

Melatonin for cognitive impairment (Review)

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[Intervention Review]

Melatonin for cognitive impairment

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ABSTRACT

Background

There are a number of studies that suggest a relationship between decline of melatonin function and the symptoms of dementia.

Objectives

The review assessed the evidence of clinical efficacy and safety of melatonin in the treatment of manifestations of dementia or cognitive impairment (CI).

Search strategy

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG), *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS were searched on 29 January 2008 using the terms: MELATONIN and N-ACETYL-5-METHOXYTRYPTAMINE. The CDCIG Specialized Register contains records from all major health care databases (*The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS) as well as from many trials databases and grey literature sources.

The search of January 2008 retrieved several studies for consideration by the authors.

Selection criteria

All relevant, randomized controlled trials in which orally administered melatonin in any dosage was compared with a control group for the effect on managing cognitive, behavioural (excluding sleep), and/or affective disturbances of people with dementia of any degree of severity.

Data collection and analysis

Two to three reviewers independently assessed the retrieved articles for relevance and methodological quality, and extracted data from the selected studies. Statistically significant differences in changes in outcomes from baseline to end of treatment between the melatonin and control groups were examined. Each study was summarized using a measure of effect (e.g. mean difference) and meta-analyses were conducted when appropriate.

Main results

Three studies met the inclusion criteria. This review revealed non-significant effects from the pooled estimates of MMSE cognitive, and ADAS-cognitive change scores. Individual study estimates for treatment effect demonstrated a significant improvement for 3 mg

melatonin compared with placebo in behavioural and affective symptoms as measured by the ADAS non-cognitive scale in a study of 20 patients, and the Neuropsychiatric Inventory (NPI) following treatment with 2.5 mg/day (SR) melatonin, but not with 10 mg/day (IR) melatonin in a larger study of 157 patients. The remainder of the treatment effects for affect, behaviour and activities of daily living were non-significant.

Authors' conclusions

There is insufficient evidence to support the effectiveness of melatonin in managing the cognitive and non-cognitive sequelae of dementia.

PLAIN LANGUAGE SUMMARY

Insufficient evidence to support the effectiveness of melatonin for managing cognitive impairment

There are a number of studies that suggest a relationship between decline of melatonin function and the symptoms of dementia. Evidence from three randomized, placebo controlled trials, designed to evaluate melatonin for sleep disorders associated with dementia, found no evidence of efficacy for cognitive function, and evidence from a single small trial that there may be some benefit for behavioural problems.

BACKGROUND

Melatonin, a naturally-occurring hormone secreted by the pineal gland in the centre of the brain, was discovered by Lerner and colleagues at Yale University School of Medicine in 1958 (Wurtman 1989). It is biosynthesized from tryptophan via serotonin. It has a number of effects relating to a variety of bodily functions. These include circadian rhythmicity (physiological sleep onset and sleep-wake cycles) and cyclic hormone release (Webb 1995); regulation of the immune system (Maestroni 1993); and more recently discovered anti-oxidant properties (Reiter 1995). In addition to the brain, there are also melatonin receptors on cells of blood vessels, ovaries and digestive system, though little is currently known about their functions.

Since melatonin is a naturally occurring substance, it is not considered a drug in most countries. However, the safety of melatonin products has not been definitely determined. Melatonin products are regulated differently in several countries. In the United States, melatonin falls under the Food and Drug Administration's Dietary Supplement Health and Education Act in the category of "other dietary supplements" and is "generally recognized as safe". In Canada, melatonin is included in the Natural Health Products Directorate of Health Canada. Melatonin is available for sale in Canada, having met the specific licensing, manufacturing, labelling, and safety standards. In the European Union, melatonin is considered a medicine or hormone and is available only by prescription. In Australia, melatonin is an unregistered product under the Therapeutic Goods administration. However, with a prescription, it can be imported for use under the Personal Import Scheme (Buscemi 2004). It should be noted that in situations where man-

ufacture and sale of melatonin is not regulated as for a drug, preparations may contain additives that have their own pharmacological actions and potential side effects (e.g. some health food store melatonin preparations are said to contain the same impurity which causes eosinophilia-myalgia syndrome when found in tryptophan preparations) (Williamson 1998).

Dementia is an acquired, persistent global impairment of intellectual function. There are various diagnostic criteria based on demonstration of acquired defects in more than one domain of cognitive function, for example: language, memory, visuo-spatial skills, emotion or personality, abstraction, calculation, judgment or executive function. It is a common affliction, affecting some 8% of adults aged over 65 years, rising to 35% of those older than age 85 years (CSHA 1994).

There are a number of factors suggesting a relationship between decline of melatonin function and the deficits of dementia (CSHA 1994). These include:

- Decline of serum melatonin levels (Mishima 1994) (to an even greater extent than in normal aging) and the breakdown of normal circadian rhythmicity (Ghali 1995; Hopkins 1992) in patients with dementia. The relationship between melatonin and circadian rhythmicity is well-established. The suprachiasmatic nuclei (SCN) of the brain are generally accepted as the "seat" of the circadian clock in humans (Moore 1992; Swaab 1985). Entrainment of the SCN (i.e. "setting" of the biological clock) is, in large part, due to rhythmic re-

lease of melatonin from the pineal gland (Dubocovich 1991).

- Disruption in sleep patterns in patients with dementia (Prinz 1982), the relationship between melatonin and sleep (Webb 1995), and the relationship between sleep and cognitive function i.e. disrupted or insufficient sleep can contribute to significant difficulties with tasks requiring mental concentration and memory function (Downey 1987). This effect is thought to be even more pronounced in people with pre- or co-existing causes of cognitive impairment (Hopkins 1995).
- Correlation between typical areas of cerebral atrophy in certain dementias (e.g. temporal lobes in Alzheimer's disease [AD]), and those areas containing melatonin receptors (Dubocovich 1991; Fauteck 1995).
- Antioxidant and antiamyloidogenic properties of melatonin (Pierrefiche 1995; Reiter 1994); and the known involvement of oxidative and amyloid-mediated brain damage in the pathogenesis of AD (Varadarajan 2000).

Breakdown in normal function of melatonin-related brain functions also may play a significant role in caregivers' ability to care for an individual with dementia. Specifically, problematic sleep-related behaviours often precipitate the decision of families to institutionalize an elderly relative with dementia (Coffey 1994).

Generally, few adverse effects have been reported in human trials in recent years (Andrade 2001; Seabra 2000; Shamir 2000). However, because of the many organ systems containing melatonin receptors, effects could be far-reaching. Furthermore, a number of older studies and animal data suggest a variety of possible side effects including:

- Worsening of depression, sleep disturbance, weight loss and an oral temperature decrease in depressed individuals (Carman 1976); also supported by a finding in depressed patients, but not in controls, of a longer duration of the nocturnal period of active melatonin secretion in winter than in summer (Wehr 2001). Furthermore, because evening melatonin should produce a circadian phase advance, it may worsen early morning awakening.
- Decreased sex drive and infertility. In many mammals, melatonin affects prolactin and gonadotropins (Griffiths 1987; Smith 1987). This also appears to be the case in humans, as high levels of melatonin have been found in women with hypothalamic amenorrhoea (Berga 1988; Laughlin 1991) and in men with hypogonadism (Karasek 1990; Puig-Domingo 1992). So too, exogenous melatonin delays sexual maturation in experimental animals (Lang 1985; Rivest 1985), and high doses of

melatonin have been used in humans as a female contraceptive (inhibiting ovulation) in combination with progesterone (Voordouw 1992).

- In mammals, melatonin may suppress insulin (Rasmussen 1999) although a lack of effect on insulin has also been found (Bizot-Espiard 1998). There is recent evidence that exogenous melatonin reduces glucose tolerance and insulin sensitivity in post-menopausal women (Cagnacci 2001).
- Melatonin has been found to increase retinal susceptibility to light-induced damage (Leino 1984; Wiechmann 1992) but also to protect the retina from oxidative damage (Siu 1999).
- Melatonin has been reported to have both vasoconstricting (Mahle 1997; Viswanathan 1997) and vasorelaxing properties (Cagnacci 2001a; Weekley 1995): it can lower blood pressure (Chuang 1993; Tom 2001) and, in animals, constrict cerebral and coronary arteries and reduce cerebral blood flow (Capsoni 1995). The arterial effect might account for several reports that melatonin causes headache, although it has also been reported to relieve headache (especially migraine) (Claustrat 1997; Gagnier 2001). Vasoconstriction could also, theoretically, compromise cerebral circulation in older people with atherosclerosis. However, another study suggests melatonin may diminish the risk of hypoperfusion-induced cerebral ischaemia by shifting the lower limit of cerebral blood flow autoregulation to a lower pressure level, improving the cerebrovascular dilatatory reserve, and thus widening the security margin (Regrigny 1998).
- At least one study reported increased seizures when melatonin was given to neurologically compromised children (Sheldon 1998), but elsewhere an anti-convulsant and neuro-protective effect has been reported (Munoz-Hoyos 1998).
- Exogenous melatonin (or its withdrawal) may trigger or worsen manic episodes in susceptible individuals (Leibenluft 1997), although it has also been found to improve sleep and decrease severity of manic symptoms in manic patients with treatment-resistant insomnia (Bersani 2000; Robertson 1997).
- The preponderance of evidence suggests that melatonin has anti-cancer properties in vitro (Hill 1988; Hu 1998), in animal studies (Kumar 2000) and in humans (Lissoni 1994; Neri 1994). However, other studies have found a lack of such effect (Panzer 1998) and there is even at least one paper supporting a pro-neoplastic effect in a compound structurally similar to melatonin (Malakhova 1986).

