23	53.4%	10.80 [-11.90 , 33.50]
Subtotal (95% CI)			**50**			**23**	**53.4%**	**10.80 [-11.90 , 33.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.93 (P = 0.35)								
1.3.2 Melatonin slow-release								
Singer 2003	163	61.2	54	155.9	45	24	46.6%	7.10 [-17.20 , 31.40]
Subtotal (95% CI)			**54**			**24**	**46.6%**	**7.10 [-17.20 , 31.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.57 (P = 0.57)								
Total (95% CI)			**104**			**47**	**100.0%**	**9.08 [-7.51 , 25.66]**
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%								
Test for overall effect: Z = 1.07 (P = 0.28)								
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%								

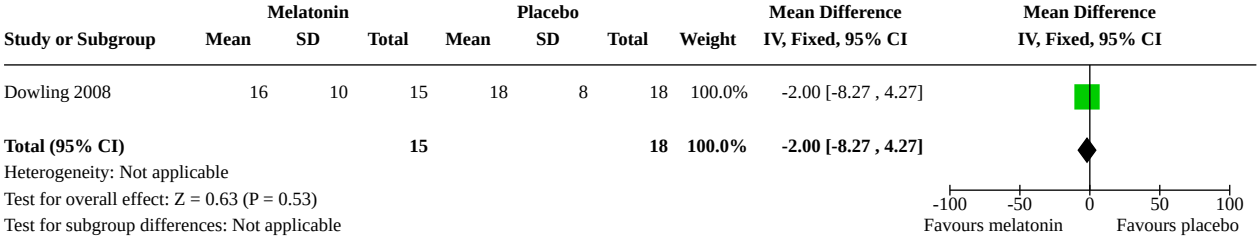


Analysis 1.4. Comparison 1: Melatonin versus placebo: efficacy, Outcome 4: Number of nocturnal awakenings

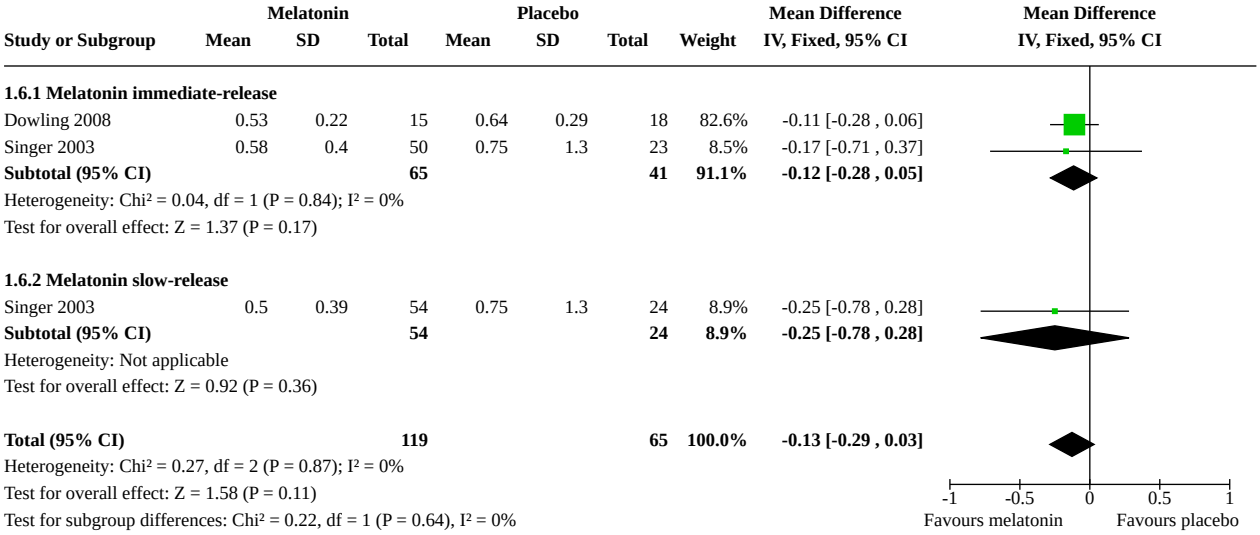
Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Dowling 2008	40	15	15	34	9	18	100.0%	6.00 [-2.65 , 14.65]
Total (95% CI)			**15**			**18**	**100.0%**	**6.00 [-2.65 , 14.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.36 (P = 0.17)								
Test for subgroup differences: Not applicable								



