Therapeutic interventions aimed at circadian rhythm disturbances in Alzheimer disease

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Abstract
Alzheimer's disease (AD) is a neurodegenerative disease without a known cure to date. The number of individuals suffering from AD is expected to increase dramatically the upcoming decades, making it a global health issue. In as many as 35-50 % of the AD patients symptoms of circadian rhythm disturbances are observed. These symptoms, rather than the cognitive decline, are often the primary cause of institutionalization. The relationship between AD and circadian rhythms is complex. The neurodegenerative processes specific to AD alter several aspects of the circadian timing system, which explains the circadian rhythm disturbances. Conversely, there is increasing evidence that circadian rhythms and sleep affect AD pathology. Currently prescribed drugs are only minimally effective and are associated with a lot of side effects. Interventions based on chronobiological principles offer an interesting and attractive alternative for improving circadian rhythm disturbances in AD patients. Interventions that appear promising are bright light therapy, melatonin supplementation and transcutaneous electrical nerve stimulation. Despite the fact that there are still uncertainties about the mechanisms and effectiveness of these interventions, the chronobiological approach seems to be a promising and viable option to reduce circadian rhythm disturbances in AD patients and in this way to improve their level of independence and quality of life. Furthermore, improvement of circadian rhythmicity may even influence AD pathology.

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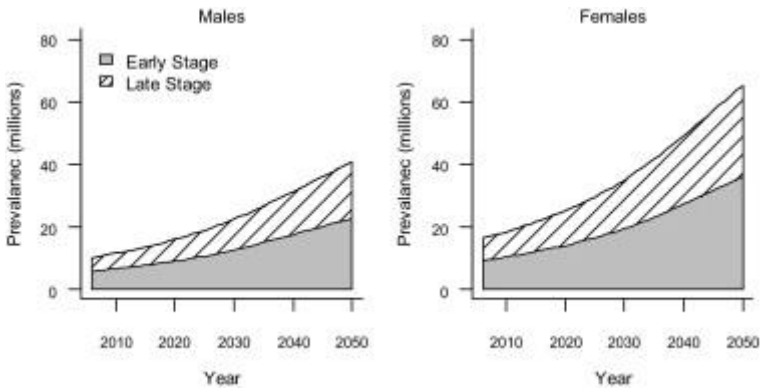
Introduction

Alzheimer's disease (AD) is a neurodegenerative disease without a cure so far. At the moment there are about 36 million people diagnosed with AD worldwide and the estimated costs associated with AD are 604 billion US dollars (Wimo and Prince, 2010). These numbers are expected to be doubled in 2030 and tripled in 2050. This will challenge our healthcare systems to meet the needs of all these patients suffering from AD (prevalence, see also figure 1). For these reasons, AD can be considered a crucial global health issue (Brookmeyer *et al.*, 2007).

In as many as 35-50 % of the AD patients symptoms of circadian rhythm disturbances are observed (Vitiello *et al.*, 1990; McCurry *et al.*, 1999). Circadian rhythm disturbances are common among elderly people, but are particularly pronounced in this group of patients (Hoogendijk *et al*., 1996). This is a result of changes associated with AD that take place at different levels, such as neurodegenerative changes in brain regions involved in the circadian clock mechanisms and a decrease in strength of environmental synchronizers (Cardinali *et al.*, 2010). Symptoms include impaired sleep, delayed sleep onset, night time wakening, decrease in slow wave sleep (SWS), reduction in REM sleep, night time wandering, excessive daytime napping and sundowning, agitation that usually occurs in the late-afternoon (Singletary and Naidoo, 2011). These symptoms become worse during the progression of the disease and have a huge negative impact on quality of life of both patient and caregiver. As a consequence, these symptoms are often the primary cause for institutionalization, rather than the cognitive deterioration caused by the disease (Bianchetti *et al.*, 1995; Moran *et al.*, 2005). Furthermore, circadian rhythm disturbances are associated with several physical conditions and depression (Maggi *et al*., 1998; Jensen *et al*., 1998). Impaired sleep, a result of circadian rhythm disturbances, has a negative impact on memory and cognitive functioning. Therefore, improvement of the circadian rhythm in AD patients may not only reduce distress of both patient and caregivers, but may also delay the progression of the disease (Moe *et al*., 1995). For these reasons, optimizing management of circadian rhythm disturbances is of the utmost importance for individuals with AD.