- Melatonin appears to enhance immune function (Maestroni 1993; Reiter 2000); this may have positive clinical effects in illnesses such as cancer, but may worsen such autoimmune conditions as arthritis (Maestroni 2001).

OBJECTIVES

The objective was a systematic review of evidence relating to the clinical efficacy and safety of melatonin in the treatment of manifestations of dementia or cognitive impairment (CI).

METHODS

Criteria for considering studies for this review

Types of studies

The review included all relevant unconfounded, randomized controlled trials, published or unpublished, in which treatment allocation was concealed and assessment of outcomes was blind. The period of treatment exceeded one day. Studies were included irrespective of the language in which they were reported.

The first treatment period of crossover studies were included where appropriate, but since most conditions under evaluation were progressive, and in order to avoid carry-over effects, data from subsequent phases were excluded.

Types of participants

Included studies involved patients with dementia of any severity or cognitive impairment. The diagnosis of dementia was based on accepted criteria such as ICD, DSM (APA 1995) and NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (McKhann 1984)). In the case of studies conducted before the widespread availability or use of the accepted criteria, the diagnosis was based on a comparable assessment using rating scales. The diagnosis of cognitive impairment was usually based on assessment using rating scales.

Types of interventions

Included trials assessed the effect of orally administered melatonin in any dosage compared with placebo, or the effect of melatonin compared with no treatment, for a minimum of one day, and with a minimum of 24 hour follow-up.

Types of outcome measures

Relevant outcomes were cognitive, behavioural and/or affective, function in activities of daily living, quality of life, caregiver stress, morbidity, mortality and length of time to institutionalization. Any trial with acceptable (i.e. objective, reproducible) measures of the above was included. Sleep was not included as it is being examined in another Cochrane review (Johnson 2001). Side-effects and safety issues relevant to the use of melatonin were assessed.

Search methods for identification of studies

See [Cochrane Dementia and Cognitive Improvement Group](#) methods used in reviews.

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG) was searched on 29 January 2008 for all years up to December 2005. This register contains records from the following major healthcare databases: *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS, and many ongoing trial databases and other grey literature sources. The following search terms were used: melatonin and N-ACETYL-5-METHOXYTRYPTAMINE.

The Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL were searched separately on 29 January 2008 for records added to these databases after December 2005 to January 2008. The search terms used to identify relevant controlled trials on dementia, Alzheimer's disease and mild cognitive impairment for the Group's Specialized Register can be found in the Group's module on *The Cochrane Library*. These search terms were combined with the following search terms and adapted for each database, where appropriate: melatonin and N-ACETYL-5-METHOXYTRYPTAMINE.

The search of January 2008 retrieved several studies for consideration by the authors.

On 29 January 2008, the Specialized Register consisted of records from the following databases:

Healthcare databases

- *The Cochrane Library*: (2006, Issue 1);
- MEDLINE (1966 to 2006/07, week 5);
- EMBASE (1980 to 2006/07);
- PsycINFO (1887 to 2006/08, week 1);
- CINAHL (1982 to 2006/06);
- SIGLE (Grey Literature in Europe) (1980 to 2005/03);
- LILACS: Latin American and Caribbean Health Science Literature (<http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&> (last searched 29 August 2006).

Conference proceedings

- ISTP (<http://portal.isiknowledge.com/portal.cgi>) (Index to Scientific and Technical Proceedings) (to 29 August 2006);
- INSIDE (BL database of Conference Proceedings and Journals) (to June 2000);.

Theses

- Index to Theses (formerly ASLIB) (<http://www.theses.com/>) (UK and Ireland theses) (1716 to 11 August 2006);
- Australian Digital Theses Program (<http://adt.caul.edu.au/>): (last update 24 March 2006);
- Canadian Theses and Dissertations (<http://www.collectionscanada.ca/thesescanada/indexe.html>): 1989 to 28 August 2006);
- DATAD - Database of African Theses and Dissertations (<http://www.aau.org/datad/backgrd.htm>);
- Dissertation Abstract Online (USA) (<http://www.lib.umi.com/dissertations/gateway>) (1861 to 28 August 2006).

Ongoing trials

UK

- National Research Register (<http://www.update-software.com/projects/nrr/>) (last searched issue 3/2006);
- ReFeR (<http://www.refer.nhs.uk/ViewWebPage.asp?Page=Home>) (last searched 30 August 2006);
- Current Controlled trials: Meta Register of Controlled trials (mRCT) (<http://www.controlled-trials.com/>) (last searched 30 August 2006) :
- ISRCTN Register - trials registered with a unique identifier
- Action medical research
- Kings College London
- Laxdale Ltd
- Medical Research Council (UK)
- NHS Trusts Clinical Trials Register
- National Health Service Research and Development Health Technology Assessment Programme (HTA)
- National Health Service Research and Development Programme 'Time-Limited' National Programmes
- National Health Service Research and Development Regional Programmes
- The Wellcome Trust
- Stroke Trials Registry (<http://www.strokecenter.org/trials/index.aspx>) (last searched 31 August 2006);

Netherlands

- Netherlands Trial Register (<http://www.trialregister.nl/trialreg/index.asp>) (last searched 31 August 2006);

USA/International

- ClinicalTrials.gov (<http://www.ClinicalTrials.gov>) (last searched 31 August 2006) (contains all records from <http://clinicalstudies.info.nih.gov/>);
- IPFMA Clinical trials Register: www.ifpma.org/clinicaltrials.html. The Ongoing Trials database within this Register searches <http://www.controlled-trials.com/isrctn>, <http://www.ClinicalTrials.gov> and <http://www.centerwatch.com/>. The ISRCTN register and [Clinicaltrials.gov](http://www.clinicaltrials.gov) are searched separately. Centerwatch is very difficult to search for our purposes and no update searches have been done since 2003.
- The IFPMA Trial Results databases searches a wide variety of sources among which are:
- <http://www.astrazenecaclinicaltrials.com> (seroquel, statins)
- <http://www.centerwatch.com>
- <http://www.clinicalstudyresults.org>
- <http://clinicaltrials.gov>
- <http://www.controlled-trials.com>
- <http://ctr.gsk.co.uk>
- <http://www.lillytrials.com> (zyprexa)
- <http://www.roche-trials.com> (anti-abeta antibody)
- <http://www.organon.com>
- <http://www.novartisclinicaltrials.com> (rivastigmine)
- <http://www.bayerhealthcare.com>
- <http://trials.boehringer-ingenelheim.com>
- <http://www.cmrinteract.com>
- <http://www.esteve.es>
- <http://www.clinicaltrials.jp>

This part of the IPFMA database is searched and was last updated on 4 September 2006;

- Lundbeck Clinical Trial Registry (<http://www.lundbecktrials.com>) (last searched 15 August 2006);
- Forest Clinical trial Registry (<http://www.forestclinicaltrials.com/>) (last searched 15 August 2006).

The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the Group's module on *The Cochrane Library*. Reference lists of retrieved articles (especially literature reviews) were examined for additional trials and proceedings of relevant conferences were searched.

Data collection and analysis

Selection of trials

Titles and abstracts of citations obtained from the search were examined by three reviewers (LJ, VD and DF) and obviously irrelevant articles discarded. In the presence of any suggestion that an article described a relevant randomized controlled trial, it was retrieved for further assessment.

Two authors (LJ, VD) independently assessed retrieved articles for inclusion in the review according to the criteria above. Disagreements were resolved by discussion, or if necessary referred to a third author (DF).

Assessment of methodology and quality

The trial conduct and methodological quality were assessed by both reviewers. Randomization and blind assessment of outcome were threshold criteria for inclusion in the review. In addition, whether participants were blind to their treatment allocation and whether drop-out was judged to be serious enough to be a potential source of bias was assessed for use in sensitivity analyses.

Concealment of allocation to treatment was rated by the following three categories:

Category A (adequate) where the report described allocation of treatment by: (i) some form of centralized randomized scheme, e.g. having provided details of an enrolled participant to an office by phone to receive the treatment group allocation; (ii) some form of randomization scheme controlled by a pharmacy; (iii) numbered or coded containers, e.g. in a pharmaceutical trial in which capsules from identical-looking numbered bottles are administered sequentially to enrolled participants; (iv) an on-site or coded computer system, given that the allocations were in a locked, unreadable file that could be accessed only after inputting the characteristics of an enrolled participant; or (v) if assignment envelopes were used, the report should at least specify that they were sequentially numbered, sealed, opaque envelopes; (vi) other combinations of described elements of the process that provided assurance of adequate concealment.