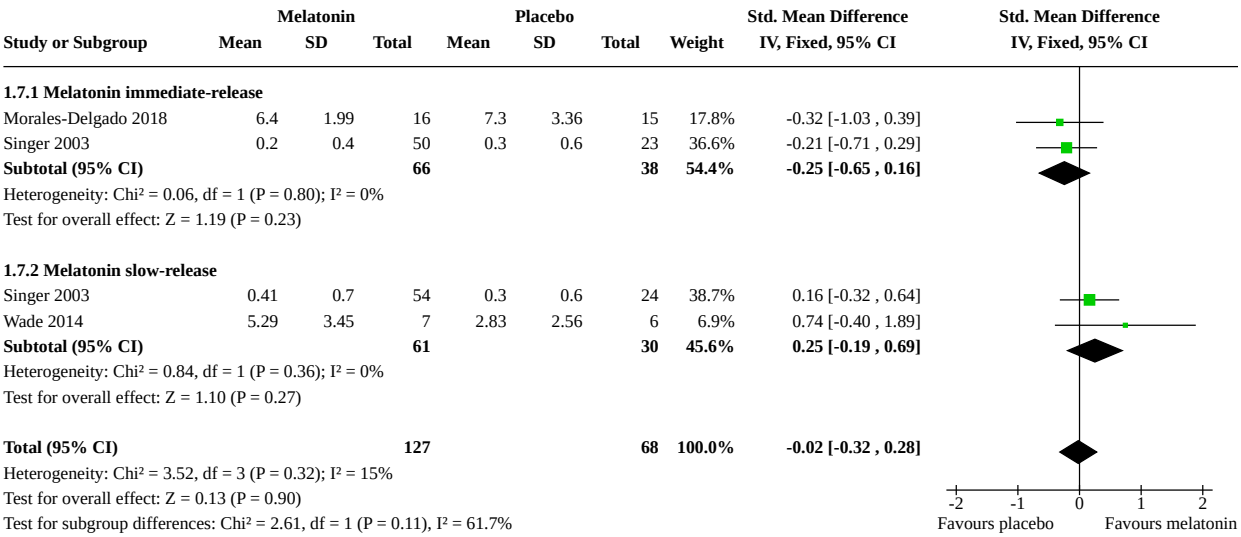
Analysis 1.5. Comparison 1: Melatonin versus placebo: efficacy, Outcome 5: Mean duration of nocturnal sleep bouts (minutes)



Analysis 1.6. Comparison 1: Melatonin versus placebo: efficacy, Outcome 6: Ratio of daytime sleep to night-time sleep

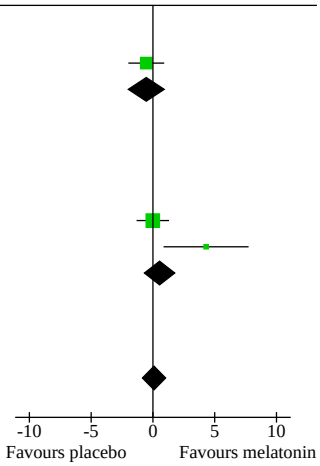


Analysis 1.7. Comparison 1: Melatonin versus placebo: efficacy, Outcome 7: Carer-rated sleep quality, change from baseline



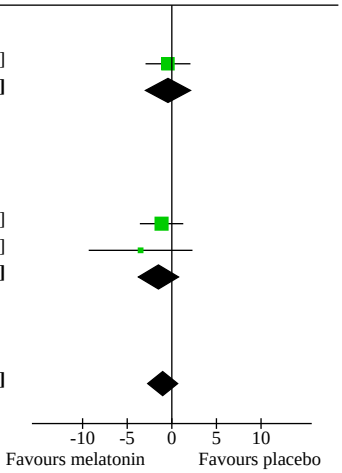
Analysis 1.8. Comparison 1: Melatonin versus placebo: efficacy, Outcome 8: MMSE, change from baseline

Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.8.1 Melatonin immediate-release								
Singer 2003	-0.2	3.4	50	0.34	2.7	23	41.7%	-0.54 [-1.99 , 0.91]
Subtotal (95% CI)			**50**			**23**	**41.7%**	**-0.54 [-1.99 , 0.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.73 (P = 0.47)								
1.8.2 Melatonin slow-release								
Singer 2003	0.33	2.8	54	0.34	2.7	24	50.9%	-0.01 [-1.32 , 1.30]
Wade 2014	1.5	2.9	6	-2.8	2.9	5	7.4%	4.30 [0.86 , 7.74]
Subtotal (95% CI)			**60**			**29**	**58.3%**	**0.54 [-0.69 , 1.76]**
Heterogeneity: Chi² = 5.26, df = 1 (P = 0.02); I² = 81%								
Test for overall effect: Z = 0.86 (P = 0.39)								
Total (95% CI)			**110**			**52**	**100.0%**	**0.09 [-0.85 , 1.03]**
Heterogeneity: Chi² = 6.49, df = 2 (P = 0.04); I² = 69%								
Test for overall effect: Z = 0.19 (P = 0.85)								
Test for subgroup differences: Chi² = 1.24, df = 1 (P = 0.27), I² = 19.1%								



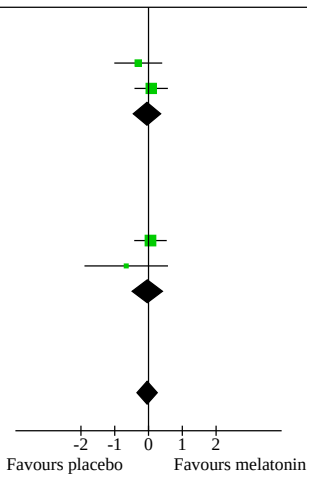
Analysis 1.9. Comparison 1: Melatonin versus placebo: efficacy, Outcome 9: ADAS-cog, change from baseline

Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 Melatonin immediate-release								
Singer 2003	0.97	5.5	50	1.4	4.9	23	44.3%	-0.43 [-2.95 , 2.09]
Subtotal (95% CI)			**50**			**23**	**44.3%**	**-0.43 [-2.95 , 2.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								
1.9.2 Melatonin slow-release								
Singer 2003	0.25	5.4	54	1.4	4.9	24	47.4%	-1.15 [-3.58 , 1.28]
Wade 2014	-2.5	3.1	6	1	6	5	8.3%	-3.50 [-9.31 , 2.31]
Subtotal (95% CI)			**60**			**29**	**55.7%**	**-1.50 [-3.74 , 0.74]**
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.46); I² = 0%								
Test for overall effect: Z = 1.31 (P = 0.19)								
Total (95% CI)			**110**			**52**	**100.0%**	**-1.03 [-2.70 , 0.65]**
Heterogeneity: Chi² = 0.92, df = 2 (P = 0.63); I² = 0%								
Test for overall effect: Z = 1.20 (P = 0.23)								
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%								



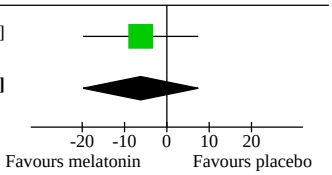
Analysis 1.10. Comparison 1: Melatonin versus placebo: efficacy, Outcome 10: ADL, change from baseline

Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.10.1 Melatonin immediate-release								
Morales-Delgado 2018	-0.5	1.38	16	-0.1	1.17	15	18.0%	-0.30 [-1.01 , 0.41]
Singer 2003	-0.49	6.7	50	-0.98	4.7	23	37.0%	0.08 [-0.42 , 0.57]
Subtotal (95% CI)			**66**			**38**	**55.0%**	**-0.05 [-0.45 , 0.36]**
Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² = 0%								
Test for overall effect: Z = 0.22 (P = 0.82)								
1.10.2 Melatonin slow-release								
Singer 2003	-0.65	6	54	-0.98	4.7	24	39.1%	0.06 [-0.42 , 0.54]
Wade 2014	0.67	1.75	6	1.8	1.3	5	5.9%	-0.66 [-1.90 , 0.58]
Subtotal (95% CI)			**60**			**29**	**45.0%**	**-0.04 [-0.48 , 0.41]**
Heterogeneity: Chi² = 1.13, df = 1 (P = 0.29); I² = 11%								
Test for overall effect: Z = 0.16 (P = 0.87)								
Total (95% CI)			**126**			**67**	**100.0%**	**-0.04 [-0.34 , 0.26]**
Heterogeneity: Chi² = 1.88, df = 3 (P = 0.60); I² = 0%								
Test for overall effect: Z = 0.27 (P = 0.79)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%								



Analysis 1.11. Comparison 1: Melatonin versus placebo: efficacy, Outcome 11: Carer burden

Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Morales-Delgado 2018	25.9	18.8	16	32.1	19.8	15	100.0%	-6.20 [-19.81 , 7.41]
Total (95% CI)			**16**			**15**	**100.0%**	**-6.20 [-19.81 , 7.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.89 (P = 0.37)								
Test for subgroup differences: Not applicable								

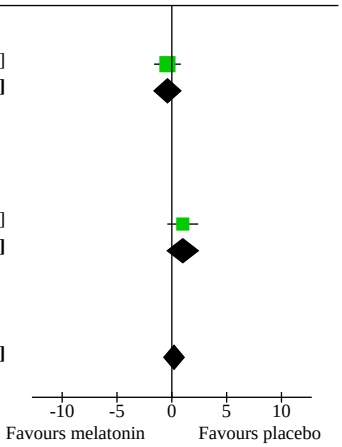


Comparison 2. Melatonin versus placebo: adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Number of adverse event reports per person	1	151	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.72, 1.12]
2.1.1 Melatonin immediate-release	1	73	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.62, 0.82]
2.1.2 Melatonin slow-release	1	78	Mean Difference (IV, Fixed, 95% CI)	1.00 [-0.41, 2.41]
2.2 Adverse event severity	1	151	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.06, 0.26]
2.2.1 Melatonin immediate-release	1	73	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.11, 0.31]
2.2.2 Melatonin slow-release	1	78	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.13, 0.33]
2.3 Reporting ≥ 1 adverse event	1	151	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.86, 1.33]

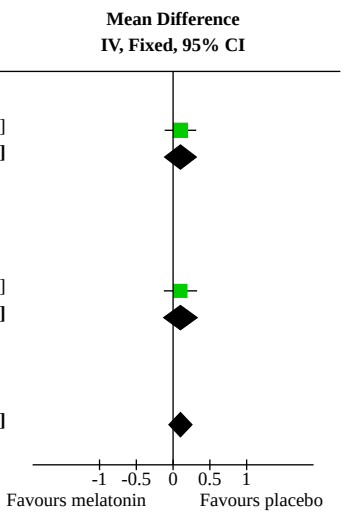
Analysis 2.1. Comparison 2: Melatonin versus placebo: adverse events, Outcome 1: Number of adverse event reports per person

