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Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia. Are there implications for delirium? A systematic review

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Objective

Circadian rhythm disturbances, like sundowning, are seen in dementia. Because the circadian rhythm is regulated by the biological clock, melatonin might be effective in the treatment of these disturbances. We systematically studied the effect of melatonin treatment in patients with dementia. In addition, we elaborate on the possible effects one might expect of melatonin treatment in patients with delirium, since dementia and delirium are strongly related. Moreover, some evidence exists that sundowning in patients with dementia and the alterations in the sleep/wake cycle, seen in patients with delirium both originate from circadian rhythm disturbances.

Design

A systematic search of the literature, published between 1985 and April 2009, was performed using PubMed and other databases. All papers on melatonin treatment in dementia were retrieved. Effects of melatonin on circadian rhythm disturbances were scored by means of scoring sundowning/agitated behaviour, sleep quality and daytime functioning.

Results

Nine papers, including four randomised controlled trials (RCTs) (n=243), and five case series (n=87) were reviewed. Two of the RCTs found a significant improvement on sundowning/agitated behaviour. All five case series found an improvement. The results on sleep quality and daytime functioning were inconclusive.

Conclusion

Sundowning/agitated behaviour improves with melatonin treatment in patients with dementia. There are several arguments that sundowning in patients with dementia and the alterations in the sleep/wake cycle in patients with delirium have a common background, namely a disturbance of the circadian rhythm. This suggests that melatonin treatment could also have the same positive effects in patients with delirium.

BACKGROUND

Patients with dementia may show sleep and behavioural problems, some of which can be described as circadian rhythm disturbances. These disturbances manifest themselves in different forms, like decreased sleep quality, sundowning/agitated behaviour and decreased daytime functioning. Sleep quality is a broad concept consisting of several aspects including sleep latency, total sleep time, number of awakenings and subjective sleep quality. Sundowning refers to the appearance or exacerbation of behavioural disturbances associated with the afternoon and/or evening hours (Cardinali et al., 2002; Volicer et al., 2001; Wick and Zanni, 2005). The American Sleep Disorder Association however, considers sundowning to include 'the sleep disturbance that is characterised by noctural wandering and confusion' (Bachman and Rabins, 2006). Sundowning is often referred to as a chronobiological disturbance because it results from specific cerebral pathophysiologic abnormalities that interfere with normal circadian and behavioural regulation (Lebert et al., 1996; Volicer et al., 2001). The reported incidence ranges from 13 to 66% (Evans, 1987; Gallagher-Thompson et al., 1992) mainly depending on the state of progression of dementia. Agitation is a well-described type of behaviour and refers to inappropriate verbal, vocal or motor behaviour that is not explained by apparent needs or by confusion per se (Cohen-Mansfield and Billig, 1986).

Circadian rhythm disturbances in dementia can be distressing for patients themselves but also for their caregivers. Because the circadian rhythm is regulated by the biological clock, melatonin or light might be an effective intervention. Melatonin is a hormone secreted by the pineal gland in response to darkness. Its secretion is controlled by the suprachiasmatic nucleus (SCN). Melatonin is metabolised from serotonin, which is derived from tryptophan (Brzezinski, 1997; Wu and Swaab, 2005). In humans, melatonin has several effects: it is involved in immunomodulation, hematopoiesis and antioxidative processes (Maestroni, 1993; Reiter et al., 2004). Also, oncostatic (Srinivasan et al., 2008) and analgesic properties (Caumo et al., 2007) have been attributed to it. However, melatonin's main effect is that it positively affects sleep onset via its synchronising effect on the SCN (Dawson and Encel, 1993;Shochat et al., 1998).

The aim of this review is to study the effect of melatonin treatment on circadian rhythm disturbances in dementia. In the discussion we elaborate on the possible implications of the results for patients with delirium. Evidence exists in support of the hypothesis that sundowning in patients with dementia and the alterations in the sleep/wake cycle, seen in patients with delirium both originate in circadian rhythm disturbances.

METHODS

Search strategy

We conducted a systematic search of the literature to identify papers on melatonin treatment in dementia. A computerised search was performed for the period 1985 to April 2009 using PubMed, Embase, CINAHL and the Cochrane Database of Systematic Reviews (CDSR). Citations of relevant papers were examined for further references. No language restrictions were made. In addition to the medical subjects headings (MeSH terms), we used text words (title/abstract). The following strategy was applied:

(1) melatonin [MeSH] OR melatonin [tiab]

(2) dementia [tiab] OR delirium, dementia, amnestic cognitive disorder [MeSH] OR central nervous system disease [MeSH]

(3) 1 AND 2.

