Melatonin for cognitive impairment (Protocol)

Forbes D, Jansen SL, Duncan V, Morgan DG

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2005, Issue 4

http://www.thecochranelibrary.com

TABLE OF CONTENTS

Melatonin for cognitive impairment (Protocol)

Forbes D, Jansen SL, Duncan V, Morgan DG

This record should be cited as:
Forbes D, Jansen SL, Duncan V, Morgan DG. Melatonin for cognitive impairment. (Protocol) *The Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD003802. DOI: 10.1002/14651858.CD003802.pub2.

This version first published online: 20 April 2005 in Issue 2, 2005.
Date of most recent substantive amendment: 25 January 2005

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
The primary objective is 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).

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 considred 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).

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 50% of people aged over 85 years.

There are a number of factors suggesting a relationship between decline of melatonin function and the deficits of dementia (Owen (unpubl)). 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 release 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 signif-

icant 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 DAT), 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 Alzheimer's Disease (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 amenorrhea (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 postmenopausal 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 functin (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).

It should be noted that in situations where manufacture 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).

OBJECTIVES

The primary objective is 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).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

The review will include 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 must exceed one day. Studies will be included irrespective of the language in which they were reported.

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

Types of participants

Included studies will involve patients with dementia of any severity or cognitive impairment. The diagnosis of dementia may be 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, it may be based on a comparable assessment using rating scales. The diagnosis of cognitive impairment is usually based on assessment using rating scales.

Types of intervention

Included trials will have 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 1 day, and with a minimum of 24 hour follow-up.

Types of outcome measures

Relevant outcomes are cognitive, behavioural and/or affective, function in activities of daily living, quality of life, caregiver stress, morbidity, mortality and length of time to institutionalization. Included will be any trial with acceptable (i.e. objective, reproducible) measures of the above. Sleep will not be included as it is being examined in another Cochrane review (Johnson 2001).

Side-effects and safety issues relevant to the use of melatonin will be assessed.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: search strategy

- The Cochrane Dementia and Cognitive Improvement Group Register of Clinical Trials (which contains up-to-date references from MEDLINE, EMBASE, PsycINFO, CINAHL, CCTR/CENTRAL and may other trial databases) will be searched for trials involving melatonin. The search terms used will be MELATONIN, and N-ACETYL-5-METHOXYTRYPTAMINE.
- Reference lists of retrieved articles (especially literature reviews) will be examined for additional trials.
- Proceedings of relevant conferences will be searched.

METHODS OF THE REVIEW

SELECTION OF TRIALS

Titles and abstracts of citations obtained from the search will be examined by both reviewers and obviously irrelevant articles discarded. In the presence of any suggestion that an article describes a relevant randomized controlled trial, it will be retrieved for further assessment.

Two authors will independently assess retrieved articles for inclusion in the review according to the criteria above. Disagreements will be resolved by discussion, or if necessary referred to a third author.

ASSESSMENT OF METHODOLOGY AND QUALITY

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

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

Category A (adequate) where the report describes allocation of treatment by: (i) some form of centralized randomized scheme, e.g. having to provide 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 administrated 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 provide assurance of adequate concealment.

Category B (intermediate) where the report describes 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 is "randomized" without further detail.

Category C (inadequate) where the report describes 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 is transparent before assignment, such as an open list of random numbers or assignments.

Trials will be included if they conform to categories A or B; those falling into category C will be excluded.

DATA EXTRACTION

Data will be extracted from published reports or requested from the first author when necessary. Summary statistics will be 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 will be extracted. Where changes from baseline are not reported, the mean, standard deviation and the number of patients for each treatment group at each time point will be extracted if available. For binary data, the numbers in each treatment group and the numbers experiencing the outcome of interest will be sought.

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

For each outcome measure, data will be sought on every patient randomized. To allow an intention-to-treat analysis, the data will be sought irrespective of compliance, whether or not the patient was subsequently deemed ineligible, or otherwise excluded from treatment or follow-up. If intention-to-treat data are not available in the publications, "on-treatment" or the data of those who complete the trial will be sought and indicated as such.