Study or Subgroup	Melatonin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.1.1 Melatonin immediate-release								
Singer 2003	2	1.9	50	2.4	2.7	23	57.1%	-0.40 [-1.62 , 0.82]
Subtotal (95% CI)			**50**			**23**	**57.1%**	**-0.40 [-1.62 , 0.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.64 (P = 0.52)								
2.1.2 Melatonin slow-release								
Singer 2003	3.4	3.4	54	2.4	2.7	24	42.9%	1.00 [-0.41 , 2.41]
Subtotal (95% CI)			**54**			**24**	**42.9%**	**1.00 [-0.41 , 2.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.39 (P = 0.16)								
Total (95% CI)			**104**			**47**	**100.0%**	**0.20 [-0.72 , 1.12]**
Heterogeneity: Chi² = 2.16, df = 1 (P = 0.14); I² = 54%								
Test for overall effect: Z = 0.43 (P = 0.67)								
Test for subgroup differences: Chi² = 2.16, df = 1 (P = 0.14), I² = 53.7%								



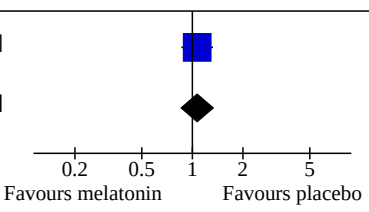
Analysis 2.2. Comparison 2: Melatonin versus placebo: adverse events, Outcome 2: Adverse event severity

Study or Subgroup	Melatonin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.2.1 Melatonin immediate-release								
Singer 2003	1.5	0.5	50	1.4	0.4	23	52.7%	0.10 [-0.11 , 0.31]
Subtotal (95% CI)			**50**			**23**	**52.7%**	**0.10 [-0.11 , 0.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.91 (P = 0.36)								
2.2.2 Melatonin slow-release								
Singer 2003	1.5	0.6	54	1.4	0.4	24	47.3%	0.10 [-0.13 , 0.33]
Subtotal (95% CI)			**54**			**24**	**47.3%**	**0.10 [-0.13 , 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.87 (P = 0.39)								
Total (95% CI)			**104**			**47**	**100.0%**	**0.10 [-0.06 , 0.26]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 1.26 (P = 0.21)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%								



Analysis 2.3. Comparison 2: Melatonin versus placebo: adverse events, Outcome 3: Reporting ≥ 1 adverse event

Study or Subgroup	Melatonin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Singer 2003	78	104	33	47	100.0%	1.07 [0.86 , 1.33]
Total (95% CI)		**104**		**47**	**100.0%**	**1.07 [0.86 , 1.33]**
Total events:	78		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
Test for subgroup differences: Not applicable						



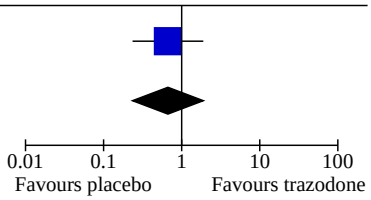
Comparison 3. Trazodone: adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Reporting ≥ 1 adverse event	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.23, 1.89]

Analysis 3.1. Comparison 3: Trazodone: adverse events, Outcome 1: Reporting ≥ 1 adverse event

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Camargos 2014	4	15	6	15	100.0%	0.67 [0.23 , 1.89]
Total (95% CI)		**15**		**15**	**100.0%**	**0.67 [0.23 , 1.89]**
Total events:	4		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable



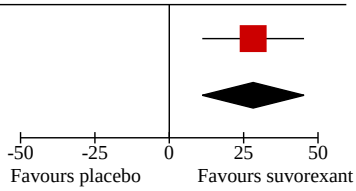
Comparison 4. Orexin antagonists versus placebo: efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Total nocturnal sleep time, change from baseline (minutes)	1	274	Mean Difference (IV, Fixed, 95% CI)	28.20 [11.10, 45.30]
4.2 Mean duration of sleep bouts, change from baseline (minutes)	1	38	Mean Difference (IV, Fixed, 95% CI)	-2.42 [-5.53, 0.70]
4.3 Sleep efficiency, % change from baseline	2	312	Mean Difference (IV, Fixed, 95% CI)	4.26 [1.26, 7.26]
4.4 Nocturnal time awake, change from baseline (minutes)	1	274	Mean Difference (IV, Fixed, 95% CI)	-15.70 [-28.10, -3.30]
4.5 Number of nocturnal awakenings, ratio vs total sleep time, change from baseline	1	274	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.50, 0.50]
4.6 Sleep latency, change from baseline (minutes)	1	274	Mean Difference (IV, Fixed, 95% CI)	-12.10 [-25.90, 1.70]
4.7 SDI, change from baseline	2	312	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.19, 0.01]
4.8 MMSE, change from baseline	1	274	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.50, 0.50]