Currently prescribed drugs have proven to be only minimally effective and are associated with a variety of side effects. Over the last decade, approaches that are based on chronobiological principles have been proposed as alternative methods to improve circadian rhythm disturbances in AD patients. Interventions that appear promising and will be discussed here are bright light therapy, melatonin supplementation and transcutaneous electrical nerve stimulation (TENS) (Wu and Swaab, 2007).



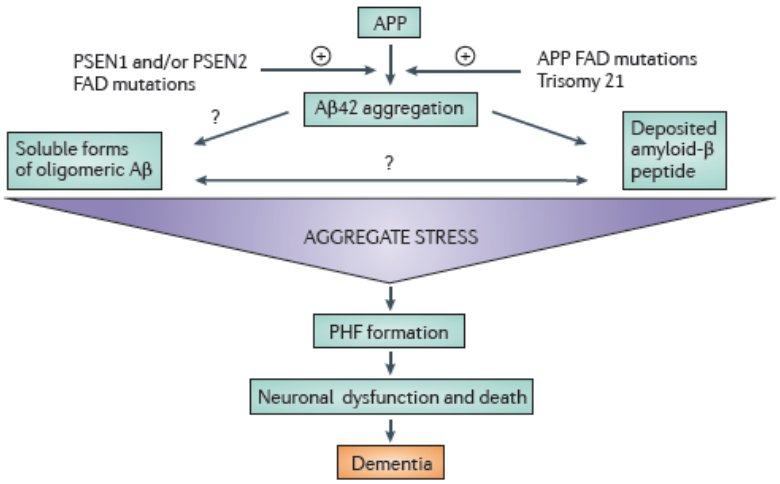
Figuur 1 - Worldwide projections of Alzheimer's prevalence (in millions) for the years 2006–2050 (Brookmeyer *et al*., 2007).

AD pathology

Dementia describes a disorder characterized by deterioration of memory and cognitive functions. In clinical terms it is described as a reduction of cognitive functioning of an individual, which results in problems during daily activities. There are multiple sets of criteria for the diagnosis of dementia, most of which describe a gradual decline in at least two cognitive domains that are related with interference in social and practical functioning. This decline has to be confirmed by clinical and neuropsychological tests. Ultimately the disease results in death of the individual within 3-9 years after diagnosis. AD is the most common cause of dementia and is a neurodegenerative disease, characterized by a dramatic loss of both neurons and synapses in multiple regions of the brain, that was first described by doctor Alois Alzheimer (Tarawneh and Holtzman, 2012; Querfurth and LaFerla, 2010).

Areas that are especially associated with this neuronal loss are the basal forebrain, hippocampus and cortex. The exact trigger of neurodegeneration in the majority of AD patients is still unclear. However, there are a number of neuropathological features associated with the disease. The best investigated pathological events are the formation of senile plaques and neurofribrillary tangles. Plaque filaments consist of amyloid-β (Aβ) deposits and are deposited extracellularly, while tangles are present intracellularly and are composed of hyper-phosphorylated tau proteins (Uzun *et al*., 2011). Aβ is a peptide that is derived from the β-amyloid precursor protein (APP) and has several isoforms. In AD the major component of plaques is the isoform $A\beta_{42}$. The peptide is present in the brain and cerebrospinal fluid of healthy individuals, which indicates that Aβ in itself is not the cause of neurodegeneration. Instead, the damage probably occurs as a result of a surplus of Aβ molecules that join into plaques (Walsh and Selkoe, 2007). Tangle formation is a result of abnormal accumulation of paired helical filaments of hyper-phosphorylated tau protein. The intracellular tangles are thought to disturb microtubule assembly, thereby interfering in protein trafficking and cytoskeletal architecture. This results in a reduced viability of the cell and ultimately in neuronal cell death (Wu *et al*., 2010).