Selection procedure

Inclusion criteria were original research, treatment with melatonin and patients with dementia. We included all prospective studies. Based on the titles and abstracts of the publications we excluded commentaries, guidelines, case-reports and reviews. We excluded studies in which another intervention was given along with melatonin and/or in which the results were not discernable. In case of double publication we used the latest publication with the largest number of included patients. In cases in which we could not find the original paper in a literature database, we contacted one of the authors.

Data extraction

We scored any outcome related to sundowning/agitated behaviour, sleep quality or daytime functioning. All data were independently abstracted by three investigators (AJ, BM and JK) in terms of study characteristics (study population, living conditions, age, sample size, study design, treatment, study

duration) and results (sundowning/agitated behaviour, sleep quality and daytime functioning). Disagreements in the abstracting of data were solved by discussion. If no consensus could be reached, the final decision was made by a fourth reviewer (SR).

RESULTS

The combination of search terms yielded 912 hits in PubMed. Other databases did not add any additional relevant papers. We screened the titles and read the abstracts of all relevant papers (see Figure 1 for detailed selection procedure). We found 13 papers on melatonin treatment in dementia. We excluded four studies. Two were excluded because it was impossible to distinguish the effect of melatonin from that of bright light (Dowling et al., 2008; Haffmans et al., 2001), one because the investigators did not compute separate results for cognitively and non-cognitively impaired patients (Riemersma-van der Lek et al., 2008), and one because we were not able to retrieve the original paper (Mishima et al., 2000). Nine studies remained for final analysis.

[FIGURE 1]

An overview of these nine studies is presented in Table 1. Four of the nine studies were RCTs. All of the RCTs compared the effect of melatonin to placebo. In one study a high and a low dose of melatonin were compared as well. The remaining five studies were case series. In the RCTs the treatment duration was between 10 days and 8 weeks, in the case series 3 weeks to 35 months. In the RCTs a total of 243 patients were included, in the case series a total of 87 patients. The mean age of the patients varied in the RCTs from 77 to 84 years and in the case-series from 72 to 85 years.

[TABLE 1]

Sundowning/agitated behaviour was assessed in eight studies. It was measured by clinical observation, actigraph, bedtime or by four different assessment scales. Two RCTs found a significant improvement of sundowning/agitated behaviour in the melatonin treatment group compared to the placebo treatment group (Asayama et al., 2003; Singer et al., 2003). One RCT did not find significant improvement (Gehrman et al., 2009), and one did not measure sundowning/agitated behaviour (Serfaty et al., 2002). All five case series studies found an improvement. In three studies that assessed sundowning/agitated behaviour by clinical observation, the syndrome disappeared in 86% (Brusco et al., 1998), 57% (Mahlberg et al., 2004) and 100% (Cardinali et al., 2002) of the cases.

Eight of the nine studies assessed sleep quality. Sleep quality was measured by structured interviews, sleep diaries, actigraph or by two different assessment scales. Noticeable is that actigraph was used in the four RCT studies, three of which did not yield a positive result (Gehrman et al., 2009; Serfaty et al., 2002; Singer et al., 2003). One RCT found a significant improvement in the sleep diary data (Singer et al., 2003). Of the five case-series studies, one found an improvement on the actigraph (Mahlberg et al., 2004), and two found significant improvement using assessment scales (Brusco et al., 1998; Cardinali et al., 2002).

Four of the nine studies assessed daytime functioning. Daytime functioning was measured by structured interviews, sleeplogs, an assessment scale and actigraph. One RCT found an improvement in daytime functioning using actigraph measurement (Asayama et al., 2003). Three case series studies did not find improvement.

DISCUSSION

This systematic review, which includes four RCTs and five case series, considering a total of 330 patients with dementia, shows variable results of melatonin treatment on three outcome measures that indicate circadian rhythm disturbances. The main positive outcome is the result on sundowning/agitated behaviour. An improvement was found in two of the four RCTs and in all case series. An improvement in sleep quality was found in two of the four RCTs and in three of the four case series. One RCT reported improvement in daytime functioning.

This review carries some limitations. First, we found four randomised trials and five case series. The level of evidence provided by the latter studies is usually less than the evidence resulting from the RCTs. Since the studies with an observational design found a larger effect of melatonin on circadian rhythm disturbances

compared to the RCTs this might be an indicator of overestimation of the true effect. Second, several aspects make an interpretation of the results difficult and the total effect hard to estimate. A variety of assessment scales were used in the different studies. The studies included patients living under different conditions, some at home, others admitted to a hospital. Also, various dosages of melatonin were given, treatment durations differed widely and sample sizes were relatively low. Additionally, not all papers gave point estimates or effect sizes. Some studies gave p-values or the number of patients that improved.

