Studies on circadian rhythm disturbances and melatonin in delirium

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Chapter 5
Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia. Are there implications for delirium? A systematic review
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Abstract

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 articles 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 articles, 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.
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Introduction
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 behavioral disturbances associated with the afternoon and/or evening hours (1-3). The American Sleep Disorder Association however, considers sundowning to include ‘the sleep disturbance that is characterized by nocturnal wandering and confusion’ (4). 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 (1, 5). The reported incidence ranges from 13% to 66% (6, 7) 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 (8).
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 (9, 10). In humans, melatonin has several effects: it is involved in immunomodulation, hematopoiesis, and antioxidative processes (11, 12). Also, oncostatic (13) and analgesic properties (14) have been attributed to it. However, melatonin’s main effect is that it positively affects sleep onset via its synchronising effect on the SCN (15, 16).
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 articles 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 articles 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).
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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 article 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 articles. We screened the titles and read the abstracts of all relevant articles (see Figure 1 for detailed selection procedure). We found thirteen articles 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 (17, 18), one because the investigators did not compute separate results for cognitively and non-cognitively impaired patients (19), and one because we were not able to retrieve the original article (20). Nine studies remained for final analysis.

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.
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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 (21, 22). One RCT did not find significant improvement (23), and one did not measure sundowning/agitated behaviour (24). All five case series studies found an improvement. In the three studies that assessed sundowning/agitated behaviour by clinical observation, the syndrome disappeared in 86% (25), 57% (26) and 100% (3) 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 (21, 23, 24). One RCT found a significant improvement in the sleep diary data (21). Of the five case-series studies, one found an improvement on the actigraph (26), and two found significant improvement using assessment scales (3, 25).

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 (22). Three case series studies did not find improvement.
## Table 1: Included studies: baseline characteristics, study design and treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Study population</th>
<th>Living conditions</th>
<th>Mean age (SD/range)</th>
<th>Sample size</th>
<th>Melatonin dosage</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singer (2003)</td>
<td>RCT, three arms</td>
<td>Alzheimer’s dementia with sleep disturbance</td>
<td>At home</td>
<td>77.4 (8.9)</td>
<td>157</td>
<td>2.5 mg sr 10mg</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Gehrman (2009)</td>
<td>RCT</td>
<td>Alzheimer’s dementia</td>
<td>Nursinghome</td>
<td>82.9 (7.0)</td>
<td>41</td>
<td>8.5 mg and 1.5 mg sr</td>
<td>10 days</td>
</tr>
<tr>
<td>Serfaty (2002)</td>
<td>RCT, double blind, crossover</td>
<td>Dementia with sleep problems</td>
<td>At home or nursinghome</td>
<td>84.2 (7.6)</td>
<td>25</td>
<td>6 mg sr</td>
<td>2 * 2 weeks</td>
</tr>
<tr>
<td>Asayama (2003)</td>
<td>RCT, double blind</td>
<td>Alzheimer’s dementia</td>
<td>Geriatric ward of hospital</td>
<td>79.2 (6.4)</td>
<td>20</td>
<td>3 mg</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Cardinali (2002)</td>
<td>Case serie</td>
<td>Alzheimer’s dementia with sleep disturbance</td>
<td>No data</td>
<td>73.9</td>
<td>45</td>
<td>6-9 mg</td>
<td>4 months</td>
</tr>
<tr>
<td>Busco (1998)</td>
<td>Case serie</td>
<td>Alzheimer’s dementia</td>
<td>No data</td>
<td>72 (9)</td>
<td>14</td>
<td>9 mg</td>
<td>22 to 35 months</td>
</tr>
<tr>
<td>Brusco (1999)</td>
<td>Case serie</td>
<td>Dementia with sleep disorder</td>
<td>No data</td>
<td>74 (12)</td>
<td>10</td>
<td>3 mg</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Mahlberg (2004)</td>
<td>Case serie</td>
<td>Alzheimer’s dementia with day/night rhythm disturbance or sundowning</td>
<td>At home</td>
<td>75.6 (10.6)</td>
<td>7</td>
<td>3 mg</td>
<td>3 weeks</td>
</tr>
</tbody>
</table>

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

### 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.
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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