At the moment the amyloid cascade hypothesis is the theory of AD pathogenesis that is held most plausible (figure 2). This hypothesis states that, although the trigger of the pathology remains uncertain for most AD patients, an excess of Aβ as a result of overproduction or decreased degradation lead to plaques. This in turn initiates tau pathology and degeneration of neurons, eventually resulting in dementia (Uzun *et al*., 2011).



Figuur 2 - The amyloid cascade hypothesis (Karran *et al*., 2011).

Interactions between AD, circadian rhythms and sleep

AD, circadian rhythms and sleep are all connected and the relationship between the three of them is complex. The pathology seen in AD causes both circadian rhythm and sleep disturbances and the subsequent cognitive and functional disabilities in everyday life. Conversely, there is increasing evidence that circadian rhythms and sleep affect AD pathology. Additionally, sleep disturbances can be a result of AD induced impairments in either the sleep regulating system or the circadian rhythm of sleep (Slats *et al*., 2012). A proposed schematic view of the interactions based on the current literature can be found in figure 3.

Effects of AD on circadian rhythms

The neurodegenerative processes specific to AD alter several aspects of the circadian timing system, which can explain the circadian rhythm disturbances in these patients. Alterations can be seen on various levels: the suprachiasmatic nucleus (SCN) is affected, the melatonin system is distorted and the input to the SCN is impaired (Wu and Swaab, 2007; Zhou *et al*., 2012). The specific alterations will be described in more detail for these different levels.

The SCN is located in the anterior hypothalamus and is considered to be the self-sustained master clock that generates and synchronizes the rhythms throughout the body. The SCN resets on a daily basis via light input from the retina during the day and melatonin secretion from the pineal gland during the night. Light input is sent via the retinohypothalamic tract to a region in SCN that is characterized by vasoactive intestinal peptide (VIP) neurons. Within the SCN the neuropeptide vasopressin (AVP) modulates most activity rhythms and also acts as the main SCN output signal to other areas in the brain. In patients with AD there is neurodegeneration of the SCN, which becomes more severe as the AD advances (Mirmiran *et al*., 1992; Harper *et al*., 2008). There is a decrease in number of both VIP and AVP expressing neurons in the SCN of AD patients and the mouse model of AD, indicating a decreased activity of the master clock (Sterniczuk *et al*., 2010; Zhou *et al*., 1995). Also, levels of AVP are 3 times lower than in age matched controls and the usual 24-hour rhythm vanishes (Ishunina and Swaab, 2002; Jing *et al*., 2009). It is noteworthy that there already seems to be a decrease in the levels AVP gene expression of individuals who were still cognitively intact, but were neuropathologically in the earliest stages of AD (Wu *et al*., 2006). Additionally, in post-mortem analysis of the brains of individuals diagnosed with AD, pretangles, tangles and amyloid plaques were observed (Stopa *et al*., 1999).

The pineal gland is under the control of the SCN and is the main producer of melatonin. Melatonin is secreted in a circadian manner with a peak during the dark phase. It is an important circadian signal that has its timing effects at the central and peripheral level by interacting with the membrane receptors MT1 and MT2 (Wu and Swaab, 2005). In AD patients, there is an overall reduction in CSF melatonin levels compared to healthy controls, especially in the dark phase, while there is an increase in daytime CSF melatonin levels. It is striking that this reduction in melatonin levels was already seen in preclinical AD patients (Zhou *et al*., 2003). Although the exact mechanism for the decrease in melatonin levels is unclear, there are some proposed explanations. The pineal gland is not destroyed by AD neurodegeneration, but the expression of CLOCK genes, which are under control of the gland, become impaired. It was proposed that this is a result of decreased output of the SCN, causing a functional disconnection between SCN and the pineal gland (Wu *et al*., 2006; Wu and Swaab, 2007). An additional detail is the decrease in MT1 expressing neurons in the early stages of AD. The number of neurons expressing MT1 also diminishes with the progression of the disease, thereby further reducing the effects of melatonin(Wu *et al*., 2007).