Category B (intermediate) where the report described allocation of treatment by: (i) use of a "list" or "table" to allocate assignments; (ii) use of "envelopes" or "sealed envelopes"; (iii) stating the study was "randomized" without further detail.

Category C (inadequate) where the report described allocation of treatment by: (i) alternation; (ii) reference to case record numbers, dates of birth, day of the week, or any other such approach; (iii) any allocation procedure that was transparent before assignment, such as an open list of random numbers or assignments.

Trials were included if they conformed to categories A or B; those falling into category C were excluded.

Data extraction

Data were extracted from published reports or requested from the first author when necessary. Summary statistics were required for each trial and each outcome. For continuous data, the mean change from baseline, the standard error of the mean change, and the number of patients for each treatment group at each assessment were extracted. Where changes from baseline were not reported, the mean, standard deviation and the number of patients for each treatment group at each time point were extracted if available.

The baseline assessment was defined as the latest available assessment prior to randomization, but no longer than two months prior.

In studies where a cross-over design was used, only data from the first treatment phase after randomization were eligible for inclusion.

Data analysis

The outcomes measured in clinical trials of dementia and cognitive impairment often arise from ordinal rating scales. Where the rating scales used in the trials have a reasonably large number of categories (more than 10) the data were treated as continuous outcomes arising from a normal distribution.

Summary statistics (sample size, mean and standard deviation) were required for each rating scale at each assessment time for each treatment group in each trial for change from baseline.

When change from baseline results were not reported, the required summary statistics were calculated from the baseline and assessment time treatment group means and standard deviations. In this case a zero correlation between the measurements at baseline and assessment time were assumed. This method overestimates the standard deviation of the change from baseline, but this conservative approach was considered to be preferable in a meta-analysis. The meta-analysis requires the combination of data from the trials. The measure of the treatment difference for any outcome was the weighted mean difference when the pooled trials used the same rating scale or test to assess an outcome, and the standardised mean difference, which is the absolute mean difference divided by the standard deviation, when they used different rating scales or tests. Due to insufficient data, the following subgroup analyses were not undertaken:

- Disease type:
 - Alzheimer's disease
 - vascular dementia
 - mixed Alzheimer's disease and vascular dementia
 - unclassified or other dementia
 - cognitive impairment
- Duration of treatment:
 - < 12 weeks
 - ≥ 12 weeks
- Severity of dementia at baseline:

- mild (MMSE > 17 or similar)
 - moderate (MMSE 10 to 17 or similar)
 - severe (MMSE < 10 or similar)
- Sensitivity analyses will be performed with regard to:

- Blinding:
 - double blind
 - single blind
- Drop-out:
 - unlikely to cause bias
 - potentially leading to bias
- Imputation of missing dichotomous data:
 - assuming missing outcomes were less favourable
 - analysis as presented

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Three articles met the criteria for relevance and validity ([Asayama 2003](#), [Serfaty 2002](#), and [Singer 2003](#)). Two additional studies seemed to meet the criteria for relevance and validity, but one author could not be located for verification of study completion ([Eeles 2003](#)), and one study was not executed because of lack of funding ([Haworth 2001](#)). Three other studies were also excluded. The articles included in this review were all randomized controlled trials published in 2002 or 2003. One study was a randomized, double blind placebo-controlled two period crossover study ([Serfaty 2002](#)), but the data following the cross-over period have been omitted from this review in accordance with the protocol. One study was conducted in Tokyo, Japan and appeared in the literature as a translated article in English ([Asayama 2003](#)). The second study was conducted in London, UK ([Serfaty 2002](#)), and the third in the United States ([Singer 2003](#)). The majority of the participants were residents of a long term care facility, nursing home or the geriatric ward of a hospital ([Asayama 2003](#); [Serfaty 2002](#); [Singer 2003](#)), while five were being cared for at home ([Serfaty 2002](#)). Consent in all three of the studies was provided by the participant's caregiver or guardian. Two of the studies ([Asayama 2003](#); [Serfaty 2002](#)) also obtained the consent of the participant. The total number of participants who were enrolled in the studies was 210 and 200 completed the protocol.

Participants

The primary basis for selection of participants in all three studies was the diagnosis of some type of dementia. One hundred seventy seven participants in two of the studies had a diagnosis of Alzheimer disease (AD) ([Asayama 2003](#)) or a NINCDS-ADRDA diagnosis of probable AD ([Singer 2003](#)), which represents 80.09% of the total participants in the three studies. In the third study, the participants had to satisfy the [APA 2004](#) (1994) criteria for a clinical diagnosis of dementia ([Serfaty 2002](#)). Participants had to be physically able to complete the study, which excluded those who had a severe physical disease or problems. All of the studies required that participants be experiencing some type of sleep disturbance. The [Singer 2003](#) study included those with AD if they averaged less than 7 hours of sleep per night (as documented by wrist actigraphy), and were noted by the caregiver to experience two or more episodes per week of disturbed night-time sleep, such as sleep latency, wandering, early wakening, and daytime somnolence. [Serfaty 2002](#) included those with a clinical diagnosis of dementia who demonstrated at least two weekly incidents of night-time agitated behavior as reported by the caregiver. Those in [Asayama 2003](#) study also were experiencing sleep disorders. In all three studies, the Mini-Mental State Examination was administered to establish the severity of dementia both at baseline and the endpoint of the study. The mean MMSE scores of all participants at baseline ranged from a low of 10.3 to a high of 14.6, falling into the severe range of cognitive impairment ([Tombaugh 1992](#)).

Intervention

Before intervention with exogenous melatonin occurred, medications were stabilized in all three studies. In the [Asayama 2003](#) study, beta-blockers were washed out for four weeks before the study, while other drugs required by participants were maintained provided that they did not affect the symptoms of AD. In the [Serfaty 2002](#) study, participants were either not taking hypnotic medication, or were receiving the same dose of medication for at least four weeks prior to entry into the trial. Psychotropic medication was not used during the study period. The participants in the [Singer 2003](#) study were excluded from the study if they had been using investigational or unapproved medications within four weeks of the screening visit.

Exogenous melatonin was administered to participants once a day at the participant's usual bedtime, or one hour prior, or at 20:30 hours. The intervention was administered by informal caregivers, researchers, physicians or registered nurses with advanced preparation. Training was provided to all those who administered the intervention. Dosage ranged from 3 to 10 mg of immediate release (IR) melatonin to 2.5 to 6 mg slow release (SR) melatonin. One study ([Singer 2003](#)) divided participants into three groups: the control group, a group which received 2.5 (SR) melatonin, and a group which received 10 mg (IR) melatonin. A 3 mg melatonin treatment was used in the [Asayama 2003](#) study. Another study ([Serfaty 2002](#)) administered 6 mg (SR) melatonin.

Outcomes

The primary goal of each of these studies was to measure the effects of exogenous melatonin on sleep disorders in participants with cognitive dementia or AD. Primary outcomes in all three studies were measured objectively using wrist actigraphy. However, this review focused on the evaluation of the secondary outcomes including changes in cognition, behaviour, affect, and function in activities of daily living. Adverse events associated with the use of Melatonin were also examined.

Cognitive changes were measured by the Mini-Mental State Examination (MMSE) in all studies. Additionally, the cognitive section of the Alzheimer's Disease Assessment Scale (ADAS-Cognitive) was employed by two studies (Asayama 2003; Singer 2003), and the Clinical Dementia Rating Scale (CDR) was employed by Asayama 2003. Behavioral and affective changes in the participants were measured using the Hamilton Depression Rating Scale (Hamilton 1960) in Singer 2003, the Neuropsychiatric Inventory (Cummings 1994) in Singer 2003, and the ADAS non-cognitive scores (Rosen 1984) in Asayama 2003. Activities of daily living (ADL) in the participants were measured in Singer 2003 using the ADL Inventory (Galasko 1997). These tests and rating scales are described in Table 1.