We excluded four studies for various reasons. Three of these focussed on light treatment with or without melatonin supplementation. The largest of these (Riemersma-van der Lek et al., 2008) also contained patients without dementia, namely 8% of the 189 included patients. It had a study arm with melatonin treatment only (n=46). The effect of melatonin on sleep was positive (increased sleep duration by 27min and shorter sleep onset latency by 8.2min). Had this RCT been included then it would have had a positive influence on the effects of melatonin on sleep quality.

We hypothesise that the finding of the effectiveness of melatonin on sundowning/agitated behaviour in dementia might also be expected in patients with delirium. Delirium is a syndrome that occurs due to a somatic disease and is frequently seen in elder patients who are admitted to hospital. Incidence varies between 22 and 83% depending on methods and population studied (Ely et al., 2001; Francis et al., 1990). Symptoms include, amongst others, a disturbance of consciousness, a change in cognition or perceptual disturbance and it has a fluctuating course. Dementia shares some important symptoms with delirium and is strongly related to it. Dementia is the main risk factor for delirium, and patients with delirium are prone to develop dementia (Fong et al., 2009; Francis and Kapoor, 1992; Rockwood et al., 1999). Symptoms observed in each of these syndromes show a large overlap. For instance, like in delirium, sundowning is associated with increased daytime sleep and disrupted night sleep (Hess, 1997), and this has been attributed to a disruption of the circadian rhythm (Okawa et al., 1991; Riemersma-van der Lek et al., 2008). The circadian rhythm disturbances in dementia may originate from a problem in translating external light/dark signal to the SCN and/or pineal gland due to degeneration of the signaling pathways and/or the SCN and/or the pineal gland (Mahlberg et al., 2004;Wu and Swaab, 2007). Patients with Alzheimer's disease may show pronounced degenerative changes in the SCN (Stopa et al., 1999). A substantial inter-individual variability in the severity of circadian disturbance in Alzheimer's disease patients exists but circadian disturbances are associated with greater severity of the dementia (Van Someren et al., 1996) (see table 2 and 3). In delirium, this translating problem could be due to chemical or inflammatory processes that cause a disruption of the signaling pathways and/or the function of the SCN and/or the pineal gland. Both conditions would be expected to result in a circadian rhythm disorder.

[TABLE 2, 3]

Melatonin has not specifically been investigated in clinical trials for its effectiveness on delirium. We presume that the effect of melatonin on symptoms of dementia that indicate circadian rhythm disturbances as sundowning/agitated behaviour, could be used as a model to predict the effects of melatonin on similar symptoms in delirium. There are indeed some indications that low-melatonin concentrations are associated with delirium. Low-melatonin concentrations have been found in diverse conditions such as surgical operation, and sleep deprivation in patients in intensive care units, suggesting a relationship between delirium and insomnia, (ICUs) (Haimov et al., 1995; Olofsson et al., 2004; Shigeta et al., 2001). Low-tryptophan levels have been associated with delirium in post-operative patients (Robinson et al., 2008; van der Mast et al., 2000). These results suggest a relationship between abnormal melatonin secretion and postoperative delirium. Furthermore, endogenous melatonin production decreases with age and higher age is a major risk factor for delirium (Magri et al., 2004; Ohashi et al., 1997; Sack et al., 1986). Although different authors have hypothesised that exogenous administration of melatonin may reduce the symptoms of delirium (Lewis and Barnett, 2004; Uchida et al., 1999), so far, clinical evidence linking melatonin treatment with a positive effect on delirium in elder patients is limited to one case report (Hanania and Kitain, 2002).

Future clinical research should clarify whether melatonin has an effect on the circadian rhythm disturbances that are seen in delirium and whether administration of melatonin is effective in the treatment of delirium. In our own clinical practice, we have several positive observations and experiences with melatonin treatment in patients with delirium with circadian rhythm disturbances who did not respond well

to standard therapy with anti-psychotics and/or benzodiazepines alone (not published). The question arises as to the dosage of melatonin that would be expected to be effective in treating a circadian rhythm disturbance. It seems plausible that a higher dose is not necessarily more effective. It is desirable to have high-plasma levels of melatonin at nighttime and low-plasma levels during the daytime as this approaches the normal physiological condition. Data are inconclusive. In one study 2.5**MG OF MELATONIN YIELDED SUPRAP**hysiological levels at daytime (Singer et al., 2003), but in another study 6**MG OF MELATONIN YIELDED NORMAL, PHYSIOL**ogical daytime plasma levels (Mishima et al., 2000). Future research should clarify the dose of melatonin to be recommended. None of the studies in this review mentioned side effects or adverse events. This makes it reasonable to assume that melatonin is safe and well-tolerated in the dosage range studied. It might contribute to a faster recuperation of delirium with few side effects.