In studies where a cross-over design was used, only data from the first treatment phase after randomization will be 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 will be treated as continuous outcomes arising from a normal distribution.

Summary statistics (sample size, mean and standard deviation) will be required for each rating scale at each assessment time for each treatment group in each trial for change from baseline. For crossover trials only the data from the first treatment period will be used.

When change from baseline results are not reported, the required summary statistics will be 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 will be assumed. This method overestimates the standard deviation of the change from baseline, but this conservative approach is 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 will be the weighted mean difference when the pooled trials use 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. The duration of the trials may vary considerably. If the range is considered too great to combine all trials into one meta-analysis, the trials will be divided into smaller time periods and a separate meta-analysis conducted for each period. Some trials may contribute data to more than one time period if multiple assessments have been done.

For binary outcomes, such as clinical improvement or no clinical improvement, the odds ratio will be used to measure treatment effect. A weighted estimate of the typical treatment effect across trials will be calculated. An overall estimate of the treatment difference will be presented. In all cases the overall estimate from a fixed effects model will be presented and a test for heterogeneity will performed. If, however, there is evidence of heterogeneity of the treatment effect between trials then only homogeneous results will be pooled, or a random-effects model will be used. In this case the confidence intervals would be broader than those of a fixed-effects model.

Depending on sufficient data, the following subgroup analyses will be 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

NOTES

This protocol now has a new set of reviewers who have made minor changes to the published protocol (23/02/05)

POTENTIAL CONFLICT OF INTEREST

None known

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the contributions of Toby Scott, the consumer editor for this protocol.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

REFERENCES

Additional references

Andrade 2001

Andrade C, Srihari BS, Reddy KP, Chandramma L. Melatonin in medically ill patients with insomnia: a double-blind, placebo-controlled study. *J Clin Psychiatry* 2001;**62**(1):41–5.

APA 1995

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th Edition. Washington, DC: American Psychiatric Association, 1995.

Berga 1988

Berga SL, Mortola JF, Yen SS. Amplification of nocturnal melatonin secretion in women with functional hypothalamic amenorrhea. *J Clin Endocrinol Metab* 1988 Jan;**66**(1):242–4.

Bersani 2000

Bersani G, Garavini A. Melatonin add-on in manic patients with treatment resistant insomnia. *Prog Neuropsychopharmacol Biol Psychiatry* 2000;**24**(2):185–91.

Bizot-Espiard 1998

Bizot-Espiard JG, Double A, Cousin B, Lesieur D, Guardiola-Lemaitre B, Delagrange P, Ktorza A, Penicaud L. Lack of melatonin effects on insulin action in normal rats. *Horm Metab Res* 1998;**30**(12):711–6.

Buscemi 2004

Buscemi N, Vandermeer B, Pandya R, Hooton N, Tjosvold L, Hartling L, Baker G, Vohra S, Klassin T. Melatonin for treatment of sleep disorders. Evidence Report/Technology Assessment No. 108. Prepared by the University of Alberta Evidence-based Practice Centre, Contract No. 290-02-0023. AHRQ Publication No. 05-E002-2 November 2004.

Cagnacci 2001

Cagnacci A, Arangino S, Renzi A, Paoletti AM, Melis GB, Cagnacci P, Volpe A. Influence of melatonin administration on glucose tolerance and insulin sensitivity of postmenopausal women. *Clin Endocrinol (Oxf)* 2001;**54**(3):339–46.

Cagnacci 2001a

Cagnacci A, Arangino S, Angiolucci M, Melis GB, Facchinetti F, Malmusi S, Volpe A. Effect of exogenous melatonin on vascular reactivity and nitric oxide in postmenopausal women: role of hormone replacement therapy. *Clinical Endocrinology* 2001;**54**(2):261–6.

