Studies on circadian rhythm disturbances and melatonin in delirium

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Introduction
The main aim of the research in this thesis was to explore the role of melatonin as a prophylactic treatment in order to influence the incidence and/or severity of delirium. Our randomized controlled trial (RCT), in which we assessed the effect of melatonin on the incidence of delirium in elderly patients acutely admitted due to hip fracture, showed that melatonin had no effect on the incidence of delirium (Chapter 6). However, we observed that compared with patients receiving placebo treatment, significantly fewer patients on melatonin experienced delirium episodes of longer than two days. In this chapter, we will discuss our results in greater perspective. Our second aim of this thesis was to investigated aspects of the role of melatonin in the pathophysiology of delirium. We did not find any new insights on the role of tryptophan in delirium and the role of polymorphisms in the MTNR1B gene (Chapter 1 and 2) with regards to delirium. Next, we explored the usefulness of electronic measurement devices in diagnosing and subtyping delirium. This turned out to be a promising method and will also be discussed (Chapter 3). Furthermore, directions for future research are given.

Position of melatonin compared to other pharmacological preventive treatment regimens
As the treatment options for delirium symptoms are not very effective once delirium is present (1-3), the pharmacological prevention of delirium may be more beneficial. However, only a few studies have investigated the preventive properties of medical treatment, and their results are varied. The most studied agents are cholinesterase inhibitors, antipsychotics and melatonin. There are five RCTs that have compared the use of cholinesterase inhibitors with placebo or aspirin. Three studies did not find any effect of cholinesterase inhibitors on the incidence of delirium (total n= 216) (4-6), while two studies showed that they decreased the incidence of delirium (total n= 263) (7, 8). Additionally, one RCT was prematurely terminated as rivastigmine was suggested to increase mortality (9). As such, at present, cholinesterase inhibitors cannot be recommended for prevention. Three non-ICU studies have investigated the preventive effect of antipsychotics, two of which investigated the preventive effect of haloperidol in hip fracture and gastrointestinal surgery patients (10, 11). The first study (n=430) did not find any difference in the incidence of delirium, but found positive effects on the duration and severity of delirium. The second study (n=80) found a lower incidence of delirium (10 vs 32%). One study investigated the preventive effect of olanzapine in elective knee or hip replacement patients (n=400) and found a reduction in the incidence of delirium (14 vs 40%). There are two ICU studies that have been reported. One study compared haloperidol versus ziprasidone and placebo in mechanically ventilated medical and surgical patients (n=101) and found that there was no difference in the incidence of delirium between the groups (12). The other study compared the preventive effect of haloperidol versus placebo in noncardiac surgery ICU patients (n=457) and found a lower incidence of delirium in the
intervention group (15 vs 23%) (13). In summary, there is some evidence supporting the prophylactic use of antipsychotics. However, in clinical practice, many doctors refrain from this in accordance with the NICE guideline and the negative reports that antipsychotic treatment can lead to serious cerebrovascular side effects and higher mortality, especially in patients with dementia (14, 15).

The results of our RCT involving melatonin seem to indicate that in vulnerable elderly patients with hip fracture, a group that is at high risk for delirium, melatonin is not effective in preventing post-operative delirium. However, recently, two RCTs comparing melatonin versus placebo were published (16, 17). These two studies showed a substantial decrease in the incidence of delirium in the melatonin groups, specifically 33% versus 9% (elective surgery patients), and 31% versus 12% (medical patients). The positive effects melatonin observed in these studies suggest a position for melatonin in the prevention of delirium as it is effective, and no side effects have been reported.

**Aspects of current and future studies on melatonin**

Apart from advanced age, cognitive impairment is one of the major risk factors for the development of delirium. Therefore, trials on delirium should include a population that accurately reflects this real-life population. In trials, the representation of patients with cognitive impairment is important because in these patients, the underlying pathophysiological mechanisms, such as imbalances in various neurotransmitter systems or the effects of inflammation on the brain via cytokines, may differ from that of patients without signs of neurodegeneration. These differences may also cause variations in the effects and side effects of medications (18, 19). However, we showed that only 14% of patients who were included in delirium trials were patients with pre-existing cognitive impairment and/or dementia (Chapter 5). Furthermore, one of the trials on melatonin excluded patients with cognitive impairment (16). As this hampers the external validity, this implies that the results of many medical trials for treating delirium cannot be applied to patients with cognitive impairment. As such, it is possible that melatonin has a different effect in patients with cognitive impairment.