Table 1. Description of Assessment Scale Used in Included Studies

<p>Mini-Mental State Examination (MMSE) used in Asayama 2003 and Singer 2003 study.</p>	<p>MMSE: Short, valid and reliable cognitive assessment tool that can evaluate the severity of dementia and chronological changes in functioning. Eleven task oriented items, key scale categories of orientation, memory and attention. Total attainable score is 30 indicating healthy cognitive status. Concurrent validity supported by correlations with the Weschler Adult Intelligence Scale ($r = .776$ with the Verbal Scale, $p < .0001$; $r = .660$ with Performance Scale, $p < .001$ (Tombaugh 1992). Twenty-four hour retest (1 tester) $r = .887$, $p < .0001$; 24 hour retest (2 testers) $r = .827$, $p < .0001$, 28 day retest $r = .988$, $p < .0001$(Folstein 1975).</p>
<p>Mini-Mental State Examination (MMSE) used in Asayama 2003 and Singer 2003 study.</p>	<p>ADAS-cognitive: Short valid measure of cognitive functional decline associated with Alzheimer's Disease (AD). Cognitive Scale (11 items, task oriented, $r = .989$ $p < .001$, for interrater reliability, test-retest reliability, $r = .915$, $p < .001$: categories include memory, language, recall, word finding difficulty, following commands). Maximum score of 70 indicates marked cognitive symptoms of AD. Non-cognitive scale (10 items, 5 point scale: Interrater reliability $r=.947$, $p < .001$, Test-retest reliability: $r = .588$, $p < .001$: categories include depressed mood, distractability, uncooperative to testing, delusions, hallucinations, pacing, tremors, decreased appetite) with maximum score of 50 indicating pres-</p>

Table 1. Description of Assessment Scale Used in Included Studies (Continued)

	<p>ence of construct. Significant correlation with the Sandoz Clinical Assessment Geriatric Score ($r = .668$, $df = 16$, $p < .01$) and total scale score, but not with noncognitive scale ($r = .252$, $df = 16$, $p > .10$) (Rosen 1984).</p>
<p>Clinical Dementia Rating Scale (CDR) used in Asayma 2003 study.</p>	<p>CDR: Valid and reliable measure of dementia and cognitive ability. Categories include memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Scale rating score ranges from 0 (healthy) to 3 (severe dementia). Caregivers rate client ability from 1 to 9 (extreme debilitation). Adequate correlations support the reliability of the instrument (Hughes 1982).</p>
<p>Neuropsychiatric Inventory (NPI) used in Singer 2003 study.</p>	<p>NPI: Valid measure of psychopathological behavior associated with dementia. Ten dichotomous subscales: constructs of delusions, hallucinations, depression, anxiety, agitation, apathy, irritability/lability, disinhibition and euphoria. Concurrent validity supported by results of correlation with BEHAVE-AD and the Hamilton Depression Rating Scale (HDRS). Between rater, test-retest, and internal consistency results support reliability of the instrument. Data is obtained from caregivers. Higher score indicates more severe psychopathology (Cummings 1994).</p>
<p>The Activities of Daily Living Questionnaire (ADL) used in Singer 2003 study.</p>	<p>ADL: Valid and reliable measure of functional decline associated with Alzheimer's disease. Inventory of 27 items ranging from 2 to 5 point scales. Test-retest reliability moderate to very good (K statistic ranged from 0.4 to 0.75, $p < .01$. Spearman rank order correlation coefficient between scaling levels of ADL and MMSE scores ($R = 0.4 - 0.7$, $p < .001$). Higher score indicates more functional ability (Galasko 1997).</p> <p>Categories: self-care, household care, employment and recreation, shopping and money, travel, and communication. Adequate reliability was supported by average correlation coefficients of 0.86. Concurrent validity was established by comparing the ADLQ with the Record of Independent Living, a previously validated measure of level of dependency in daily living activities.</p> <p>Negatively correlated with the Mini-Mental State Examination and positively correlated with the Clinical Dementia Rating Scale.</p>

Table 1. Description of Assessment Scale Used in Included Studies (Continued)

Hamilton Depression Rating Scale (HDRS) used in Singer 2003 study.	HDRS: Clinical utility demonstrated for screening and assessment of depression. Primary psychometric research reported inter-rater correlations ranging from 0.84 to 0.90, although interviewer subjectivity may exist (Galasko 1960). Bagby 2004 reported adequate convergent and discriminant validity, but inadequate content validity. Williams 2001 supported standardization of versions of the scale and the 24 item symptom ratings to increase validity and reliability.
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Risk of bias in included studies

Essential principles of assessing methodological quality for the development of systematic reviews include study methods of design, allocation concealment, blinding of the interventions and outcome, and assessment of attrition (Higgins 2008; Forbes 2003). Selection bias can be addressed through a randomization process that controls for potential confounding factors and comparability of baseline states of the control and intervention groups. Performance bias refers to the systematic differences in the care provided to the participants in the comparison groups resulting from causes other than the intervention. Decreasing these types of bias can be achieved through single or double blinding techniques where those receiving care and those providing care are unaware of the assigned intervention, and the provision of training to those providing the intervention. Detection bias refers to systematic differences between the comparison groups in assessment of outcomes. Blinding of outcome assessors limits detection bias. The length of the study and characteristics of participants must also be considered in the examination of attrition bias as systematic differences may exist in loss of participants between the comparison groups. The three first authors of the included research studies were contacted to obtain details of the random allocation and concealment process referred to in the published articles. The key codes for the double blind allocation sequence in all three studies were not

opened until after the data analyses were completed. Pharmaceutical staff in one study labeled the placebo and melatonin medication through a random number treatment order allocation sequence (Asayama 2003). Another study (Serfaty 2002) used a computer generated numbering system to achieve randomized allocation to treatment or control group. Serfaty 2002 also described the evaluation process for the double blind technique employed to address performance bias. Researchers, participants and care providers reported they were unaware of the nature of the drug (melatonin or a placebo) administered during the intervention phase of the research. Singer 2003 reported that randomization and code development was done at the Alzheimer’s Disease Cooperative Study Unit (ADCS) at the University of California San Diego. Sealed code breakers were delivered to all sites and collected following study completion. A block randomization process was applied to all ADCS study protocols. The three studies were rated as adequate for design and allocation concealment to intervention; those who assessed outcomes were also blind to allocation to the intervention or control group. All authors provided information in the publications or as requested by the reviewers detailing the procedures used to train those administering the intervention and cognitive and non-cognitive assessment instruments (Asayama 2003; Serfaty 2002; Singer 2003). This information is summarized in Table 2.

Table 2. Description of Methodological Quality of Included Studies

Control Confounders	Attrition/Compliance
Asayama 2003 Randomized concealed allocation. Medications stabilized, one study setting, no severe physical diseases and no disorders that could cause sleep disorders other than AD. Baseline level of cognitive impairment for placebo and intervention group in moderate range of cognitive impairment according to MMSE scores. Training was provided to those who were providing the intervention and collecting data.	100% compliance with administration of MMSE, ADAS-cog and ADAS non-cog scales.

Table 2. Description of Methodological Quality of Included Studies (Continued)

Serfaty 2002 Randomized concealed allocation. Medications stabilized, informal caregivers received training for intervention in two settings, training also provided for administration of Mini Mental State Examination. Study exclusion criteria reported.	85% compliance with administration of MMSE.
Singer 2003 Randomized concealed allocation. None of the potential covariates were significantly different between the groups at baseline (age, duration of AD, sex, dementia severity, and years of education). Training provided to those administering intervention and assessment scales in long term care and private home settings. Medications stabilized. Study exclusion criteria reported.	96% compliance with administration of MMSE, ASAS-cog, NPI, ADL, NPI

Exclusion criteria of the studies addressed potential confounding factors such as unstable physical disease (Asayama 2003; Serfaty 2002; Singer 2003), depression (Serfaty 2002; Singer 2003) and acute sleep disturbance (Asayama 2003; Singer 2003). Singer 2003 reported that none of the potential covariates were significantly different between the groups at baseline (age, duration of AD, sex, dementia severity, and years of education). The MMSE mean baseline scores ranged from 10.3 to 14.6 as supported by data obtained from the publication of Asayama 2003 and Singer 2003 and upon request from Serfaty 2002.

Medications were stabilized in all three studies. One study reported that essential drug therapy was maintained, however, drugs such as beta-blockers that may affect AD were eliminated four weeks prior to the study (Asayama 2003). Singer 2003 identified that participants were excluded from this study if: (1) they received investigational or unapproved medications within four weeks of the screening visit prior to the study, (2) psychotropic sleep medication was discontinued within two weeks of the screening visit prior to the trial, or (3) melatonin was administered within two weeks of the screening visit.

The size of study samples varied across the research studies (see Characteristics of Included Studies Table). However, attrition rates were consistently low. One hundred percent compliance (n = 20 at baseline and endpoint) with the Mini Mental State Examination was achieved in Asayama 2003. Singer 2003 provided unpublished data indicating a 96% participant compliance rate (n = 157 at baseline, n = 151 at endpoint) with the administration of the cognitive and non-cognitive assessment instruments used in the study. Unpublished data prepared by Serfaty 2002 indicated an 85% compliance rate (n = 33 at baseline, n = 29 at endpoint) with the administration of the Mini Mental State Examination.

See additional Table Description of Rating Scales used in the studies (Table 1).

Effects of interventions

Data were pooled from the studies based on critical appraisal of the rationale for selecting the particular dose of melatonin in each study. Although no consensus appeared to exist in the literature on melatonin dosage, support was found for the efficacy, safety and tolerance of melatonin across a pharmacologic dosage range of 1 - 10 mg in populations without dementia (Krinsky 2004). Singer 2003 also reported that therapeutic blood levels were attained with administration of 2.5 mg (SR) and 10 mg (IR) of melatonin in pharmacokinetic studies conducted in elderly healthy subjects and elderly subjects with AD.