The circadian clock entrains to the daily 24-hour cycle through cues in the environment. Light is the strongest Zeitgeber for the SCN, although melatonin also plays a substantial role (Wu and Swaab, 2007; Dubocovich *et al*., 2003). The pathways responsible for light input become less sensitive or even dysfunctional during AD and at the same time the Zeitgeber strength is possibly reduced as a consequence of impairments in the SCN (Wu and Swaab, 2007). Moreover, during aging

the capacity of the lens to transmit light decreases and the retinas and optic nerves of AD patients show degenerative changes (Guo *et al*., 2010). The fact that AD patients often receive less exposure to light adds to the decreased input to the SCN and the subsequent disturbances in circadian rhythms (Van Someren *et al*., 1996).

Altogether this evidence suggests that AD pathology causes impairments in systems regulating circadian rhythms. The resulting circadian rhythm disturbances may in turn have their negative impact on sleep.

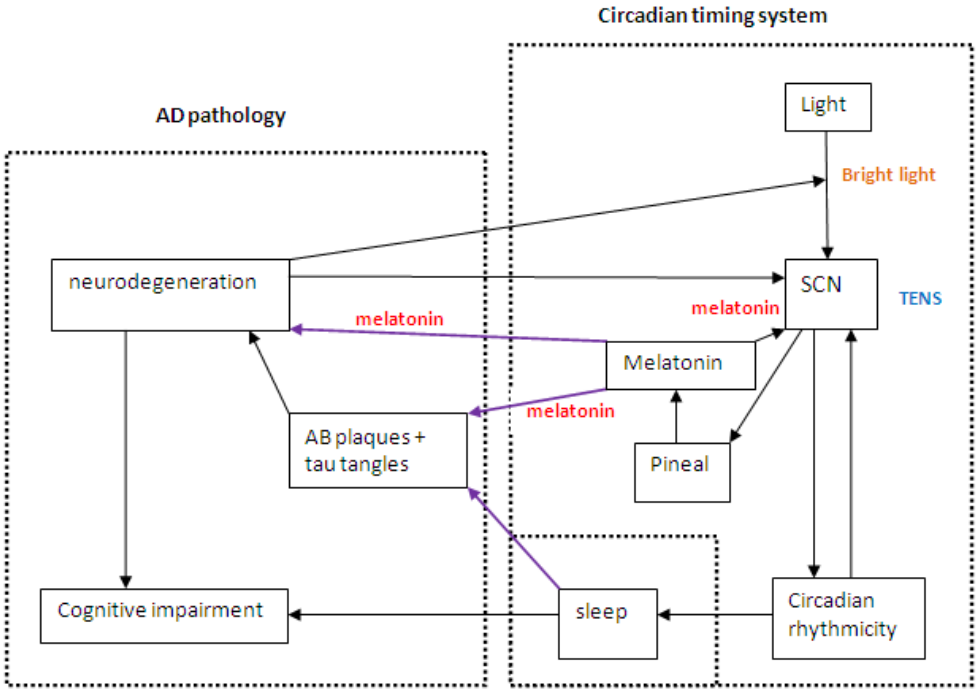


Figure 2 - Interactions between the different components of AD, circadian rhythms and sleep. Light is considered the strongest environmental cue that entrains the SCN, also known as the master circadian clock. The SCN sends signals to the pineal gland, which controls melatonin secretion. Melatonin in turn is a second strong synchronizing agent that gives feedback to the SCN. In addition to controlling the pineal gland, the SCN regulates circadian rhythms throughout the body. Sleep is one of the functions that is strongly connected to this system. All the SCN- driven rhythms provide feedback to the SCN as well. AD neurodegeneration, which is associated with Aβ plaques and hyper-phosphorylated tau tangles, affects the circadian timing system. Both the SCN and the light input pathway are impaired due to AD pathology and as a result, circadian rhythm disturbances arise. Conversely, there are indications that the circadian timing system affects AD pathology as well. Melatonin has some neuroprotective properties and may be able to counteract plaque and tangle formation. In addition, sleep may affect Aβ formation and thereby neurodegeneration as well. The effects of melatonin and sleep on AD neurodegeration are not as well established as the other connections and deserve further investigation. Finally, cognitive functioning is influenced by AD related neurodegeneration and by the circadian timing system through sleep.
The purple arrows indicate interactions that are less well established. The coloured words indicate target points for the alternative interventions aimed at improving circadian rhythm disturbances.

Effects of the circadian system on AD

