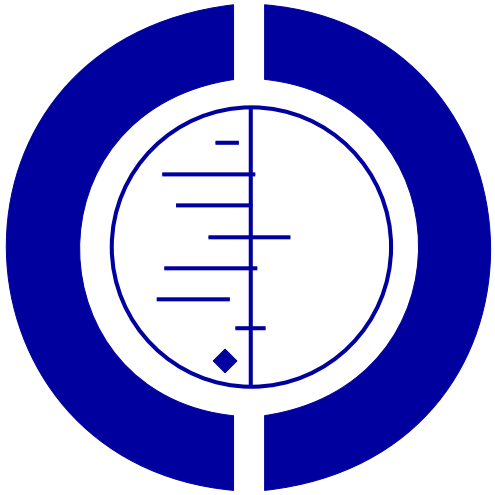
Melatonin for cognitive impairment (Protocol)

Rusak-Maguire A, Forbes D



This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2005, Issue 1

http://www.thecochranelibrary.com

TABLE OF CONTENTS

Melatonin for cognitive impairment (Protocol)

Rusak-Maguire A, Forbes D

This record should be cited as:
Rusak-Maguire A, Forbes D. Melatonin for cognitive impairment. (Protocol) *The Cochrane Database of Systematic Reviews* 2002, Issue 2. Art. No.: CD003802. DOI: 10.1002/14651858.CD003802.

This version first published online: 22 April 2002 in Issue 2, 2002.
Date of most recent substantive amendment: 14 February 2002

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 clinical efficacy and safety of melatonin in 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.

Melatonin has been available from health food stores at various times in the United States and Canada, though its sale on the open market in Canada, Europe and Australia has been prohibited pending further study.

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:

- The 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 (e.g. Webb 1995). The suprachiasmatic nuclei (SCN) of the brain are generally accepted as the "seat" of the circadian clock in humans (Swaab 1985, Moore 1992). 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).

- The 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).

- The 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 (Reiter 1994, Pierrefiche 1995); and known involvement of

oxidative and amyloid-mediated brain damage in 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. As well, 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). As well, 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 appears to be the case in humans also, as high levels of melatonin have been found in women with hypothalamic amenorrhea (Berga 1988, Laughlin 1991) and in men with hypogonadism (Puig-Domingo 1992, Karasek 1990). As well, 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), (though 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 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), to lower blood pressure (Tom 2001, Chuang 1993) and in animals, to constrict cerebral and coronary arteries and reduce cerebral blood flow (Capsoni 1995). The arterial effect might account for several reports that melatonin causes headache, though it has also been reported to relieve headache (especially migraine) (Gagnier 2001, Claustrat 1997). Vasoconstriction could also, theoretically, compromise cerebral circulation in older people with atherosclerosis, though 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 may cause vivid dreams and even nightmares, according to several studies.
- Exogenous melatonin (or its withdrawal) may trigger or worsen manic episodes in susceptible individuals (Leibenluft 1997), though 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 (Reiter 2000, Maestroni 1993); 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 clinical efficacy and safety of melatonin in 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

Participants included will be of any age and either sex with a diagnosis of dementia of the Alzheimer type, vascular dementia, mixed vascular and Alzheimer's dementia, unclassified or other dementia, or unclassified cognitive impairment not fulfilling the criteria for dementia, as diagnosed by DSM-III, -IIIR, or -IV; or by ICD-9 or -10.

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 features are cognitive, behavioural and/or affective, including formal cognitive function, function in activities of daily living, quality of life, caregiver stress, morbidity, mortality, length of time to institutionalization. Included will be any trial with acceptable (i.e. objective, reproducible) measures of the above.

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

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Dementia and Cognitive Improvement Group search strategy

1. 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/all subheadings, and N-ACETYL-5-METHOXYTRYPTAMINE.

2. Companies involved in manufacturing or marketing melatonin will be asked to provide information on randomised trials not otherwise available.

3. Reference lists of retrieved articles (especially literature reviews) will be examined for additional trials.

4. Books concerning melatonin or treatment of Alzheimer's disease will be handsearched for additional trials.

5. 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.