Capsoni 1995

Capsoni S, Stankov BM, Fraschini F. Reduction of regional cerebral

blood flow by melatonin in young rats. *Neuroreport* 1995;**6**(9):1346–8.

Carman 1976
Carman JS, Post RM, Buswell R, Goodwin FK. Negative effects of melatonin on depression. *Am J Psychiatry* 1976;**133**(10):1181–6.

Chuang 1993
Chuang JI, Chen SS, Lin MT. Melatonin decreases brain serotonin release, arterial pressure and heart rate in rats. *Pharmacology* 1993;**47**(2):91–7.

Claustrat 1997
Claustrat B, Brun J, Geoffriau M, Zaidan R, Mallo C, Chazot G. Nocturnal plasma melatonin profile and melatonin kinetics during infusion in status migrainosus. *Cephalalgia* 1997;**17**(4):511–7.

Coffey 1994
Coffey CE, Cummings JL, eds. *Textbook of Geriatric Neuropsychiatry*. Washington DC: American Psychiatric Press, 1994.

Downey 1987
Downey R, Bonnet MH. Performance during frequent sleep disruption. *Sleep* 1987;**10**:354–363.

Dubocovich 1991
Dubocovich ML. Melatonin receptors in the central nervous system. *Adv Exp Med Biol* 1991;**294**:255–265.

Fauteck 1995
Fauteck J D, Bockmann J, Böckers T M, Wittkowski W, Köhling R, Lücke A, Straub H, Speckmann E-J, Tuxhorn L, Wolf P, Pannek H, Oppel F. Melatonin reduces low-Mg2+ epileptiform activity in human temporal slices. *Exp Brain Res* 1995;**107**:321–325.

Gagnier 2001
Gagnier JJ. The therapeutic potential of melatonin in migraines and other headache types. *Altern Med Rev* 2001;**6**(4):383–9.

Ghali 1995
Ghali L, Hopkins RW, Rindlisbacher P. The fragmentation of the rest/activity cycles in Alzheimer's disease. *Int J Geriatric Psychiatry* 1995;**10**:299–304.

Griffiths 1987
Griffiths D, Bjoro T, Gautvik K, Haug E. Melatonin reduces the production and secretion of prolactin and growth hormone from rat pituitary cells in culture. *Acta Physiol Scand* 1987;**131**(1):43–9.

Hill 1988
Hill SM, Blask DE. Effects of the pineal hormone melatonin on the proliferation and morphological characteristics of human breast cancer cells (MCF-7) in culture. *Cancer Res* 1988;**48**(21):6121–6.

Hopkins 1992
Hopkins RW, Rindlisbacher P. Fragmentation of activity periods in Alzheimer's disease. *Int J Geriatric Psychiatry* 1992;**7**:805–812.

Hopkins 1995
Hopkins RW, Rindlisbacher P. Some Clinical Consequences of the Rest and Activity Disturbance in Alzheimer's Disease. *Am J Alzheimer's Care Related Disord Res* 1995;**10**:16–25.

Hu 1998
Hu DN, McCormick SA, Roberts JE. Effects of melatonin, its precursors and derivatives on the growth of cultured human uveal melanoma cells. *Melanoma Res* 1998;**8**(3):205–10.

Johnson 2001
Johnson F, Stevens T. Pharmacological interventions for sleep disorder in people with dementia. In: *The Cochrane Database of Systematic Reviews*, 4, 2001.Chichester, UK: John Wiley & Sons, Ltd.

Karasek 1990
Karasek M, Pawlikowski M, Nowakowska-Jankiewicz B, Kolodziej-Maciejewska H, Zieleniewski J, Cieslak D, Leidenberger F. Circadian variations in plasma melatonin, FSH, LH, and prolactin and testosterone levels in infertile men. *J Pineal Res* 1990;**9**(2):149–57.

Kumar 2000
Kumar CA, Das UN. Effect of melatonin on two stage skin carcinogenesis in Swiss mice. *Med Sci Monit* 2000;**6**(3):471–5.