<table>
<thead>
<tr>
<th>Study</th>
<th>Tool</th>
<th>NPI</th>
<th>Yes</th>
<th>In 2.5 mg arm (p=.05)</th>
<th>Actigraph daily sleep diary</th>
<th>No</th>
<th>Not given in 2.5 mg arm (p&lt;0.03)</th>
<th>No data</th>
<th>No data</th>
<th>No data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singer (2003)</td>
<td>NPI</td>
<td>Yes</td>
<td>Yes</td>
<td>No data</td>
<td>Actigraph daily sleep diary</td>
<td>No</td>
<td>Not given in 2.5 mg arm (p&lt;0.03)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Gehman (2009)</td>
<td>ABRS</td>
<td>No</td>
<td>No</td>
<td>Not given</td>
<td>Actigraph daily sleep diary</td>
<td>No</td>
<td>Not given in 2.5 mg arm (p&lt;0.03)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Serfaty (2002)</td>
<td>No data</td>
<td>No</td>
<td>No</td>
<td>Not given</td>
<td>Actigraph daily sleep diary</td>
<td>No</td>
<td>Not given in 2.5 mg arm (p&lt;0.03)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Asayama (2003)</td>
<td>ADAS non-cog</td>
<td>Yes</td>
<td>(&lt;0.002)</td>
<td>Actigraph daily sleep diary</td>
<td>No</td>
<td>Not given in 2.5 mg arm (p&lt;0.03)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Cardinali (2002)</td>
<td>Clinical observation</td>
<td>Yes</td>
<td>Disappeared in all patients</td>
<td>SSPQ</td>
<td>Yes</td>
<td>(&lt;0.0001)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Brusco (1998)</td>
<td>Clinical observation</td>
<td>Yes</td>
<td>No longer detectable in 12 out of 14 patients</td>
<td>VAS</td>
<td>Yes</td>
<td>(&lt;0.0001)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Brusco (1999)</td>
<td>Coefficient of variation of bedtime</td>
<td>Yes</td>
<td>(&lt;0.003)</td>
<td>Structured interviews and sleeplogs</td>
<td>No</td>
<td>Not given in 2.5 mg arm (p&lt;0.03)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Cohen-Mansfield (2000)</td>
<td>CMAI</td>
<td>Yes</td>
<td>Not given</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>CMAI</td>
<td>No</td>
<td>Not given</td>
<td></td>
</tr>
<tr>
<td>Mahilberg (2004)</td>
<td>Clinical observation</td>
<td>Yes</td>
<td>Disappeared in 4 out of 7 patients</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>Actigraph</td>
<td>No</td>
<td>Not given</td>
<td></td>
</tr>
</tbody>
</table>


* 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.

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 articles 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 focused on light treatment with or without melatonin supplementation. The largest of these (19) 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 27 minutes and shorter sleep onset latency by 8.2 minutes). Had this RCT been included than it would have had a positive influence on the effects of melatonin on sleep quality.

### Table 3: Description of assessment scales used in included studies

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Name</th>
<th>Used in study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPI-Q</td>
<td>Neuropsychiatric Inventory Questionnaire</td>
<td>Singer (2003)</td>
<td>Assessment of behaviors 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 (49).</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analog Scale</td>
<td>Brusco (1998)</td>
<td>A 100-millimeter continuous scale originally developed for pain measurement (51), but it also is used to measure alertness after sleep, attitudes toward the environment, quality of life and anxiety (52).</td>
</tr>
<tr>
<td>ABRS</td>
<td>Agitated Behaviour Rating Scale</td>
<td>Gehrman (2009)</td>
<td>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(53).</td>
</tr>
</tbody>
</table>
We hypothesize 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 elderly patients who are admitted to hospital. Incidence varies between 22 and 83% depending on methods and population studied (27, 28). 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 (29-31). 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 (32), and this has been attributed to a disruption of the circadian rhythm (19, 33). 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 (26, 34). Patients with Alzheimer’s disease may show pronounced degenerative changes in the SCN (35). 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 (36). 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.

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 insomina, (ICUs) (37-39). Low tryptophan levels have been associated with delirium in postoperative patients (40, 41). 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 (42-44). Although different authors have hypothesised that exogenous administration of melatonin may reduce the symptoms of delirium (45, 46), so far, clinical evidence linking melatonin treatment with a positive effect on delirium in elderly patients is limited to one case report (47).

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 supraphysiological levels at daytime (21), but in another study 6 mg of melatonin yielded normal, physiological daytime plasma levels (20). 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.

**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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