Studies on circadian rhythm disturbances and melatonin in delirium

de Jonghe, A.-M.

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Delirium
Delirium is the most frequently observed neuropsychiatric syndrome in acutely admitted elderly patients in hospitals. For the diagnosis of delirium, the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV are used (1). They are based on clinical observations, and indicate that delirium is present when the patient suffers from a disturbance of consciousness, a change in cognition or the development of a perceptual disturbance. It usually develops in a short period of time, has a tendency to fluctuate, and is caused by the direct physiological consequences of a general medical condition. Delirium is often precipitated by an acute infection, an operation, or an intensive care unit (ICU) stay, and it is associated with predisposing factors, such as old age, and the presence of premorbid conditions, such as dementia and genetic predisposition (2). The incidence of delirium varies depending on the assessment methods employed and the population studied. In a cohort of hip fracture patients studied by our group, the incidence was 51% (3). Once delirium is diagnosed, three clinical subtypes are discernable, specifically, hypo-, mixed-, and hyperactive delirium. This is important as the subtypes may require different treatment approaches, both medical and non-medical. For instance, according to the Dutch delirium guideline, patients with hypo active delirium are only treated with antipsychotics in case of frank psychotic experiences, while patients with hyperactive delirium receive antipsychotics more often. However, in practice, determining the subtypes can be challenging. Electronic movement measurement devices could prove to be useful because patients with delirium also exhibit disturbances in their circadian sleep wake rhythm, which is reflected in their 24 h motor activity behavior. As such, this type of device could be useful for diagnosing delirium, which is a diagnosis that is frequently missed. This is a problem because although delirium has generally been regarded as a transient disorder, it has become increasingly clear that these patients face substantially increased risks. Compared with patients who do not develop delirium, they may need to stay longer in the hospital or in critical care, have an increased incidence of dementia, more hospital-acquired complications, are more likely to be admitted to long-term care after hospital discharge, and are more likely to die (4, 5). Additionally, in patients with pre-existing cognitive impairment, a significant decline in cognitive abilities is observed after delirium and can affect self-maintenance and independent living (6).

Disruption of the sleep-wake cycle and the role of melatonin
In the newest edition of the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) from the American Psychiatric Association, the criteria for delirium have changed (7). Surprisingly, a disturbance of sleep-wake rhythm is not included in these new criteria, although there is growing clinical awareness and objective evidence that circadian rhythm disturbances are present across the course of a delirium episode. This occurs both in adults and elderly patients and presents as fragmented sleep during the night and sleepiness during the day (8-10). This observed disruption of the sleep wake cycle indicates a disturbance of the circadian rhythm. As such, although the disruption of the
sleep-wake cycle is not included in the formal diagnostic criteria for delirium, it is indeed a core feature of the condition. The circadian rhythm is endogenous and is dictated by the suprachiasmatic nucleus (SCN), the biological clock. The hormone melatonin, also called the sleep hormone, is secreted in response to darkness by the pineal gland in the brain. It can influence this endogenous process, and it regulates the cerebral biological clock via melatonin receptors, thus playing an important role in the regulation of the sleep-wake cycle (11). In turn, melatonin secretion is controlled by the SCN, and melatonin production is suppressed by light. During evening hours, serum melatonin levels start to rise and this continues until approximately 2 to 4 a.m., when it reaches its peak concentration. Thereafter, melatonin levels decline again until they reach their low daytime level (12).

Different authors have hypothesized that the exogenous administration of melatonin may reduce certain symptoms of delirium. This was based on the indirect evidence of the association between abnormal melatonin levels and delirium (13, 14) that was described in a case report (15). Abnormal melatonin concentrations have been shown to be present in conditions that are associated with delirium; healthy elderly persons have been shown to have decreased peaks of nocturnal melatonin concentrations compared to younger persons (16, 17). Also, in elderly persons with insomnia, serum melatonin concentrations were also found to be lower, with later nocturnal peak concentrations, compared to age-matched controls without insomnia (18). In ICU patients, the loss of circadian rhythm has also been associated with an abolition of the expected nocturnal rise of melatonin (19).

Furthermore, a disturbed circadian pattern of melatonin secretion has been observed in patients with sepsis (20). Additionally, there have been indications that melatonin treatment is effective for treating sleep-wake cycle disturbances in ICU patients and in patients with dementia (21-23). Moreover, it has been demonstrated that treatment with melatonin increases total sleeping time and reduced sleep latency in elderly patients (24), and enhances sleep time and night activity in patients with Alzheimer’s dementia (25, 26).

A disturbed circadian pattern of melatonin secretion has also been found in delirious patients, specifically, in ICU and post-operative patients with delirium (27, 28). In another study of medical patients, differences in urinary melatonin metabolite concentrations were found during delirium and after recovery from delirium (29). These results suggest an association between delirium and disturbed melatonin secretion patterns.