Lang 1985
Lang U, Aubert ML, Rivest RW, Vinas-Bradtke JC, Sizonenko PC. Inhibitory action of exogenous melatonin, 5-methoxytryptamine, and 6-hydroxymelatonin on sexual maturation of male rats: activity of 5-methoxytryptamine might be due to its conversion to melatonin. *Biol Reprod* 1985;**33**(3):618–28.

Laughlin 1991
Laughlin GA, Loucks AB, Yen SS. Marked augmentation of nocturnal melatonin secretion in amenorrheic athletes, but not in cycling athletes: unaltered by opioidergic or dopaminergic blockade. *J Clin Endocrinol Metab* 1991;**73**(6):1321–6.

Leibenluft 1997
Leibenluft E, Feldman-Naim S, Turner EH, Wehr TA, Rosenthal NE. Effects of exogenous melatonin administration and withdrawal in five patients with rapid-cycling bipolar disorder. *J Clin Psychiatry* 1997;**58**(9):383–8.

Leino 1984
Leino M, Aho IM, Kari E, Gynther J, Markkanen S. Effects of melatonin and 6-methoxy-tetrahydro-beta-carboline in light induced retinal damage: a computerized morphometric method. *Life Sci* 1984;**35**(20):1997–2001.

Lissoni 1994
Lissoni P, Meregalli S, Fossati V, Paolorossi F, Barni S, Tancini G, Frigerio F. A randomized study of immunotherapy with low-dose subcutaneous interleukin-2 plus melatonin vs chemotherapy with cisplatin and etoposide as first-line therapy for advanced non-small cell lung cancer. *Tumori* 1994;**80**(6):464–7.

Maestroni 1993
Maestroni GJ. The immunoneuroendocrine role of melatonin. *J Pineal Res* 1993;**14**(1):1–10.

Maestroni 2001
Maestroni GJ. The immunotherapeutic potential of melatonin. *Expert Opin Investig Drugs* 2001;**10**(3):467–76.

Mahle 1997
Mahle CD, Goggins GD, Agarwal P, Ryan E, Watson AJ. Melatonin modulates vascular smooth muscle tone. *J Biol Rhythms* 1997;**12**(6):690–6.

Malakhova 1986
Malakhova NV, Raushenbakh MO. [Transplacental carcinogenic effect of the serotonin derivative 5-methoxyindoleacetic acid]. *Biull Eksp Biol Med* 1986;**101**(5):605–7.

McKhann 1984
McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 1984;**34**:939–944.

Mishima 1994
Mishima K, Okawa M, Hishikawa Y, Hozumi S, et al. Morning bright light therapy for sleep and behavior disorders in elderly patients with dementia. *Acta Psychiatrica Scandinavica* 1994;**89**(1):1–7.

Moore 1992
Moore RY. The organization of the human circadian timing system. *Prog Brain Res* 1992;**93**:101–117.

Munoz-Hoyos 1998
Munoz-Hoyos A, Sanchez-Forte M, Molina-Carballo A, Escames G, Martin-Medina E, Reiter RJ, Molina-Font JA, Acuna-Castroviejo D. Melatonin's role as an anticonvulsant and neuronal protector: experimental and clinical evidence. *J Child Neurol* 1998;**13**(10):501–9.

Neri 1994
Neri B, Fiorelli C, Moroni F, Nicita G, Paoletti MC, Ponchietti R, Raugei A, Santoni G, Trippitelli A, Grechi G. Modulation of human lymphoblastoid interferon activity by melatonin in metastatic renal cell carcinoma. A phase II study. *Cancer* 1994;**73**(12):3015–9.

Owen (unpubl)
Owen JA, Hopkins RW, Ginsburg ML, et al. A double-blind placebo-controlled long-term trial of melatonin in patients with Alzheimer's disease undergoing concurrent therapy with Aricept. Unknown.