The dosage of melatonin used in the literature varies from 0.1 mg to 50 mg/kg (20, 21). We used 3 mg of melatonin as this is a frequently used dosage in studies with melatonin, including clinical trials (22-24). In the other RCTs, 0.5 and 8 mg melatonin were used. The question arises as to the dosage of melatonin that would be most effective. Information on the effects of melatonin supplementation with regard to required dosages and supplementation duration are however, scarce (25). It is plausible that a higher dose is not necessarily more effective, as melatonin levels normally fluctuate. It is most likely desirable to have high plasma levels of melatonin at night, but low plasma levels during the day as this approaches the normal physiological condition. Three studies (20, 26, 27) looked at the duration melatonin levels remained above a set threshold and of these, two studies (20, 27) found that melatonin levels in the high-dose group (respectively 4.0 mg and 3.0 mg) were maintained above 50 pg/ml for more than 10 hours, which was
significantly longer than in the low-dose groups. Thus, the dosage in our study might have influenced the physiological concentrations during the day, and thus the effect. This is also because a loss of response to melatonin treatment has previously been found to be associated with sustained high melatonin levels (28). Furthermore, melatonin levels are also subject to individually altered pharmacokinetics and dynamics. It was shown that the increment in serum melatonin levels induced by a low oral dose was greater and more variable among older people compared to younger persons (29). This causes intra-individual variability, higher maximum concentrations and risk of prolonged, elevated, endogenous melatonin levels after exogenous melatonin administration in older adults, and it might also cause a decrease in the desired effect. It may be that for each person, the serum levels should be determined after supplementation in order to tailor the best individual dosage.

Studies on physiological melatonin levels in healthy elderly persons have indicated that lower nighttime peak levels are present in older persons compared to younger persons (30, 31). The consequence of this finding is largely unknown, but research suggests that this decrease in melatonin levels with age results in decreased sleep efficiency and in an increased incidence of circadian rhythm disturbance (32). Additionally, melatonin levels have been reported to be lower in patients with dementia, compared to controls (33, 34). It would be interesting to prospectively investigate whether persons with lower nighttime melatonin levels are indeed prone to developing delirium. This could be studied in nursing home patients.

Unfortunately, very few studies have investigated melatonin levels and its course in delirious patients. Some studies have compared the postoperative levels of melatonin in delirious and non-delirious patients and have found an association between delirium and a disturbance in melatonin metabolism. A few studies also showed melatonin trajectories or patterns (35-37). The low number of studies could be due to practical obstacles. For example, samples need to be obtained at night when personnel are often not readily available, and samples need to be taken from patients who are already in distress due to delirium. Samples can be obtained from saliva, blood or urine, of which urine samples may be the most feasible, especially for peri-operative patients who already have an indwelling catheter. Preferably, future studies that investigate melatonin levels in delirious and non-delirious elderly (medical and surgical) patients should measure melatonin level trajectories in different settings in the hospital.

Electronic movement measurement devices can capture rest-activity patterns and can possibly assist in diagnosing delirium and determining delirium subtypes. Thus, the use of these devices, in combination with melatonin level measurements (in blood, urine or saliva), offers new challenges for diagnostic and pathophysiological studies. Some studies have presented promising results, showing that it takes delirious patients longer to fall asleep and that they sleep for shorter intervals and get less sleep during the night as a whole. Additionally, they experience more transitions between rest and activity (Chapter 3). Studies have also shown that various rest-activity parameters are different in delirious
versus non-delirious patients and between patients with short-term delirium and those with sustained delirium (38) in addition to showing that these devices are helpful in determining delirium subtypes (39-41). Although a promising method, its clinical application requires further development. Practical problems that are encountered include the extent to which the actometer is tolerated by the patients. Studies have indicate that they are well tolerated, but we experienced some problems with actometers that remained on the side table after showering or were almost lost with the laundry. Recently, a new device that is able to measure 24 h motor patterns, the Everon™ system (Earlsense LTD, Israel), was developed (42). A key feature of the Everon system is that it contains a non-contact sensitive mechanical sensor that is placed under the patient's mattress. In delirious patients, this type of device may be advisable because of the absence of any extra burden for the delirious patient.

Thus far, we have only investigated the effect melatonin in delirium. Another aspect that could be interesting for future research is the possible synergistic effect of adding light to melatonin treatment. Apart from melatonin, the circadian timing system is sensitive to environmental light (43) and may not function optimally in the absence of this synchronizing effect. For instance, in patients with dementia, the combination of melatonin with light attenuated agitated behavior (44). Additionally, bright light therapy as part of a multicomponent management program has been shown to improve sleep and functional outcomes in delirious older hospitalized adults (45). It would be interesting to investigate whether melatonin in combination with light would further improve patient outcome.