Both reviewers 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 an editor of the Cochrane Dementia and Cognitive Improvement Group.

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 to the following three categories:

Category A (adequate) where the report describes allocation of treatment by: (i) some form of centralized randomized scheme, such as 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, such as 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 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

To enable an intention-to-treat analysis, data will be sought for every patient, irrespective of compliance, whether or not the patient was subsequently deemed ineligible or otherwise excluded from the treatment or follow-up. Where dichotomous data are missing, patients will be assumed to have suffered the less favourable outcome. If continuous data are missing, "on-treatment" results will be extracted and indicated as such.

For continuous and ordinal variables, both change from baseline and final value will be extracted where available. The baseline score will be taken to be the latest score on or before the date of randomization provided the data do not relate to a time more than two months before randomization. No results concerning the efficacy or safety of the treatment will be extracted from pre-randomization periods, or from any open-label extension periods.

For cross-over studies, results from the first treatment period only will be extracted.

DATA ANALYSIS

Meta-analysis will be performed on data from studies considered to address sufficiently similar patients and outcomes.

Dichotomous outcomes will be pooled using the method of Mantel and Haenszel.

For continuous variables, change from baseline will be analysed in preference to final values. Where studies use the same scale of measurement, treatment effects will be assessed by a difference in means; where a variety of scales have been used to measure the same clinical outcome, a standardized mean difference will be used.

A test for heterogeneity will be undertaken prior to each meta-analysis, and if positive a random-effects analysis will be performed.

Depending on sufficient data, the following subgroup analyses will be undertaken:
1. Disease type:
 - Alzheimer's disease
 - vascular dementia
 - mixed Alzheimer's disease and vascular dementia
 - unclassified or other dementia
 - cognitive impairment
2. Duration of treatment
 - < 12 weeks
 - >= 12 weeks
3. Severity of dementia at baseline
 - mild (MMSE > 17 or similar)
 - moderate (MMSE 10-17 or similar)
 - severe (MMSE < 10 or similar)

Sensitivity analyses will be performed with regard to:
1. Blinding
 - double blind
 - single blind
2. Drop-out
 - unlikely to cause bias
 - potentially leading to bias
3. Imputation of missing dichotomous data
 - assuming missing outcomes were less favourable
 - analysis as presented

ACKNOWLEDGEMENTS

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

POTENTIAL CONFLICT OF INTEREST

The principal reviewer has been involved in an unfunded double-blind placebo-controlled long-term trial of melatonin in patients with Alzheimer's disease undergoing concurrent therapy with donepezil.

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 Jan;**62**(1):41–5.

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 Feb;**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 Dec;**30**(12):711–6.

Brock 1991

Brock MA. Chronobiology and aging. *J Am Geront Soc* 1991;**39**: 74–91.

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 Mar;**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 Feb;**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 Jun 19;**6** (9):1346–8.

Carman 1976

Carman JS, Post RM, Buswell R, Goodwin FK. [Negative effects of melatonin on depression]. *Am J Psychiatry* 1976 Oct;**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 Aug;**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 Jun;**17**(4):511–7.

Coffey 1994

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

Cummings 1992

Cummings JL, DF Benson. 2 Edition. Newton MA: Butterworth-Heinemann (Reed Publishing), 1992.

Cupp 1997

Cupp MJ. [Melatonin]. *Am Fam Phys* 1997 Oct 1;**56**(5).

de Lourdes 2000

de Lourdes M, Seabra V, 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 Nov; **29**(4):193–200.

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.

Ellis 1996

Ellis CM, Lemmens G, Parkes JD. [Melatonin and insomnia]. *J Sleep Res* 1996 Mar;**5**(1):61–5.

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.

Fekete 1985

Fekete M, Van Ree JM, Niesink RJM, De Wied D. Disruption of circadian rhythms induces retrograde amnesia. *Physiol Behav* 1985; **34**:883–887.

Gagnier 2001

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

Garfinkel 1995

Garfinkel D, Laudon M, Nof D, Zisapel N. [Improvement of sleep quality in elderly people by controlled-release melatonin]. *Lancet* 1995 Aug 26;**346**(8974):541–4.

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 Sep;**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 Nov 1;**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 Jun;**8**(3):205–10.