Conflict of interest

None known.

CONCLUSION

In summary, the results of the case series in our review suggest that melatonin is effective on sundowning in patients with dementia. The results of the RCTs are inconclusive. Since there are several arguments that sundowning in patients with dementia and the alterations in the sleep/wake cycle in patients with delirium have a common background, namely a disturbance of the circadian rhythm, we think it is likely that melatonin will be effective in the treatment of delirium.

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[TABLES AND FIGURES]

Melatonin effect in dementia and delirium

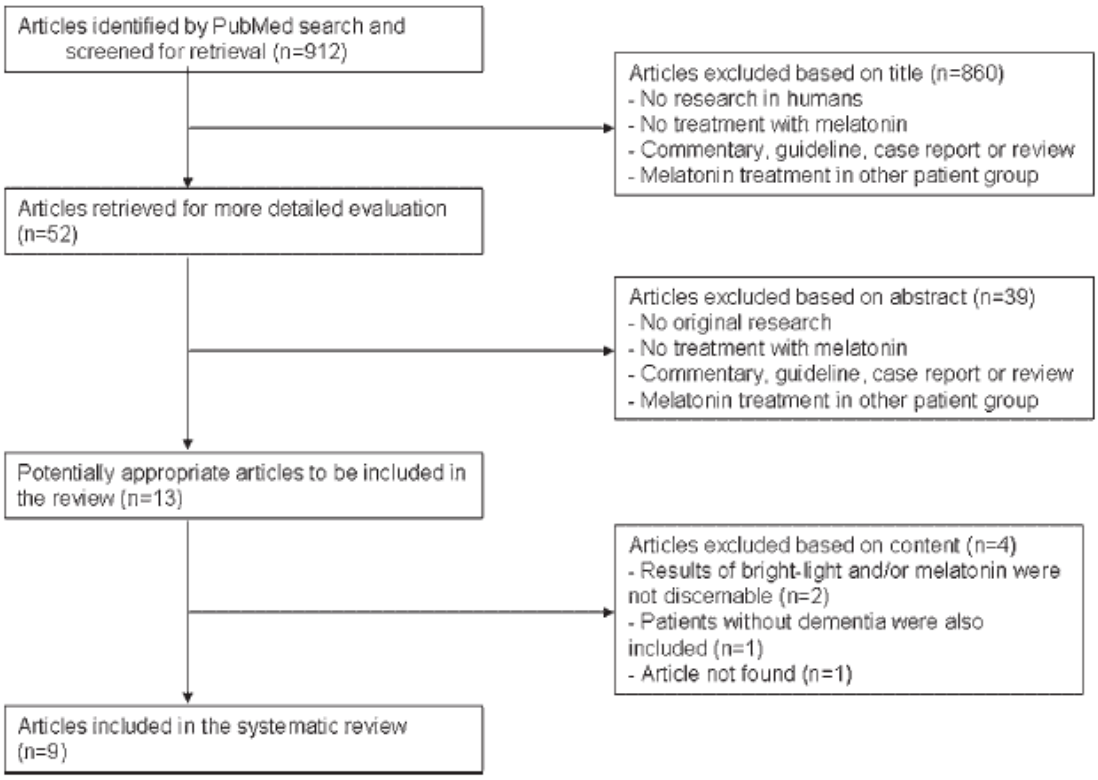

Figure 1 Flow diagram of search strategy and study selection

Table 1 Included studies: baseline characteristics, study design and treatment

Author	Study design	Study population	Living conditions	Mean age (SD/range)	Sample size	Melatonin dosage	Treatment duration
Singer (2003)	RCT, three arms	Alzheimer's dementia with sleep disturbance	At home	77.4 (8.9)	157	2.5 mg sr 10 mg	8 weeks
Gehrman (2009)	RCT	Alzheimer's dementia	Nursinghome	82.9 (7.0)	41	8.5 mg and 1.5 mg sr	10 days
Serfaty (2002)	RCT, double blind, crossover	Dementia with sleep problems	At home or nursinghome	84.2 (7.6)	25	6 mg sr	2 × 2 weeks
Asayama (2003)	RCT, double blind	Alzheimer's dementia	Geriatric ward of hospital	79.2 (6,4)	20	3 mg	4 weeks
Cardinali (2002)	Case serie	Alzheimer's dementia with sleep disturbance	No data	73.9	45	6–9 mg	4 months
Busco (1998)	Case serie	Alzheimer's dementia	No data	72 (9)	14	9 mg	22–35 months
Brusco (1999)	Case serie	Dementia with sleep disorder	No data	74 (12)	10	3 mg	3 weeks
Cohen-Mansfield (2000)	Case serie	Alzheimer's dementia	Nursinghome	85 (79–92)	11	3 mg	3 weeks
Mahlberg (2004)	Case serie	Alzheimer's dementia with day/night rhythm disturbance or sundowning	At home	75.6 (10.6)	7	3 mg	3 weeks

RCT: Randomised Controlled Trial. sr = slow release. mg = milligram.

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Table 2 Included studies: results of the effect of melatonin on circadian rhythm disturbances expressed in effect on sundowning/agitated behaviour, sleep quality and daytime functioning

	1) sundowning/agitated behaviour			2) sleep quality			3) daytime functioning		
Study	Tool	Outcome improved?*	Specification	Tool	Outcome improved?*	Specification	Tool	Outcome improved?*	Specification
Singer (2003)	NPI	Yes	In 2.5 mg arm ($p = .05$)	Actigraph daily sleep diary	No Yes	Not given In 2,5 mg arm($p = 0.03$)	No data	No data	No data
Gehrman (2009)	ABRS CMAI	No No	Not given Not given	Actigraph	No	Not given	No data	No data	No data
Serfaty (2002)	No data	No data	No data	Actigraph VAS	No No data	Not given No data	No data	No data	No data