Analysis 4.1. Comparison 4: Orexin antagonists versus placebo: efficacy, Outcome 1: Total nocturnal sleep time, change from baseline (minutes)

Study or Subgroup	MD	SE	Suvorexant Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Herring 2020	28.2	8.7247	135	139	100.0%	28.20 [11.10 , 45.30]
Total (95% CI)			**135**	**139**	**100.0%**	**28.20 [11.10 , 45.30]**

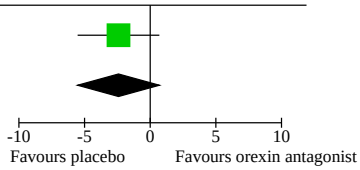
Heterogeneity: Not applicable
Test for overall effect: Z = 3.23 (P = 0.001)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Orexin antagonists versus placebo: efficacy, Outcome 2: Mean duration of sleep bouts, change from baseline (minutes)

Study or Subgroup	Orexin antagonist Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NCT03001557	-1.415	4.5066	26	1	4.57	12	100.0%	-2.42 [-5.53 , 0.70]
Total (95% CI)			**26**			**12**	**100.0%**	**-2.42 [-5.53 , 0.70]**

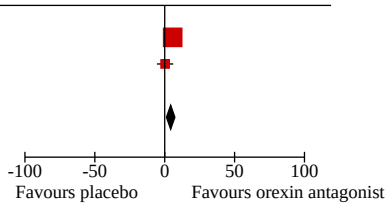
Heterogeneity: Not applicable
Test for overall effect: Z = 1.52 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Orexin antagonists versus placebo: efficacy, Outcome 3: Sleep efficiency, % change from baseline

Study or Subgroup	MD	SE	Orexin antagonist Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Herring 2020	5.7	1.7857	135	139	73.5%	5.70 [2.20 , 9.20]
NCT03001557	0.26	2.9737	26	12	26.5%	0.26 [-5.57 , 6.09]
Total (95% CI)			**161**	**151**	**100.0%**	**4.26 [1.26 , 7.26]**

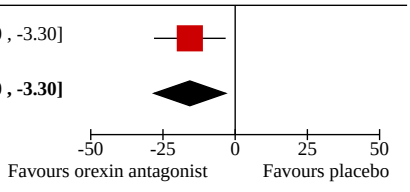
Heterogeneity: Chi² = 2.46, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 2.78 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: Orexin antagonists versus placebo: efficacy, Outcome 4: Nocturnal time awake, change from baseline (minutes)

Study or Subgroup	MD	SE	Orexin antagonist Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Herring 2020	-15.7	6.3266	135	139	100.0%	-15.70 [-28.10 , -3.30]
Total (95% CI)			**135**	**139**	**100.0%**	**-15.70 [-28.10 , -3.30]**

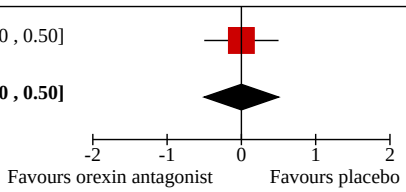
Heterogeneity: Not applicable
Test for overall effect: Z = 2.48 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 4.5. Comparison 4: Orexin antagonists versus placebo: efficacy, Outcome 5: Number of nocturnal awakenings, ratio vs total sleep time, change from baseline

Study or Subgroup	MD	SE	Orexin antagonist Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Herring 2020	0	0.2551	135	139	100.0%	0.00 [-0.50 , 0.50]
Total (95% CI)			**135**	**139**	**100.0%**	**0.00 [-0.50 , 0.50]**

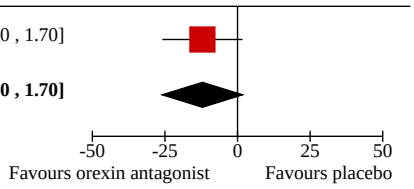
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 4.6. Comparison 4: Orexin antagonists versus placebo: efficacy, Outcome 6: Sleep latency, change from baseline (minutes)

Study or Subgroup	MD	SE	Orexin antagonist Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Herring 2020	-12.1	7.0409	135	139	100.0%	-12.10 [-25.90 , 1.70]
Total (95% CI)			**135**	**139**	**100.0%**	**-12.10 [-25.90 , 1.70]**

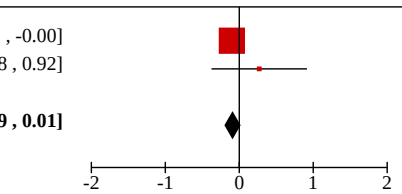
Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 4.7. Comparison 4: Orexin antagonists versus placebo: efficacy, Outcome 7: SDI, change from baseline

Study or Subgroup	MD	SE	Orexin antagonist Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Herring 2020	-0.1	0.051	135	139	97.7%	-0.10 [-0.20 , -0.00]
NCT03001557	0.27	0.3292	26	12	2.3%	0.27 [-0.38 , 0.92]
Total (95% CI)			**161**	**151**	**100.0%**	**-0.09 [-0.19 , 0.01]**