Study outcomes are presented under the following headings:

Cognition

MMSE change scores from Asayama 2003 (melatonin 3 mg, 4 weeks at endpoint from baseline), Serfaty 2002 (melatonin 6 mg (SR), 2 weeks at endpoint from baseline), and Singer 2003 (melatonin 2.5 mg (SR), 7 weeks at endpoint from baseline) revealed a non-significant effect for changing cognition (WMD 0.18, 95% CI -0.73, 1.10). Non-significant results for melatonin treatment effect were also obtained from the pooled estimate including the second pharmacologic treatment dose (melatonin 10 mg (IR), 7 weeks from baseline) from the Singer 2003, and Asayama 2003, and Serfaty 2002 studies (WMD -0.14 95% CI -1.14, 0.86). Further cognitive outcomes were measured using the CDR Scale (Asayama 2003) and ADAS-Cognitive Scale (Asayama 2003, Singer 2003). Data, provided by Asayama 2003 upon request, indicated there were no mean CDR change differences between the melatonin and placebo groups. Analyses of the ADAS cognitive change scores provided evidence for a significant effect of 3 mg melatonin measured at 4 weeks from baseline (Asayama 2003) (WMD -4.60, 95% CI -7.81, -1.39). However, improvement in the combined ADAS-cognitive scores was non-significant for melatonin 3 mg (Asayama 2003) and melatonin 2.5 mg (SR) (Singer 2003), measured at 4 and 7 weeks respectively from baseline (WMD -2.64 95% CI -5.99, 0.71). Results measuring cognitive improvement from the meta-analysis studies using melatonin 3 mg (Asayama 2003) and melatonin 10 mg (IR) (Singer 2003)

were also non-significant (WMD -2.33 95% CI -6.40, 1.74).

Behavioral and affective

Two studies measured behavioral and affective change: [Asayama 2003](#) used the ADAS non-cognitive scale, and [Singer 2003](#) used the Hamilton Depression Rating Scale (HDRS), and the Neuropsychiatric Inventory (NPI). The three scales appeared to measure different constructs of behaviour and affect, therefore the change scores could not be pooled. A significant treatment effect for administration of 3 mg of melatonin ([Asayama 2003](#)) was supported in the analyses of the ADAS non-cognitive change score at 4 weeks from baseline (WMD -3.30 95% CI -4.85, -1.75), and the NPI change score ([Singer 2003](#)) at the 7 week endpoint measure of 2.5 mg (SR) melatonin (WMD -6.23 95% CI -11.93, -0.53). Non-significant results were revealed between the [Singer 2003](#) 10 mg (IR) melatonin comparison groups at the 7-week endpoint measure using the NPI scores (WMD 0.63 95% CI -4.58, 5.84). When changes in the HDRS scores were compared between those who received melatonin and placebo, there were no significant differences in change in scores from baseline to end of treatment for administration of 2.5 mg (SR) melatonin (WMD 1.49 95% CI -0.29, 3.27) or 10 mg (IR) melatonin (WMD -0.20 95% CI -1.88, 1.48) ([Singer 2003](#)).

Activities of daily living

The ADL Inventory was used to rate items describing activities of daily living in [Singer 2003](#), the only study to measure functional outcomes. Change scores for the control groups and intervention groups were calculated following 7 weeks of treatment from baseline. Non-significant results were revealed for treatment with 2.5 mg (SR) melatonin (WMD 0.33 95% CI -1.76, 2.42) and 10 mg (IR) melatonin (WMD 0.49 95% CI -1.80, 2.78).

DISCUSSION

No significant evidence was revealed in this review for the effect of melatonin administration on cognitive impairment associated with dementia and AD. Individual study estimates for the treatment effect demonstrated a significant improvement in behavioural and affective symptoms as measured by the ADAS non-cognitive scale for 3 mg melatonin ([Asayama 2003](#)), and the NPI following treatment with 2.5 mg (SR) melatonin ([Singer 2003](#)). The remainder of the treatment effects for affect, behaviour and activities of daily living were non-significant.

Several factors must be examined when considering the strength of the conclusions.

Significant heterogeneity may exist within the study groups. The type of dementia, length of time to institutionalization, and severity of the disease at the time of enrolment (only [Singer 2003](#) reported average duration of AD at time of enrolment as 4.9 years,

SD 3.0 years) may have influenced the outcomes. As participants in the three studies were experiencing a severe degree of dementia, the findings may not be applicable to milder forms of cognitive impairment. Power analyses were not conducted in the individual studies to determine if the sample sizes were large enough to detect a difference if one existed. Although the endpoint sample size (N=151) reported by [Singer 2003](#) could be considered adequate in the context of sleep-research studies, it is smaller than those obtained in multicenter psychotropic medication trials. Therefore, sample sizes were too small (n = 20, [Asayama 2003](#); n = 29, [Serfaty 2002](#); n = 151, [Singer 2003](#)) to undertake sensitivity and subgroup analyses, and may have influenced the pooled estimate of the different interventions (i. e., melatonin 3 mg, [[Asayama 2003](#)], melatonin 6 mg [[Serfaty 2002](#)], and melatonin 10 mg, (IR) [[Singer 2003](#)]).

Other explanations for the non-significant treatment effects may be related to the short time interval of the studies. Detection of differences between treatment and control groups from baseline to end of treatment may be difficult to detect due to small increments of change and may require longer periods of time. However, all studies incorporated random allocation to intervention, and blind assessment of outcomes, thus meeting the validity inclusion criteria for adequate design, allocation to intervention, performance, detection, and attrition bias. MMSE baseline scores were determined to be in the moderate range and 80.09% of the total participants in the three studies had a probable diagnosis of AD. Further efforts were made in all three studies to control for potential confounding variables through exclusion criteria for clinically significant co-morbidity.

It should be noted that the primary goal of each of these studies was to measure the effects of exogenous melatonin on sleep disorders in participants with cognitive dementia or AD. Sleep disorders associated with the type or stage of dementia may have influenced the outcome scores examined in this review. [Asayama 2003](#) proposed that melatonin may indirectly affect cognitive and non-cognitive function through an improved sleep wake rhythm. [Singer 2003](#) discussed the possible hypnotic effect of melatonin.

Several outcomes of interest were not addressed by the included studies. Longer term studies are needed to examine outcomes such as morbidity, mortality, and length of time to institutionalization. Only one study ([Serfaty 2002](#)) alluded to caregiver stress, indicating that as only 5 study participants resided with a carer at home, statistical analysis of the carer's sleep quality was not possible. Two studies collected data on adverse events (AE) associated with the use of melatonin ([Serfaty 2002](#); [Singer 2003](#)). [Serfaty 2002](#) asserted there were no AEs, as the carers were asked to report any AEs and none were reported. [Singer 2003](#) provided descriptive information regarding the occurrence and severity of reported AEs from the 3 groups in the study. AEs in all 3 groups were defined as "abnormal behavior, ache/pain, falls, fatigue, gastrointestinal distress, infection, respiratory/pulmonary symptom,

skin/subcutaneous tissue, urinary symptoms” (p. 898) with an additional notation of fatigue in the placebo group. Non-significant effects were found for the mean number of AEs reported, severity (rated from 1 [mild] to 3 [severe], seriousness (rated as 1 [serious] or 2 [not serious]), and relatedness (rated as 1 [definitely related] to 5 [not related]). Based on an unadjusted P value ($p = .04$), Singer 2003 reported that AEs in the control group were more serious than those in the melatonin 10 mg (IR) treatment group, and a higher number of AEs were found in the ML 2.5 (SR) group than in the ML 10 (IR) group.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of melatonin for treatment of cognitive impairment associated with dementias and AD.

Implications for research

Results may be strengthened by longitudinal studies that examine the influence of melatonin over an extended time span. In addition, studies should not incorporate a crossover design due to the potential residual effect following cross over. Single interventions should be tested so that the effects can be clearly attributed to one intervention. Several articles could not be included in the review due to the inability to separate the effects of Bright Light Therapy from Melatonin.

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Jansen SL, Forbes DA, Duncan V, Morgan DG. Melatonin for cognitive impairment. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD003802.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Asayama 2003

Methods	Randomized controlled, double blind trial 4 weeks duration
Participants	3 males 17 females Mean age: 79.2 (SD: 6.4). Placebo group; n=9 (Mean age: 79.4 (SD: 5.3); 2 males, 7 females). Melatonin treatment group: n=11 (Mean age: 78.9 (SD: 7.3); 1 male, 10 females) All diagnosed with AD. Setting: geriatric ward of a hospital from 2000-2002. Diagnosed with AD with brain CT or brain MRI and EEG and DSM-1V and NINCDS-ARDRA. Baseline moderate MMSE rating for both groups.
Interventions	1. Melatonin 3 mg administered at 20:30 hours 2. placebo
Outcomes	Cognitive and non-cognitive changes in CDR, MMSE, and ADAS-cognitive and non-cognitive (behavioral and affective scores). Outcome measured at 4 weeks.
Notes	PI: Dr. Kentaro Asayama, Department of Neuropsychiatry, Nippon Medical School. E-mail: asayama@nms.ac.jp

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Serfaty 2002

Methods	Randomized, controlled, double blind placebo-controlled two period crossover design (2 weeks + 2 weeks)
Participants	16 males 9 females Mean age: 84.2 (SD 7.6). Diagnosed with DSM-1V . Clinical Diagnosis: AD (18); MultiInfarct Dementia (4); Mixed Dementia (3).