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.

Kayumov 2001

Kayumov L, Brown G, Jindal R, Buttoo K, Shapiro CM. [A randomized, double-blind, placebo-controlled crossover study of the effect of exogenous melatonin on delayed sleep phase syndrome]. *Psychosom Med* 2001 Jan-Feb;**63**(1):40–8.

Kumar 2000

Kumar CA, Das UN. [Effect of melatonin on two stage skin carcinogenesis in Swiss mice]. *Med Sci Monit* 2000 May-Jun;**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 Oct;**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 Dec;**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 Sep;**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 Nov 12;**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 Dec 31;**80**(6):464–7.

Maestroni 1993

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

Maestroni 2001

Maestroni GJ. The immunotherapeutic potential of melatonin. *Expert Opin Investig Drugs* 2001 Mar;**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 Dec; **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 May;**101**(5):605–7.

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 Oct;**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 Jun 15;**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.

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 Jan 9;**122**(1-2):17–23.

Pierrefiche 1995

Pierrefiche G, Laborit H. Oxygen free radicals, melatonin, and aging. *Experimental Gerontology* 1995 May-Aug;**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 Nov 5;**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 Feb;**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 Jul;**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 May 31;**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 Jan;**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 Feb;**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 Jun;**36**(6):822–5.

Sandyk 1991
Sandyk R. Age-related disruption of circadian rhythms: possible relationship to memory impairment and implications for therapy with magnetic fields. *Intern J Neuroscience* 1991;**59**:259–262.

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 Nov;**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 Aug;**61**(8):556–8.

Sheldon 1998
Sheldon SH. [Pro-convulsant effects of oral melatonin in neurologically disabled children]. *Lancet* 1998 Apr 25;**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 Sep;**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 Mar;**79**(2):379–90.

Stege 1999
Stege GJ, Bosman GJ. The biochemistry of Alzheimer's disease. *Drugs & Aging* 1999 Jun;**14**(6):437–46.

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 Jul;**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 Jun;**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 Dec 22;**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 Jan;**74**(1):108–17.

Waldhauser 1988
Waldhauser F, Weiszenbacher G, Tatzer E, et al. Alterations in nocturnal serum melatonin levels in humans with growth and aging. *J Clin Endocrinol Metab* 1988;**66**:648–652.

Webb 1982
Webb WB. Sleep in older persons: sleep structures of 50- to 60-year-old men and women. *J Gerontology* 1982;**37**:581–586.

Webb 1995
Webb SM, Puig-Domingo M. Role of melatonin in health and disease. *Clinical Endocrinology (Oxf)* 1995 Mar;**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 Oct;**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 Dec;**58**(12):1108–14.

Weitzman 1982
Weitzman ED, Moline ML, Czeisler CA, Zimmerman JC. Chronobiology of Aging: temperature, sleep-wake rhythms and entrainment. *Neurobiology of Aging* 1982;**3**:299–309.

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

Wurtman 1989
Wurtman RJ, Wurtman JJ. Carbohydrates and Depression. *Scientific American* 1989.

* *Indicates the major publication for the study*

COVER SHEET

Title	Melatonin for cognitive impairment
Authors	Rusak-Maguire A, Forbes D
Contribution of author(s)	ARM: drafting protocol; all correspondence; selection of studies, in-and exclusion of studies, data into revman, data-analyses, drafting review DF: commenting on review drafts, in-exclusion of studies -Contact reviewer on this review is J Grimley Evans -Consumer editor on this review is Toby Scott
Issue protocol first published	2002/3
Review first published	/
Date of most recent amendment	26 August 2004
Date of most recent SUBSTANTIVE amendment	14 February 2002
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Anysia Rusak-Maguire MD, FRCPC Consultant Geriatric Psychiatrist Homewood Health Centre Hamilton 3 Guelph N1E 6K9 CANADA Telephone: +1 705 494 3054 E-mail: rusaanys@homewoodhealth.com Facsimile: +1 705 494 3097

Cochrane Library number	CD003802
Editorial group	Cochrane Dementia and Cognitive Improvement Group
Editorial group code	HM-DEMENTIA