Panzer 1998
Panzer A, Lottering ML, Bianchi P, Glencross DK, Stark JH, Seegers JC. Melatonin has no effect on the growth, morphology or cell cycle of human breast cancer (MCF-7), cervical cancer (HeLa), osteosarcoma (MG-63) or lymphoblastoid (TK6) cells. *Cancer Lett* 1998;**122**(1-2):17–23.

Pierrefiche 1995
Pierrefiche G, Laborit H. Oxygen free radicals, melatonin, and aging. *Experimental Gerontology* 1995;**30**(3-4):213–27.

Prinz 1982
Prinz PN, Vitaliano PP, Vitiello MV, Bokan J, Raskind M, Peskind E, Gerber C. Sleep, EEG and mental function changes in senile dementia of the Alzheimer's type. *Neurobiology of Aging* 1982;**3**:361–370.

Puig-Domingo 1992
Puig-Domingo M, Webb SM, Serrano J, Peinado MA, Corcoy R, Ruscalleda J, Reiter RJ, de Leiva A. Brief report: melatonin-related hypogonadotropic hypogonadism. *N Engl J Med* 1992;**327**(19):1356–9.

Rasmussen 1999
Rasmussen DD, Boldt BM, Wilkinson CW, Yellon SM, Matsumoto AM. Daily melatonin administration at middle age suppresses male rat visceral fat, plasma leptin, and plasma insulin to youthful levels. *Endocrinology* 1999;**140**(2):1009–12.

Regrigny 1998
Regrigny O, Delagrange P, Scalbert E, Atkinson J, Lartaud-Idjouadiene I. Melatonin improves cerebral circulation security margin in rats. *Am J Physiol* 1998;**275**(1 Pt 2):H139–44.

Reiter 1994
Reiter RJ, Tan DX, Poeggeler B, et al. Melatonin as a free radical scavenger: implications for aging and age-related diseases. *Annals of the New York Academy of Sciences* 1994;**719**:1–12.

Reiter 1995
Reiter RJ, Melchiorri D, Sewerynek E, Poeggeler B, Barlow-Walden L, Chuang J, Ortiz GG, Acuna-Castroviejo D. A review of the evidence supporting melatonin's role as an antioxidant. *J Pineal Res* 1995;**18**(1):1–11.

Reiter 2000
Reiter RJ, Calvo JR, Karbownik M, Qi W, Tan DX. Melatonin and its relation to the immune system and inflammation. *Annals of the New York Academy of Sciences* 2000;**917**:376–86.

Rivest 1985
Rivest RW, Lang U, Aubert ML, Sizonenko PC. Daily administration of melatonin delays rat vaginal opening and disrupts the first estrous cycles: evidence that these effects are synchronized by the onset of light. *Endocrinology* 1985;**116**(2):779–87.

Robertson 1997
Robertson JM, Tanguay PE. Case study: the use of melatonin in a boy with refractory bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 1997;**36**(6):822–5.

Seabra 2000
Seabra ML, Bignotto M, Pinto LR Jr, Tufik S. Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment. *J Pineal Res* 2000;**29**(4):193–200.

Shamir 2000
Shamir E, Barak Y, Plopsky I, Zisapel N, Elizur A, Weizman A. Is melatonin treatment effective for tardive dyskinesia?. *J Clin Psychiatry* 2000;**61**(8):556–8.

Sheldon 1998
Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. *Lancet* 1998;**351**(9111):1254.

Siu 1999
Siu AW, Reiter RJ, To CH. Pineal indoleamines and vitamin E reduce nitric oxide-induced lipid peroxidation in rat retinal homogenates. *J Pineal Res* 1999;**27**(2):122–8.

Smith 1987
Smith AJ, Mondain-Monval M, Andersen Berg K, Simon P, Forsberg M, Clausen OP, Hansen T, Moller OM, Scholler R. Effects of melatonin implantation on spermatogenesis, the moulting cycle and plasma concentrations of melatonin, LH, prolactin and testosterone in the male blue fox (Alopex lagopus). *J Reprod Fertil* 1987;**79**(2):379–90.