Serfaty 2002 (Continued)

	Carers: multiple carers (20), single carer (5). Setting: nursing home room (16), home setting (5), hospital setting (4). Mean MMSE at baseline = 13.4 (SD 8.5). Demographic description of four remaining participants was not published.
Interventions	1. Melatonin 6 mg (SR) given at participants' usual bedtime. 2. placebo
Outcomes	Cognitive change in MMSE. Outcome measured at 2 weeks.
Notes	PI: Dr. Marc Serfaty, Department of Psychiatry and Behavioral Sciences, Royal Free and University College Medical School, London E-mail: mserfaty@rfc.ucl.ac.uk. Requested mean change score and MMSE demographics.
Risk of bias	
Item	Authors' judgement Description
Allocation concealment?	Yes

Singer 2003

Methods	Randomized, controlled, double blind study, 7 weeks duration
Participants	157 in total 88 females 69 males Mean age: 77.4 (SD 8.9) NINCDS-ADRD diagnosis of probable AD. Setting: Long Term care facility and private homes. Extensive baseline data for all 3 groups on data abstraction tool. Baseline moderate MMSE for all groups.
Interventions	1. Melatonin 2.5 mg (SR) or 10 mg (IR) given once a day 1 hour prior to usual bedtime. 2. placebo
Outcomes	Cognitive and non-cognitive changes in MMSE, CDR, ADAS-cognitive and ADAS non-cognitive, NPI behavioral and affective. Outcome measured at 7 weeks.
Notes	PI: Dr. Clifford Singer, Sleep and Mood Disorders Laboratory, Oregon Health and Science University. E-mail: singer@ohsu.edu

Singer 2003 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	

Characteristics of excluded studies [ordered by study ID]

Baskett 2003	Study exclusion criteria included cognitive impairment as measured by score below 26 on Mini-Mental State Examination. Sleep quality was only outcome measured by the study.
Bourne 2006	Participants were not diagnosed with dementia or cognitive impairment.
Dowling 2008	Unable to separate effects of combined interventions of bright light therapy and melatonin.
Eeles 2003	No record of study completion.
Furio 2007	This melatonin for cognitive impairment study does not include those with dementia (only a 12% risk of developing dementia).
Haffmans 2001	Unable to separate effects of combined interventions of bright light therapy and melatonin.
Haworth 2001	Reply from author on 20 February 2005 indicated that study did not proceed due to lack of funding.
Peck 2004	Participants were not diagnosed with dementia or cognitive impairment.
Riemersma 2004	Unable to separate effects of combined interventions of melatonin and bright light therapy.
Riemersma vanderlek 2005	Unable to separate effects of combined interventions of bright light therapy and melatonin.
Savaskan 2006	Literature review. The article does mention two placebo controlled trials, however they are not named in the text.
Singer 2005	Sleep quality was only outcome measured by the study.
Tozawa 1998	Sleep waking and activity levels were measured concomitantly in the study.
Valontoni 2005	Sleep outcomes were the only outcome measured in the first study. The second study measured sleep quality and activity levels for fairly healthy older adults living in rest homes.

DATA AND ANALYSES

Comparison 1. Melatonin vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MMSE change scores at endpoint (4 weeks, MLT 3 mg; 2 weeks, MLT 6 mg, 7 weeks, MLT 2.5 mg (SR) from baseline	3	150	Mean Difference (IV, Random, 95% CI)	0.18 [-0.73, 1.10]
2 MMSE change scores at endpoint (4 weeks, MLT 3 mg; 2 weeks, MLT 6 mg, 7 weeks, MLT 10 mg from baseline	3	146	Mean Difference (IV, Random, 95% CI)	-0.14 [-1.14, 0.86]
3 ADAS-cognitive change scores at endpoint (4 weeks, 3 mg MLT; 7 weeks, 2.5 mg MLT) from baseline	2	121	Mean Difference (IV, Random, 95% CI)	-2.64 [-5.99, 0.71]
4 ADAS-cognitive change scores at endpoint (4 weeks, 3 mg MLT; 7 weeks, 10 mg MLT) from baseline	2	117	Mean Difference (IV, Random, 95% CI)	-2.33 [-6.40, 1.74]

Comparison 2. Melatonin vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Affective and Behavioral change score in ADAS non-cognitive at endpoint (4 weeks, 3 mg MLT) from baseline	1	20	Mean Difference (IV, Fixed, 95% CI)	-3.3 [-4.85, -1.75]
2 Neuropsychiatric and Behavioral change score in NPI at endpoint (7 weeks, 2.5 mg MLT) from baseline	1	101	Mean Difference (IV, Fixed, 95% CI)	-6.23 [-11.93, -0.53]
3 Neuropsychiatric and Behavioral change score in NPI at endpoint (7 weeks, 10 mg MLT) from baseline	1	97	Mean Difference (IV, Fixed, 95% CI)	0.63 [-4.58, 5.84]
4 Hamilton Depression Rating Scale change score at endpoint (7 weeks, 2.5 mg MLT(SR) from baseline	1	101	Mean Difference (IV, Fixed, 95% CI)	1.49 [-0.29, 3.27]

5 Hamilton Depression Rating Scale change score at endpoint (7 weeks, 10 mg MLT) from baseline	1	97	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.88, 1.48]
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Comparison 3. Melatonin vs placebo

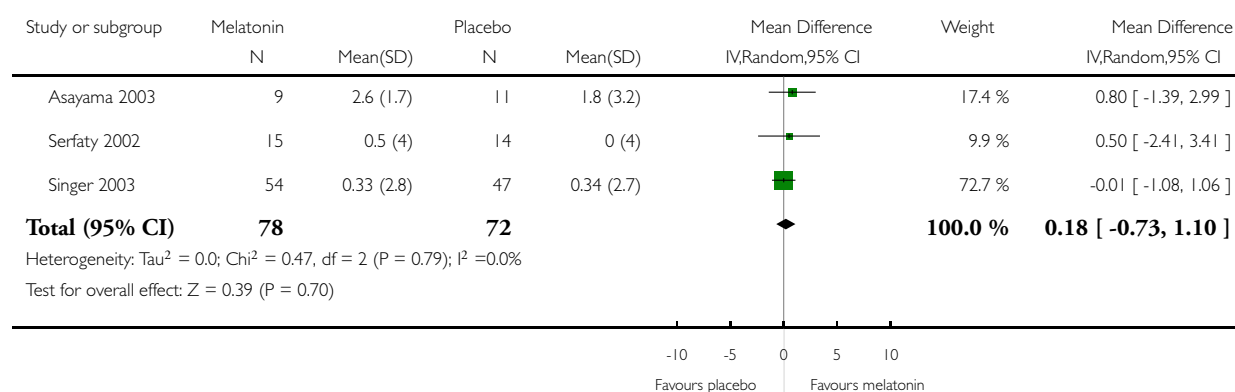
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADL change score at endpoint (7 weeks, 2.5 mg MLT) from baseline	1	101	Mean Difference (IV, Fixed, 95% CI)	0.33 [-1.76, 2.42]
2 ADL change score at endpoint (7 weeks, 10 mg MLT) from baseline	1	97	Mean Difference (IV, Fixed, 95% CI)	0.49 [-1.80, 2.78]

Analysis 1.1. Comparison 1 Melatonin vs placebo, Outcome 1 MMSE change scores at endpoint (4 weeks, MLT 3 mg; 2 weeks, MLT 6 mg, 7 weeks, MLT 2.5 mg (SR) from baseline.