Several mechanisms could be responsible for this abnormal pattern of melatonin metabolism, for instance, a lack of tryptophan, the amino acid from which serotonin, the precursor of melatonin, is built, (30). Tryptophan has become a focus in delirium research because low levels of tryptophan have been reported in patients with delirium (31, 32). This led to the tryptophan depletion theory, which states that the depletion of tryptophan leads to a central serotonin deficiency that contributes to a delirious state. In addition to abnormal secretion patterns by the pineal gland, there could be a decline in the number of melatonin receptors due to neurodegeneration, which occurs in patients with dementia (33). Alternatively, polymorphisms in the genes that encode for melatonin receptors could lead to abnormalities in the function of these receptors. This may also explain the absence of a straightforward response to melatonin. Investigation of the relationship between
specific single nucleotides polymorphisms in the genes that encode for the melatonin receptors could also show whether such polymorphisms could account for abnormalities in the function of these receptors.

**Current treatment policy**
Currently, the prophylactic medical treatment of delirium consists mainly of antipsychotics (34, 35), because two studies have shown the preventive effect of such compounds (36, 37). The use of these antidopaminergic drugs is aimed at reducing psychotic symptoms, including hallucinations and delusions, by lowering the dopaminergic excess, which is present during delirious state. However, the safety of this type of pharmacological treatment is uncertain. The U.S. Food and Drug Administration (FDA) discourages clinicians from prescribing antipsychotics to delirious dementia patients and from using these medications prophylactically (38), due to a ten-fold increased risk of cerebrovascular accidents in the first weeks of treatment and a higher frequency of prolonged QT-interval and mortality (39-42). Furthermore, pharmacological treatment with antipsychotics might lead to other side effects, such as drowsiness and concomitant falls. The NICE guideline does not recommend prophylactic treatment with antipsychotics in patients with an increased risk of delirium (5, 43). In addition, they recommend limiting antipsychotics for treating delirium only to patients who are distressed or considered a risk to themselves or others, and for whom verbal and non-verbal de-escalation techniques are ineffective or inappropriate. There are also no specific recommendations for patients with cognitive impairment, and it is not explicitly stated that previously published evidence was not derived from the groups for which the treatment will be prescribed. This is remarkable as it is quite possible that patients with cognitive impairment have not been adequately represented in trials investigating medical treatment for delirium. For practical and statistical reasons, these trials often only include patients who are relatively healthy, and consequently, the responses of patients who will actually use the medication in daily life may differ in important ways from those of patients who were included in the trials (44). Given the risk of serious side effects with antipsychotics, safer treatment options are warranted, including the possibility of targeting other pathophysiological mechanisms of delirium apart from dopamine excess. It is possible that melatonin could prove to be such an option, and if it can indeed influence the circadian rhythm disturbances in delirium, it could aid in the prevention of or recovery from delirium.

**Aim and outline of this thesis**
The circadian sleep/wake rhythm disturbances that are seen in delirium and the role of melatonin supplementation provide a new angle in delirium research. More research is needed to determine the role of melatonin in the pathophysiological mechanisms of delirium and to determine whether the restoration of the circadian rhythm with melatonin supplementation may be a new, safe and effective method of intervention. The aim of the research in this thesis is to explore the role of melatonin as a prophylactic
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treatment for delirium in influencing incidence and /or severity of delirium, to determine the role of melatonin in the pathophysiology of delirium, and to explore the usefulness of the sleep-wake rhythm disturbances as a starting point in the diagnosis and subtyping of delirium.

In Part I, three observational studies related to circadian rhythm disturbances in the pathophysiology of delirium are presented. In Chapter 2, we investigate whether the tryptophan depletion theory in delirium can be confirmed in our previous cohort of elderly hip fracture patients. Chapter 3 focuses on genetics, and investigates the association between polymorphisms in the melatonin receptor 1B gene and the risk of delirium. In Chapter 4, we investigated the usefulness of electronic measurement devices in capturing the rest-activity patterns in patients with delirium, and its translational application in diagnosing delirium and determining its subtype. In Part II, we provide a background for our double-blind, randomized, placebo-controlled trial (RCT) in two reviews and present our RCT. In Chapter 5, we investigate the effectiveness of melatonin treatment on circadian rhythm disturbances in dementia, and whether there are implications for melatonin treatment in patients with delirium. In Chapter 6, we investigate whether patients with cognitive impairment are present in previously published studies on the medical (prophylactic) treatment of delirium and if not so, discuss the arguments for not including them. In Chapter 7, we present the double-blind, placebo-controlled RCT in which we investigated the prophylactic properties of melatonin versus placebo on delirium in hip fracture patients. Part III comprises the summary in Chapter 8, and the general discussion in Chapter 9, in which we discuss the implications of the findings reported in this thesis and give directions for further research.
Chapter 1

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