The non-chronobiologic properties of melatonin

The main effect of melatonin is that it positively affects sleep onset by synchronizing the biological clock (46-48). So far, the focus on the role of melatonin in delirium has largely been on these chronobiological properties. The positive findings on the incidence of delirium in the two other melatonin studies can possibly be explained by this property of melatonin. However, in humans, melatonin has also several other effects, including immunomodulation and hematopoietic processes (49, 50), and has oncostatic, analgesic, anxiolytic and antioxidative properties (50-54). Due to the efficacy of melatonin in preventing oxidative damage in both cultured neuronal cells and in the brains of animals treated with various neurotoxic agents, it has been suggested that melatonin has a potential therapeutic value as a neuroprotective drug in the treatment of several diseases, including Alzheimer's disease and Parkinson's disease (53). Given the pathophysiological similarities between delirium and other diseases, such as dementia, the antioxidative properties of melatonin may also play a direct role in the pathophysiology of delirium. Furthermore, delirium is thought to be caused primarily by central nervous system inflammation and dopaminergic dysfunction. Melatonin is one of the many anti-inflammatory molecules that are produced at the sites of lesions during the recovery phase of an inflammatory response and is involved in the modulation of central
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dopaminergic functions (53, 55-58). A possible explanation of the positive effects of melatonin on the duration of delirium in our study could be that these antioxidative and anti-inflammatory properties and the modulation of dopaminergic functions require time to become effective after the supplementation of melatonin and are thus effective after a critical period of two days. Future pathophysiological research should be aimed at better understanding these functions of melatonin.

Difficulties in delirium research and their consequences
In our RCT, 60% of the included patients had known pre-existing cognitive impairments. Because these patients are unable to consent for participation to a trial themselves, additional arrangements need to be taken. A formal legal representative should be approached to obtain informed consent. Furthermore, this affects the design of the trial, because in the Netherlands, these patients are only allowed to participate in a trial using the 'no, unless' principle. This principle states that research in this group is possible, if (1) the investigation can benefit the subjects involved, (2) this research can only be performed with the inclusion of subjects from the category to which the subject belongs, and (3) the risk is negligible and the objections are minimal. Both approaching a legal representative and arranging these legal issues with the medical authorities require extra effort on the part of the research group and may present possible hurdles along the way. These legal issues could easily prevent researchers from including patients with dementia and/or delirium. We have tried to determine why patients with cognitive impairment were not included in RCTs/CCTs on medical intervention in delirium (Chapter 5). We found that the motivations of the researchers for excluding patients with cognitive impairment varied and were frequently related to dementia. In short, facing a more extensive contact with the medical ethical board before obtaining permission to begin the study, needing more time to approach a legal representative for informed consent, and dealing with the aspects of dementia while judging the presence or severity of delirium demand extraordinary effort from the research team and are most likely the reasons that these patients are frequently excluded.

Another practical, but no less important problem, is the lack of funding for pharmacological delirium research. Charity foundations and wealthy patient representative associations, for instance the Dutch Cancer Society and the Kidney Foundation, are lacking for this patient group. Our RCT was funded by an unrestricted grant from the Dutch National Program of Innovative Care (NPO) for vulnerable older persons. This is a program from ZonMw, a Dutch institute that funds health research and stimulates the use of knowledge to help improve health and healthcare in the Netherlands. To maintain independence, these types of funds are preferable to pharmaceutically initiated and/or funded trials. However, at the same time, these types of funding sources are scarce, and depend worldwide on (semi) governmental organizations and thus, also on political will and economic opportunities. For instance, the NPO is not continued in its present form, and despite our current experience in this field and
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eagerness to move forward, funding is lacking. This is all the more surprising given that the number of patients who can be considered the ‘oldest old’ is steadily increasing, resulting in an greater prevalence of dementia and, thus, an increasing number of patients who will face delirium and its consequences in the near future (59). These consequences will result in an increased economic health care burden, as these patients will need to be institutionalized more often compared to their non-delirious hospital counterparts. Non-pharmacological delirium intervention programs, such as the Hospital Elder Life program, have already proved to be cost-effective (60, 61). In addition, seeing the large pharmacological effects of melatonin, research on the cost-effectiveness of this intervention would also be very interesting.

Conclusion
Approaching delirium from the perspective of the circadian rhythm provides new and challenging opportunities for pathophysiological and treatment studies. Within a short period of time, three RCTs showing positive effects of melatonin on delirium incidence and duration have been conducted. This implies a potential utility for melatonin as a prophylactic intervention. Future studies should focus on its pathophysiological basis, both non-chronobiological and chronobiological, and should determine which patients may benefit most and the appropriate dosage.
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