Review: Melatonin for cognitive impairment

Comparison: 1 Melatonin vs placebo

Outcome: 1 MMSE change scores at endpoint (4 weeks, MLT 3 mg; 2 weeks, MLT 6 mg, 7 weeks, MLT 2.5 mg (SR) from baseline

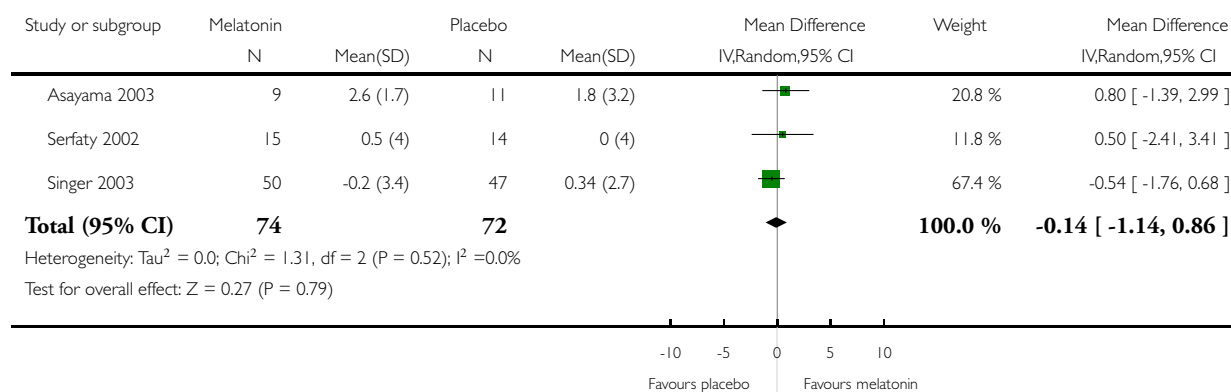


Analysis 1.2. Comparison 1 Melatonin vs placebo, Outcome 2 MMSE change scores at endpoint (4 weeks, MLT 3 mg; 2 weeks, MLT 6 mg, 7 weeks, MLT 10 mg from baseline.

Review: Melatonin for cognitive impairment

Comparison: 1 Melatonin vs placebo

Outcome: 2 MMSE change scores at endpoint (4 weeks, MLT 3 mg; 2 weeks, MLT 6 mg, 7 weeks, MLT 10 mg from baseline)

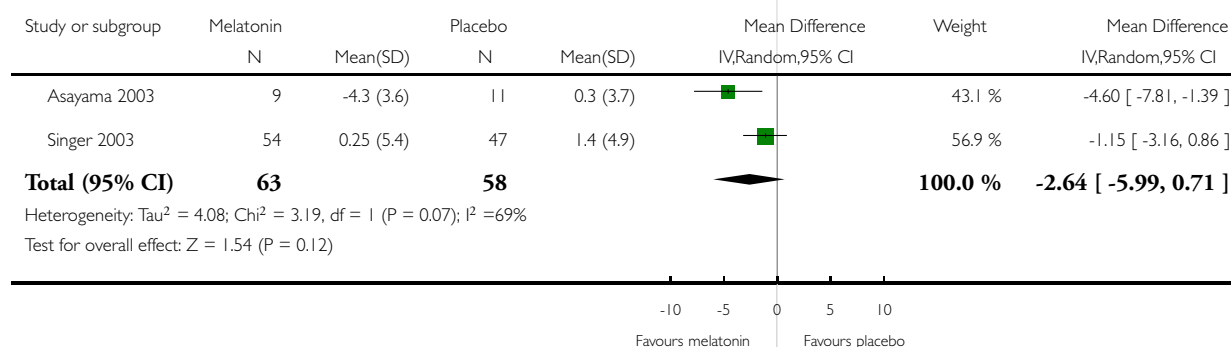


Analysis 1.3. Comparison 1 Melatonin vs placebo, Outcome 3 ADAS-cognitive change scores at endpoint (4 weeks, 3 mg MLT; 7 weeks, 2.5 mg MLT) from baseline.

Review: Melatonin for cognitive impairment

Comparison: 1 Melatonin vs placebo

Outcome: 3 ADAS-cognitive change scores at endpoint (4 weeks, 3 mg MLT; 7 weeks, 2.5 mg MLT) from baseline

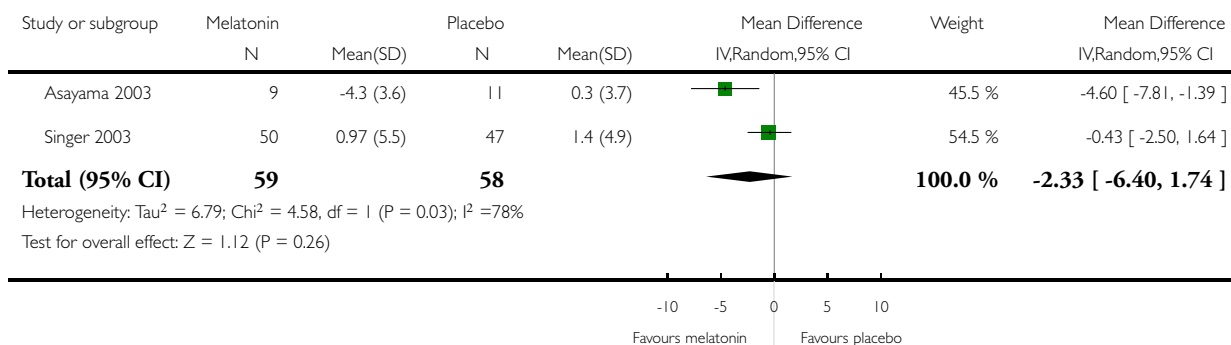


Analysis 1.4. Comparison 1 Melatonin vs placebo, Outcome 4 ADAS-cognitive change scores at endpoint (4 weeks, 3 mg MLT; 7 weeks, 10 mg MLT) from baseline.

Review: Melatonin for cognitive impairment

Comparison: 1 Melatonin vs placebo

Outcome: 4 ADAS-cognitive change scores at endpoint (4 weeks, 3 mg MLT; 7 weeks, 10 mg MLT) from baseline

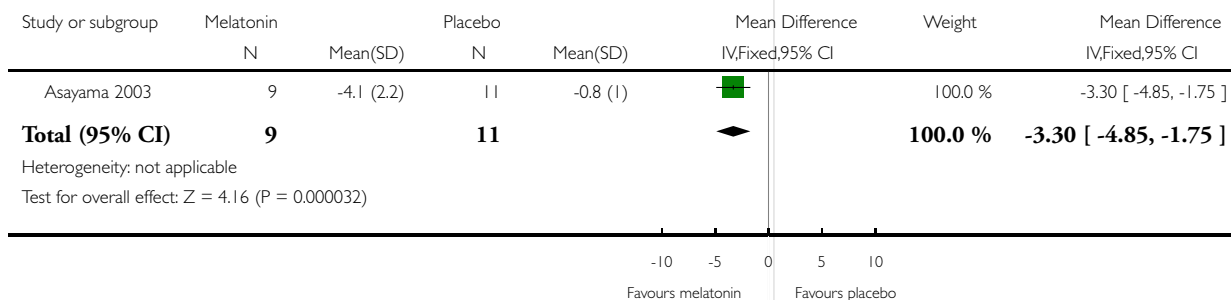


Analysis 2.1. Comparison 2 Melatonin vs placebo, Outcome 1 Affective and Behavioral change score in ADAS non-cognitive at endpoint (4 weeks, 3 mg MLT) from baseline.

Review: Melatonin for cognitive impairment

Comparison: 2 Melatonin vs placebo

Outcome: 1 Affective and Behavioral change score in ADAS non-cognitive at endpoint (4 weeks, 3 mg MLT) from baseline

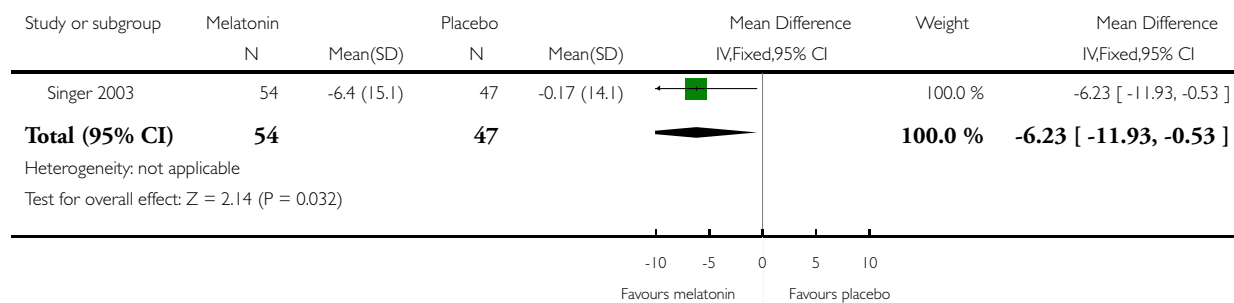


Analysis 2.2. Comparison 2 Melatonin vs placebo, Outcome 2 Neuropsychiatric and Behavioral change score in NPI at endpoint (7 weeks, 2.5 mg MLT) from baseline.