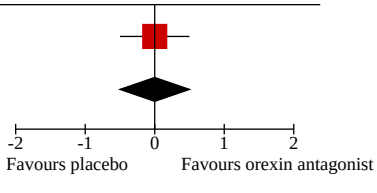
Heterogeneity: Chi² = 1.23, df = 1 (P = 0.27); I² = 19%
Test for overall effect: Z = 1.81 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 4.8. Comparison 4: Orexin antagonists versus placebo: efficacy, Outcome 8: MMSE, change from baseline

Study or Subgroup	MD	SE	Orexin antagonist Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Herring 2020	0	0.2551	135	139	100.0%	0.00 [-0.50 , 0.50]
Total (95% CI)			**135**	**139**	**100.0%**	**0.00 [-0.50 , 0.50]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



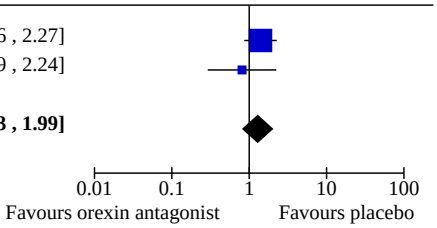
Comparison 5. Orexin antagonists versus placebo: adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Reporting ≥ 1 adverse event	2	323	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.83, 1.99]

Analysis 5.1. Comparison 5: Orexin antagonists versus placebo: adverse events, Outcome 1: Reporting ≥ 1 adverse event

Study or Subgroup	Orexin antagonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Herring 2020	32	142	23	143	80.7%	1.40 [0.86 , 2.27]
NCT03001557	7	26	4	12	19.3%	0.81 [0.29 , 2.24]
Total (95% CI)		**168**		**155**	**100.0%**	**1.29 [0.83 , 1.99]**
Total events:	39		27			

Heterogeneity: Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy (including additional terms from supplementary search)	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois) [Date of most recent search: Feb 2020]	sleep OR circadian OR insomnia OR sleeplessness OR somatic OR somnolence OR "rest activity"	Mar 2016: 271 Oct 2018: 23 Feb 2020: 247
2. MEDLINE In-process and other non-indexed citations and MEDLINE OvidSP (1950 onwards) [Date of most recent search: Feb 2020]	1. exp Dementia/ 2. Delirium/ 3. Wernicke Encephalopathy/ 4. Delirium, Dementia, Amnestic, Cognitive Disorders/ 5. dement*.mp. 6. alzheimer*.mp. 7. (lewy* adj2 bod*).mp. 8. deliri*.mp. 9. (chronic adj2 cerebrovascular).mp. 10. ("organic brain disease" or "organic brain syndrome").mp. 11. ("normal pressure hydrocephalus" and "shunt*").mp.	Mar 2016: 2176 Oct 2018: 556 Feb 2020: 501

(Continued)

12. "benign senescent forgetfulness".mp.

13. (cerebr* adj2 deteriorat*).mp.

14. (cerebral* adj2 insufficient*).mp.

15. (pick* adj2 disease).mp.

16. (creutzfeldt or jcd or cjd).mp.

17. huntington*.mp.

18. binswanger*.mp.

19. korsako*.mp.

20. "cognit* impair*".mp.

21. neurodegenerat*.mp.

22. cerebrovascular.mp.

23. neuropsychiatric.mp.

24. neurobehavioral.mp.

25. or/1-24

26. exp Sleep/

27. sleep*.ti,ab.

28. "Sleep Initiation and Maintenance Disorders"/

29. insomnia.mp.

30. exp sleep disorders, circadian rhythm/ or "disorders of excessive somnolence"/

31. (hypersomnia or parasomnia).mp.

32. circadian.mp.

33. “rest-activity”.ti,ab.

34. somnolence.ti,ab.

35. sundowning.ti,ab.

36. or/26-35

37. 25 and 36

38. randomized controlled trial.pt.

39. controlled clinical trial.pt.

40. randomized.ab.

41. placebo.ab.

42. drug therapy.fs.

43. randomly.ab.

44. trial.ab.

45. groups.ab.

(Continued)

	46. or/38-45 47. (animals not (humans and animals)).sh. 48. 46 not 47 49. 37 and 48	
3. Embase OvidSP (1980 onwards) [Date of most recent search: Feb 2020]	1. exp dementia/ 2. Lewy body/ 3. delirium/ 4. Wernicke encephalopathy/ 5. cognitive defect/ 6. dement*.mp. 7. alzheimer*.mp. 8. (lewy* adj2 bod*).mp. 9. deliri*.mp. 10. (chronic adj2 cerebrovascular).mp. 11. ("organic brain disease" or "organic brain syndrome").mp. 12. "supranuclear palsy".mp. 13. ("normal pressure hydrocephalus" and "shunt*").mp. 14. "benign senescent forgetfulness".mp. 15. (cerebr* adj2 deteriorat*).mp. 16. (cerebral* adj2 insufficient*).mp. 17. (pick* adj2 disease).mp. 18. (creutzfeldt or jcd or cjd).mp. 19. huntington*.mp. 20. binswanger*.mp. 21. korsako*.mp. 22. CADASIL.mp. 23. or/1-22 24. *sleep/ 25. sleep*.ti,ab. 26. insomnia.ti,ab. 27. circadian rhythm*.ti,ab. 28. (hypersomnia or parasomnia).ti,ab. 29. “rest-activity”.ti,ab. 30. somnolence.ti,ab.	Mar 2016: 832 Oct 2018: 461 Feb 2020: 421