Swaab 1985
Swaab DF, Fliers E, Partiman TS. The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. *Brain Res* 1985;**342**:37–44.

Tom 2001
Tom B, De Vries P, Heiligers JP, Willems EW, Scalbert E, Delagrange P, Saxena PR. The lack of vasoconstrictor effect of the pineal hormone

melatonin in an animal model predictive of antimigraine activity. *Cephalalgia* 2001;**21**(6):656–63.

Varadarajan 2000
Varadarajan S, Yatin S, Aksenova M, Butterfield DA. Review: Alzheimer's amyloid beta-peptide-associated free radical oxidative stress and neurotoxicity. *Journal of Structural Biology* 2000;**130**(2-3): 184–208.

Viswanathan 1997
Viswanathan M, Scalbert E, Delagrange P, Guardiola-Lemaitre B, Saavedra JM. Melatonin receptors mediate contraction of a rat cerebral artery. *Neuroreport* 1997;**8**(18):3847–9.

Voordouw 1992
Voordouw BC, Euser R, Verdonk RE, Alberda BT, de Jong FH, Drogendijk AC, Fauser BC, Cohen M. Melatonin and melatonin-progestin combinations alter pituitary-ovarian function in women and can inhibit ovulation. *J Clin Endocrinol Metab* 1992;**74**(1):108–17.

Webb 1995
Webb SM, Puig-Domingo M. Role of melatonin in health and disease. *Clinical Endocrinology (Oxf)* 1995;**42**(3):221–34.

Weekley 1995
Weekley LB. Pharmacologic studies on the mechanism of melatonin-induced vasorelaxation in rat aorta. *Journal of Pineal Research* 1995; **19**(3):133–8.

Wehr 2001
Wehr TA, Duncan WC Jr, Sher L, Aeschbach D, Schwartz PJ, Turner EH, Postolache TT, Rosenthal NE. A circadian signal of change of season in patients with seasonal affective disorder. *Arch Gen Psychiatry* 2001;**58**(12):1108–14.

Wiechmann 1992
Wiechmann AF, O'Steen WK. Melatonin increases photoreceptor susceptibility to light-induced damage. *Invest Ophthalmol Vis Sci* 1992;**33**(6):1894–902.

Wurtman 1989
Wurtman RJ, Wurtman JJ. Carbohydrates and Depression. *Scientific American* 1989;**260**(1):68–75.

COVER SHEET

Title	Melatonin for cognitive impairment
Authors	Forbes D, Jansen SL, Duncan V, Morgan DG
Contribution of author(s)	All correspondence: DF Search for Trials: VD Obtaining Copies of Trial Reports: VD Selection of Trials for inclusion/exclusion: LJ, VD, DM, DF Extraction of Data: VD, LJ Entry of data: VD, LJ, DF Interpretation of data analysis: DF, VD, LJ, DM Drafting review: DF, VD, LJ, DM -Contact editor: Rupert McShane -Consumer editor: Toby Scott
Issue protocol first published	2002/3

Date of most recent amendment	16 February 2005
Date of most recent SUBSTANTIVE amendment	25 January 2005
Review expected to be published in	Issue 2, 2007
What's New	Author change from: Rusak-Maguire A, Forbes D to: Forbes D, Jansen SL, Duncan V, Morgan DG
Contact address	A/Prof Dorothy Forbes RN, PhD CIHR New Investigator School of Nursing, Faculty of Health Sciences University of Western Ontario 107 Wiggins Road Room H33, Health Sciences Addition London Ontario N6A 5C1 CANADA E-mail: dforbes6@uwo.ca Tel: 519-661-2111 Fax: 519-661-3928
DOI	10.1002/14651858.CD003802.pub2
Cochrane Library number	CD003802
Editorial group	Cochrane Dementia and Cognitive Improvement Group
Editorial group code	HM-DEMENTIA