Review: Melatonin for cognitive impairment

Comparison: 2 Melatonin vs placebo

Outcome: 2 Neuropsychiatric and Behavioral change score in NPI at endpoint (7 weeks, 2.5 mg MLT) from baseline

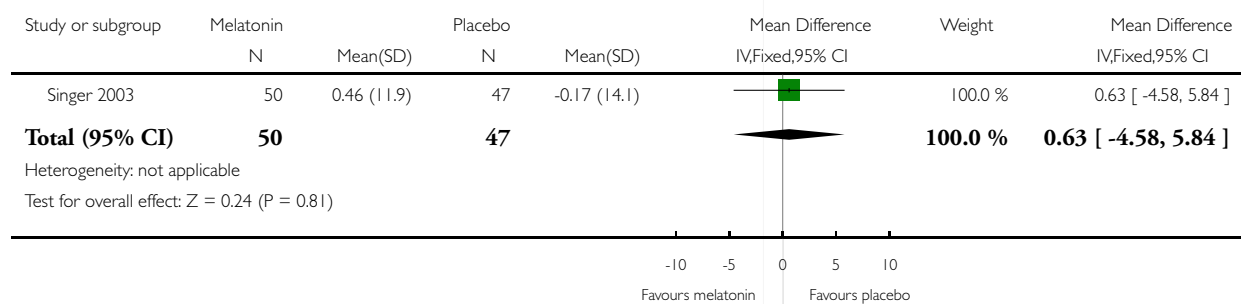


Analysis 2.3. Comparison 2 Melatonin vs placebo, Outcome 3 Neuropsychiatric and Behavioral change score in NPI at endpoint (7 weeks, 10 mg MLT) from baseline.

Review: Melatonin for cognitive impairment

Comparison: 2 Melatonin vs placebo

Outcome: 3 Neuropsychiatric and Behavioral change score in NPI at endpoint (7 weeks, 10 mg MLT) from baseline

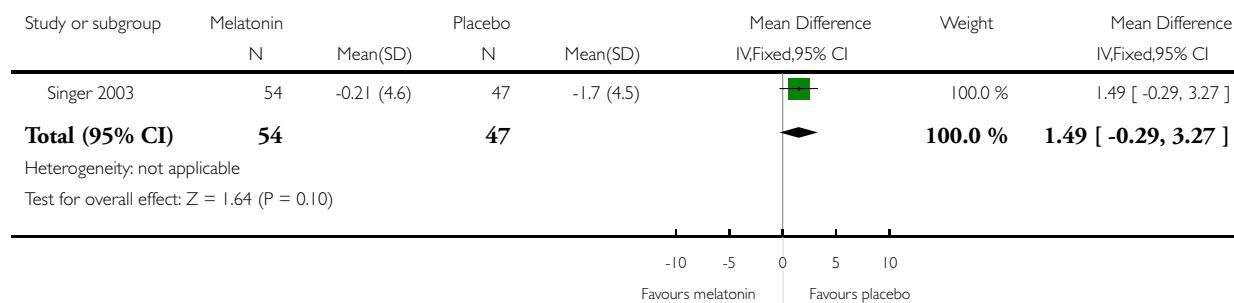


Analysis 2.4. Comparison 2 Melatonin vs placebo, Outcome 4 Hamilton Depression Rating Scale change score at endpoint (7 weeks, 2.5 mg MLT(SR) from baseline.

Review: Melatonin for cognitive impairment

Comparison: 2 Melatonin vs placebo

Outcome: 4 Hamilton Depression Rating Scale change score at endpoint (7 weeks, 2.5 mg MLT(SR) from baseline)

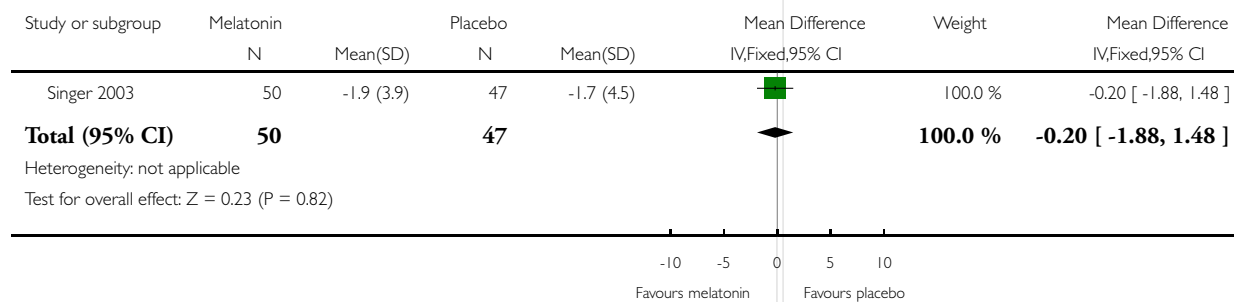


Analysis 2.5. Comparison 2 Melatonin vs placebo, Outcome 5 Hamilton Depression Rating Scale change score at endpoint (7 weeks, 10 mg MLT) from baseline.

Review: Melatonin for cognitive impairment

Comparison: 2 Melatonin vs placebo

Outcome: 5 Hamilton Depression Rating Scale change score at endpoint (7 weeks, 10 mg MLT) from baseline)

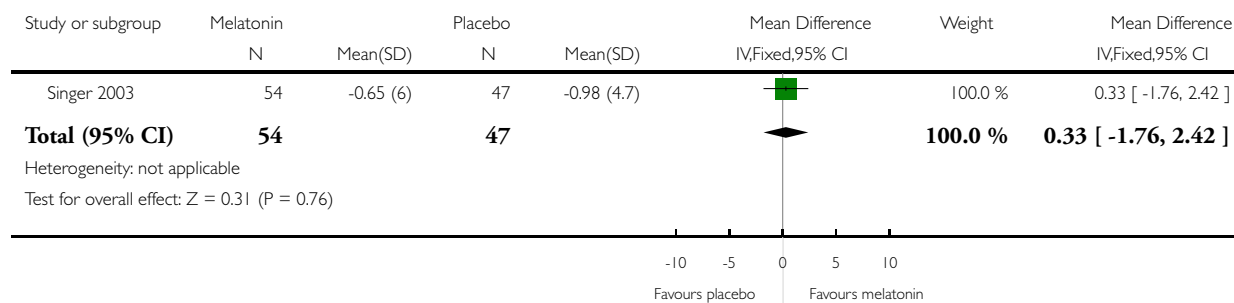


Analysis 3.1. Comparison 3 Melatonin vs placebo, Outcome 1 ADL change score at endpoint (7 weeks, 2.5 mg MLT) from baseline.

Review: Melatonin for cognitive impairment

Comparison: 3 Melatonin vs placebo

Outcome: 1 ADL change score at endpoint (7 weeks, 2.5 mg MLT) from baseline

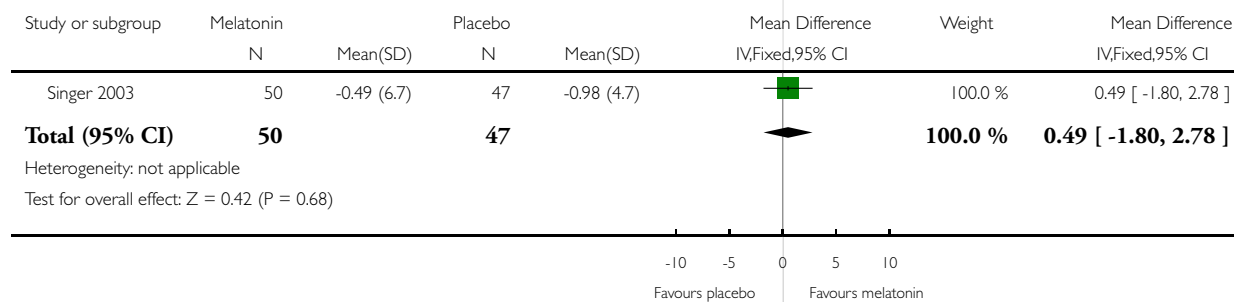


Analysis 3.2. Comparison 3 Melatonin vs placebo, Outcome 2 ADL change score at endpoint (7 weeks, 10 mg MLT) from baseline.

Review: Melatonin for cognitive impairment

Comparison: 3 Melatonin vs placebo

Outcome: 2 ADL change score at endpoint (7 weeks, 10 mg MLT) from baseline



WHAT'S NEW

Last assessed as up-to-date: 1 June 2008.

2 June 2008	Amended	Converted to new review format.
2 June 2008	New search has been performed	An update search in January 2008 retrieved some new studies for consideration by the authors; all studies identified have been excluded

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 1, 2006

15 November 2005	New citation required and conclusions have changed	Substantive amendment
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CONTRIBUTIONS OF AUTHORS

All correspondence: DF

Search for trials: VD

Obtaining copies of trial reports: VD

Selection of trials for inclusion/exclusion: LJ, VD, DF

Extraction of data: LJ, VD

Entry of data: LJ, VD

Interpretation of data analysis: DF, LJ, VD, DM

Drafting review: LJ, DF, VD, DM

-Contact editor: Rupert McShane

-Consumer editor: Toby Scott

This review was peer reviewed in January 2006

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

Antioxidants [*therapeutic use]; Cognition Disorders [*drug therapy; etiology]; Dementia [*drug therapy; etiology]; Melatonin [deficiency; *therapeutic use]; Randomized Controlled Trials as Topic; Sleep Initiation and Maintenance Disorders [drug therapy]

MeSH check words

Humans