(Continued)

	31. sundowning.ti,ab. 32. or/24-31 33. 23 and 32 34. randomized controlled trial/ 35. randomly.ab. 36. placebo*.ti,ab. 37. "double-blind*".ti,ab. 38. trial.ti,ab. 39. RCT.ti,ab. 40. or/34-39 41. 33 and 40	
4. PsycINFO OvidSP (1806 onwards) [Date of most recent search: Feb 2020]	1. exp Dementia/ 2. exp Delirium/ 3. exp Huntingtons Disease/ 4. exp Kluver Bucy Syndrome/ 5. exp Wernickes Syndrome/ 6. exp Cognitive Impairment/ 7. dement*.mp. 8. alzheimer*.mp. 9. (lewy* adj2 bod*).mp. 10. deliri*.mp. 11. (chronic adj2 cerebrovascular).mp. 12. ("organic brain disease" or "organic brain syndrome").mp. 13. "supranuclear palsy".mp. 14. ("normal pressure hydrocephalus" and "shunt*").mp. 15. "benign senescent forgetfulness".mp. 16. (cerebr* adj2 deteriorat*).mp. 17. (cerebral* adj2 insufficient*).mp. 18. (pick* adj2 disease).mp. 19. (creutzfeldt or jcd or cjd).mp. 20. huntington*.mp. 21. binswanger*.mp. 22. korsako*.mp. 23. ("parkinson* disease dementia" or PDD or "parkinson* dementia").mp.	Mar 2016: 440 Oct 2018: 169 Feb 2020: 107

(Continued)

	24. or/1-23 25. Sleep/ 26. sleep*.ti,ab. 27. insomnia.ti,ab. 28. Sleep Disorders/ 29. (hypersomnia or parasomnia).mp. 30. circadian.mp. 31. “rest-activity”.ti,ab. 32. somnolence.ti,ab. 33. sundowning.ti,ab. 34. or/25-33 35. 24 and 34 36. trial.ti,ab. 37. placebo*.ti,ab. 38. "double-blind*".ti,ab. 39. RCT.ti,ab. 40. randomi?ed.ab. 41. randomly.ab. 42. groups.ab. 43. or/36-42 44. 35 and 43	
5. CINAHL EBSCOhost (1974 onwards) [Date of most recent search: Feb 2020]	S1 (MH "Dementia+") S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") S3 (MH "Wernicke's Encephalopathy") S4 TX dement* S5 TX alzheimer* S6 TX lewy* N2 bod* S7 TX deliri* S8 TX chronic N2 cerebrovascular S9 TX "organic brain disease" or "organic brain syndrome" S10 TX "normal pressure hydrocephalus" and "shunt*" S11 TX "benign senescent forgetfulness" S12 TX cerebr* N2 deteriorat*	Mar 2016: 401 Oct 2018: 89 Feb 2020: 242

(Continued)

	S13 TX cerebral* N2 insufficient* S14 TX pick* N2 disease S15 TX creutzfeldt or jcd or cjd S16 TX huntington* S17 TX binswanger* S18 TX korsako* S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 S20 (MH "Sleep") OR (MH "Sleep Disorders, Circadian Rhythm") S21 TX sleep* S22 TX circadian S23 TX insomnia S24 TX hypersomnia S25 TX parasomnia S26. “rest-activity”.ti,ab. S27. somnolence.ti,ab. S28. sundowning.ti,ab. S29 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 S27 S19 and S29 S30 (MH "Randomized Controlled Trials") S31 TX placebo* S32 TX "double-blind*" OR "single-blind*" S33 AB groups S34 AB RCT OR CCT S35 AB random* S36 S30 or S31 or S32 or S33 or S34 or S35 S37 AND S27	
6. ISI Web of Knowledge (Clarivate) [Date of most recent search: Feb 2020]	Topic=(sleep* OR insomnia* OR circadian OR hypersomnia OR parasomnia OR “rest-activity” OR somnolence OR sundowning) AND Topic=(alzheimer* OR AD) AND Topic=(randomly OR placebo OR groups OR trial OR RCT OR randomized OR randomised) Timespan=All Years.	Mar 2016: 1798 Oct 2018: 154 Feb 2020: 422
7. LILACS BIREME [Date of most recent search: Feb 2020]	sueño OR sleep OR arrastar OR insomnia OR insomina [Words] and alzheimer OR alzheimers OR alzheimer's OR dementia OR demenc$ [Words]	Mar 2016: 65 Oct 2018: 6 Feb 2020: 5

(Continued)

