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.

Objective
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.

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 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.

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

Synopsis
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 cannot 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 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) (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...
circuitadian rhythm (Ghali 1995; Hopkins 1992) in patients with dementia. The relationship between melatonin and circadian rhythm is well-established. The suprachiasmatic nucleus (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). Abnormality in the relationship between SCN and melatonin may result in sleep disorders (Middleton and Thakuria 1999). The diagnosis of sleep disorders may require melatonin measurement in saliva and urine, allowing for a more personalized approach to treatment for such disorders (Molinari 2001). Abnormal sleep patterns have been noted in people with dementia (Peiperl 1995; Reiter 1994); and the known involvement of oxidative and amyloid-mediated brain damage in the pathogenesis of AD (Varadarajan 2000).

In general, the major effects of melatonin are summarized in a number of review articles (Asayama 2003; Bersani 2000; Cagnacci 2001; Dubocovich 1991; Fauteck 1995). Melatonin may have anti-cancer properties in vitro (Anastasi 1993; Lissoni 1994; Neri 1994). However, other studies have found a lack of such effect (Panzer 1998). There is evidence to support the role of melatonin in the regulation of the circadian rhythm in humans (Dubocovich and Voordouw 1992). Exogenous melatonin delays sexual maturation in experimental animals (Lang 1985; Rivest 1985), and high doses of melatonin may be used in humans as a female contraceptive (combination : ovulation) in combination with progestrone (Voordouw 1992).

In women, melatonin may suppress insulin (Rasmussen 1999) although a lack of effect on insulin has also been found (Brot-Espard 1998). There is evidence to suggest that exogenous melatonin reduces glucocorticoid and insulin sensitivity in post-menopausal women (Bejerano 1998). Melatonin has been reported to have both vasoconstricting (Cagnacci 2001; Griffo 2004) and vasorelaxing properties (Cagnacci 2001; Weekley 1995): it can lower blood pressure (Chuang 1993; Tom 2001) and, in animals, constrict cerebral and coronary arteries and reduce cerebral blood flow (Cagnacci 1995). The arterial effect might account for several reports that melatonin causes headache, although it has also been reported to relieve headache (especially migraine) (Clausrat 1997; Gaon 2001). Vasoconstriction could also, theoretically, compromise cerebral circulation in older people with atherosclerosis. However, another study suggests melatonin may diminish the risk of hyperfusion-induced cerebral ischaemia by shifting the lower limit of cerebral blood flow autoregulation to a lower pressure level, improving the cerebrovascular dilatory reserve, and thus widening the supply margin (Bejerano 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 (Artigas-Hoyos 1998). Exogenous melatonin (or its withdrawal) may trigger or worsen manic episodes in susceptible individuals (Lebenbluff 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 1992). There is evidence to suggest that melatonin has anti-cancer properties in vitro (Hill 1988, Hu 1998), in animal studies (Kumar 2001) and in humans (Lovisoni 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 (Malahova 1998). Moreover, melatonin has also been reported to improve immune function (Johnson 2000), which may have positive clinical effects in illnesses such as cancer, but may worsen such autoimmune conditions as arthritis (Maestroni 2001).

Methods of the review

Description of studies

Methodological quality

Results

Discussion

No significant evidence was revealed in this review for the effect of melatonin administration on cognitive impairment associated with dementia and AD. The preponderance of evidence suggests that melatonin has anti-cancer properties in vitro (Hill 1988; Hu 1998), in animal studies (Kumar 2001) 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 (Malakova 1998). Moreover, melatonin has also been reported to improve immune function (Johnson 2000), which may have positive clinical effects in illnesses such as cancer, but may worsen such autoimmune conditions as arthritis (Maestroni 2001).
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.

Reviews’ 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.

References to studies included in this review

Asayama 2003 {published and unpublished data}
Serfaty 2002 {published and unpublished data}
Singer 2003 {published and unpublished data}

References to studies excluded from this review

Baskett 2003 {published data only}
Bourne 2006 {unpublished data only}
Bourne R. Evaluation of melatonin therapy on sleep and delirium in intensive care patients. 2006:--.
Dowling 2008 {published data only}
Eeles 2003
Eeles . The effect of melatonin on sleep pattern and levels of agitation in patients with dementia. National Research Register 2003:--.
Furio 2007 {published data only}
Haffmans 2001 {published data only}
Haffmans 2004
Haffmans RF, Amsterdam, Netherlands . Light and Melatonin: Effect on sleep, mood and cognition in demented elderly. Neurobiology of Aging 1998;19:S213-.
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Haworth J. A pilot, double-blind, placebo controlled, parallel group study of the effect of melatonin treatment in patients with Alzheimer’s disease and sleep. 2001:--.
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Riemersma RF, Amsterdam, Netherlands . Light and Melatonin: Effect on sleep, mood and cognition in demented elderly. Neurobiology of Aging 2004;25:194-.
Riemersma 2005 {published data only}
Riemersma van der Lek. The effect of light and/or melatonin on sleep, mood, cognition and behavior in demented elderly. 2005:--.
Savaskan 2006 {published data only}
Singer 2005 {unpublished data only}
Singer C. Quetiapine for the treatment of insomnia associated with Alzheimer’s disease. 2005:--.
Tozawa 1998 {published and unpublished data}
Tozawa 2006
Valontin 2005 {published data only}

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In: Diagnostic and Statistical Manual of Mental Disorders Washington, DC: American Psychiatric Association, 1995:--.