Asayama (2003)	ADAS non-cog	Yes	($p = 0.002$)	Actigraph	Yes	No data	Actigraph	Yes	Not given
Cardinali (2002)	Clinical observation	Yes	Disappeared in all patients	SSPQ	Yes	($p < 0.0001$)	No data	No data	No data
Brusco (1998)	Clinical observation	Yes	No longer detectable in 12 out of 14 patients	VAS	Yes	($p = 0.0001$)	No data	No data	No data
Brusco (1999)	Coefficient of variation of bedtime	Yes	($p < 0.003$)	Structured interviews and sleep logs	No	Not given	Structured interviews and sleeplog	No	Not given
Cohen-Mansfield (2000)	CMAI	Yes	Not given	No data	No data	No data	CMAI	No	Not given
Mahlberg (2004)	Clinical observation Actigraph	Yes No data	Disappeared in 4 out of 7 patients No data	Actigraph	Yes	Not given	Actigraph	No	Not given

NPI: Neuropsychiatric Inventory. ABRS: Agitated Behaviour Rating Scale. CMAI: Cohen-Mansfield Agitation Inventory. ADAS non-cog: Alzheimer's Disease Assessment scale non-cognitive section. VAS: Visual Analog Scale. SSPQ: Standard Sleep Pattern Questionnaire.

*Based on the statement of the authors. This does not imply that it is also statistically significant.

If a p-value is not given, than the original study did not give a p-value.

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Table 3 Description of assessment scales used in included studies

Abbreviation	Name	Used in study	Description
CMAI	Cohen-Mansfield agitation inventory	Cohen-Mansfield (2000) Gehrman (2009)	A 29-item caregiver rating questionnaire for the assessment of agitation in elderly persons (Cohen-Mansfield et al., 1989)
NPI-Q	Neuropsychiatric inventory questionnaire	Singer (2003)	Assessment of behaviours commonly observed in patients with dementia. It assesses the severity of the symptom in the patient and the distress the symptom causes in the caregiver (Cummings et al., 1994)
ADAS-non cog	Alzheimer's disease assessment scale	Asayama (2003)	Designed to evaluate the severity of non-cognitive behavioural dysfunctions characteristic of persons with Alzheimer's disease (Rosen et al., 1984).
SSPQ	Standard Sleep pattern questionnaires	Cardinali (2002)	Standard sleep pattern questionnaires.
VAS	Visual analog scale	Brusco (1998)	A 100 millimeter continuous scale originally developed for pain measurement (Huskisson, 1974), but it also is used to measure alertness after sleep, attitudes towards the environment, quality of life and anxiety (Wewers and Lowe, 1990).
ABRS	Agitated behaviour rating scale	Gehrman (2009)	Consists of one domain with 14 items that range from attention span to self-abuse. Developed to assess the nature and extent of agitation during the acute phase of recovery from acquired brain injury (Bliwise, 1993).