8. CENTRAL [Date of most recent search: Feb 2020]	#1 MeSH descriptor Dementia explode all trees #2 MeSH descriptor Delirium, this term only #3 MeSH descriptor Wernicke Encephalopathy, this term only #4 MeSH descriptor Delirium, Dementia, Amnestic, Cognitive Disorders, this term only #5 dement* #6 alzheimer* #7 "lewy* bod*" #8 deliri* #9 "chronic cerebrovascular" #10 "organic brain disease" or "organic brain syndrome" #11 "normal pressure hydrocephalus" and "shunt*" #12 "benign senescent forgetfulness" #13 "cerebr* deteriorat*" #14 "cerebral* insufficient*" #15 "pick* disease" #16 creutzfeldt or jcd or cjd #17 huntington* #18 binswanger* #19 korsako* #20 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19) #21 MeSH descriptor Sleep, this term only #22 sleep* #23 circadian #24 insomnia #25 hypersomnia #26 parasomnia #27 “rest-activity” OR insomnolence OR sundowning #28 (#22 OR #23 OR #24 OR #25 OR #26 OR #27) #29 (#20 AND #28)	Mar 2016: 455 Oct 2018: 533 Feb 2020: 707
9. Clinicaltrials.gov (www.clinicaltrials.gov) [Date of most recent search: Feb 2020]	sleep OR insomnia OR circadian OR hypersomnia OR parasomnia OR insomnia OR somnolence OR sundowning OR “rest-activity” | Interventional Studies | alzheimer OR alzheimer's OR alzheimers OR dementia	Mar 2016: 68 Oct 2018: 72 Feb 2020: 91

(Continued)

10. ICTRP Search Portal (apps.who.int/trialsearch; includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry – India; Clinical Research Information Service – Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register) [Date of most recent search: Feb 2020]	(sleep OR insomnia OR somnolence OR sundowning) AND alzheimer	Mar 2016: 29 Oct 2018: 1 Feb 2020: 14
TOTAL before deduplication		Mar 2016: 6535 Oct 2018: 2064 Feb 2020:2757 TOTAL: 11356
TOTAL after software deduplication		Mar 2016: 5571 Oct 2018: 1575 Feb 2020:2057 TOTAL: 9203
TOTAL after first assess and sent to authors		Mar 2016: 341 Oct 2018: 134 TOTAL: 475
Full-text assessment		Mar 2016: 102 April 2020: 9 TOTAL: 111

WHAT'S NEW

Date	Event	Description
19 February 2020	New citation required but conclusions have not changed	New studies included. Conclusions unchanged.
19 February 2020	New search has been performed	The most recent search for this review was performed on 19 February 2020

HISTORY

Protocol first published: Issue 6, 2011
Review first published: Issue 3, 2014

Date	Event	Description
5 October 2018	New search has been performed	The most recent search for this review was performed on 5 October 2018
14 November 2016	New search has been performed	One new study added. Conclusions unchanged.
14 November 2016	New citation required but conclusions have not changed	One new study added. Conclusions unchanged.

CONTRIBUTIONS OF AUTHORS

In the previous two version of this review, JMcC, ALS and Dr Daniel Cohen all contributed to screening of search results, selection of studies, extraction of data, design and interpretation of analyses.

For this update, these tasks were done by JMcC and ALS only.

The review was written largely by JMcC with contributions from ALS.

DECLARATIONS OF INTEREST

JMcC: none.

ALS: none.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original review (2012)

Three of the original authors left the team and a new author (ALS) was added.

We changed outcomes from those specified in the published protocol. This change was made prior to conduct of the search and identification of studies.

The protocol stated that cross-over studies would be excluded if it was not possible to extract paired data from the study report. However, we decided that Serfaty 2002 should be included in order to give a fuller account of the evidence available.

In the first review update (2016)

The following changes were planned before the updated search was conducted.

We extended the scope of the review to include participants with any subtype of dementia (not just dementia due to Alzheimer's disease).

We planned additional subgroup analyses, based on the subtype of dementia.

We added GRADE ratings of the certainty of the evidence supporting each effect estimate, and 'Summary of findings' tables that included seven predefined outcomes.

In the second review update (2020)

We made a clarification to the criteria for considering studies for inclusion, namely a decision to exclude single-dose studies in which the primary objective was to assess the effect of a drug on sleep architecture (rather than to improve symptoms of disordered sleep).

We involved a panel of carers in selecting and prioritising review outcomes. Outcomes were added to the review and the list of outcomes included in the 'Summary of findings' tables was amended.

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [*complications]; Azepines [adverse effects] [therapeutic use]; Caregiver Burden [drug therapy]; Cognition [drug effects]; Indenes [adverse effects] [therapeutic use]; Melatonin [adverse effects] [therapeutic use]; Pyridines [adverse effects] [therapeutic use]; Pyrimidines [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Sleep [drug effects] [physiology]; Sleep Wake Disorders [*drug therapy] [etiology]; Time Factors; Trazodone [adverse effects] [therapeutic use]; Triazoles [adverse effects] [therapeutic use]

MeSH check words

Humans