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In: Diagnostic and Statistical Manual of Mental Disorders Washington, DC: American Psychiatric Association, 1994:--.

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Berra 1988

Bersani 2000

Bizot-Espiard 1998

Buscemi 2001

Cagnacci 2001

Cagnacci 2001a

Capsoni 1999

Carman 1976

Chuang 1993

Claustrat 1997

Coffey 1997

CSHA 1994

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Fauteck 1997
Fauteck JD, Bockmann J, Böckers TM, Wittkowski W, Köhling R, Lücke A. Melatonin reduces low-Mg2+ epileptiform activity in human

Galasko 1997

Ghali 1995

Griffiths 1987

Hill 1988

Hopkins 1992

Hopkins 1995

Prinz PN, Vitaliano PP, Vitiello MV, Bokan J, Raskind M, Peskind E, Gerber C. Sleep, EEG and mental function changes in senile dementia. Prinz 1982


Lang 1985


Laughlin 1991


Leibenuft 1997


Leino 1984


Lissoni 1994


Maestroni 1993


Maestroni 2001


Mahle 1997


Malakhova 1986


McKann 1984


Mishima 1994


Moore 1992


Munoz-Hoyos 1998


Neri 1994


Panzer 1998

Panzer A, Lottering ML, Bianchi P, Glencross DK, Stark JH, Seegers JG. 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 Letters 1998;122:17-23.

Pierrefiche 1995


Prinz 1982


Puig-Domingo 1992


Rasmussen 1999


Regnery 1998

Reiter 1994

Reiter 1995

Reiter 2000

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;116:779-87.

Robertson 1997

Rosen 1984

Seabra 2000

Shamir 2000

Sheldon 1985

Siu 1999

Smith 1987

Swaab 1985

Tombaugh 1992

Varadarajan 1999

Viswanathan 1992

Voonouw 1992

Webb 1999
Webb SM, Puig-Domingo M. Role of melatonin in health and disease. Clinical Endocrinology (Oxf) 1999;52:221-34.

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Williamson 1998

Wurtman 1989

Graphs

Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tbody>
<tr>
<td>Melatonin vs placebo</td>
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<td>Outcome title</td>
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<tr>
<td>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</td>
<td>3</td>
<td>150</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>0.18 [-0.73, 1.10]</td>
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<tr>
<td>2 MMSE change scores at endpoint (4 weeks, MLT 3 mg; 2 weeks, MLT 6 mg, 7 weeks, MLT 10 mg from baseline</td>
<td>3</td>
<td>146</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.14 [-1.14, 0.86]</td>
</tr>
<tr>
<td>3 ADAS-cognitive change scores at endpoint (4 weeks, 3 mg MLT; 7 weeks, 2.5 mg MLT) from baseline</td>
<td>2</td>
<td>121</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-2.64 [-5.99, 0.71]</td>
</tr>
<tr>
<td>4 ADAS-cognitive change scores at endpoint (4 weeks, 3 mg MLT; 7 weeks, 10 mg MLT) from baseline</td>
<td>2</td>
<td>117</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-2.33 [-6.40, 1.74]</td>
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Melatonin vs placebo

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<th>Statistical method</th>
<th>Effect size</th>
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<tr>
<td>1 Affective and Behavioral change score in ADAS non-cognitive at endpoint (4 weeks, 3 mg MLT) from baseline</td>
<td>1</td>
<td>20</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-3.04 [-4.85, -1.25]</td>
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<tr>
<td>2 Neuropsychiatric and Behavioral change score in NPI at endpoint (7 weeks, 2.5 mg MLT) from baseline</td>
<td>1</td>
<td>101</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-6.24 [-11.93, -0.53]</td>
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<tr>
<td>3 Neuropsychiatric and Behavioral change score in NPI at endpoint (7 weeks, 10 mg MLT) from baseline</td>
<td>1</td>
<td>97</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.64 [-4.58, 5.84]</td>
</tr>
<tr>
<td>4 Hamilton Depression Rating Scale change score at endpoint (7 weeks, 2.5 mg MLT(SR) from baseline</td>
<td>1</td>
<td>101</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>1.50 [-0.29, 3.27]</td>
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<tr>
<td>5 Hamilton Depression Rating Scale change score at endpoint (7 weeks, 10 mg MLT) from baseline</td>
<td>1</td>
<td>97</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.20 [-1.88, 1.48]</td>
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Melatonin vs placebo

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<td>1 ADL change score at endpoint (7 weeks, 2.5 mg MLT) from baseline</td>
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<td>101</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.33 [-1.76, 2.42]</td>
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<tr>
<td>2 ADL change score at endpoint (7 weeks, 10 mg MLT) from baseline</td>
<td>1</td>
<td>97</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.50 [-1.80, 2.78]</td>
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