Recent studies suggest that mechanisms involved in circadian rhythmicity and sleep have their effect on characteristics of AD pathology. A study by Kang *et al*. (2009) demonstrated that there is a circadian rhythm in CSF Aβ levels, with elevated levels while awake, compared to asleep. Moreover, induced sleep deprivation caused a significant rise in brain interstitial fluid (ISF) Aβ levels of mice, compared to periods of unrestricted sleep. Afterwards the mice spent an increased amount of time on sleeping, which resulted in an immediate reduction of ISF Aβ levels. Infusion of hypocretin, the neuropeptide important in regulating the sleep-wake flip-flop, caused a significant increase in ISF Aβ. Furthermore, chronic sleep restriction resulted in formation of bigger Aβ plaque deposition in the brains of APP transgenic mice, a mouse model for AD. This suggests that the state of wakefulness is

connected to ISF Aβ levels and that sleep deprivation has a negative impact on AD pathology (Slats *et al*.,2012).

Melatonin may influence AD pathophysiology in multiple ways (Wang and Wang, 2006). First, melatonin has various anti-amyloidogenic effects. *In vitro* melatonin reduces the secretion of APP and the formation of amyloid fibrils and *in vivo* it is able to decrease cerebral Aβ concentrations in mice (Ionov *et al*., 2011; Lahiri *et al*., 2004). Second, melatonin reduces tau hyperphosphorylation (Deng *et al*., 2005). Finally, melatonin has antioxidant and neuroprotective effects. It has shown to prevent cells from oxidative damage induced by Aβ and subsequent apoptosis (Pappolla, et al., 2000; Matsubara *et al*., 2003). Jing *et al*. (2009) showed that AVP, similar to melatonin, has the ability to protect against Aβ induced damage.

Aside from the fact that circadian rhythms and sleep affect the neurological pathology of AD, they also play a role in memory and cognition, two things that are clearly affected in AD patients. Circadian rhythm disturbances contribute to cognitive deterioration in healthy subjects, AD patients and individuals with mild cognitive impairment, a condition intermediate between 'normal' and AD (Bonanni *et al*., 2005; Cochrane *et al*., 2012). Furthermore, additional studies have shown that sleep disturbances, caused by either impairments in the sleep regulating system or the circadian rhythm of sleep, are associated with a decrease in memory and a more rapid decline of cognitive functions. Therefore it may be that circadian rhythm disturbances exacerbate cognitive impairments in AD patients (Moe *et al*., 1995; Mortimer *et al*., 1992).

Conventional pharmacological interventions aimed at AD and rhythm disturbances

The therapeutic interventions currently used or under investigation can be divided into several classes: preventive, disease-modifying and symptomatic treatments. At the moment treatments are mainly aimed at symptom control (Huang and Mucke, 2012).

Acetylcholine esterase inhibitors and NMDA-type glutamate antagonists are the two most widely used drugs that are approved by the FDA for the treatment of AD. Acetylcholine esterase inhibitors decrease the speed at which acetylcholine is degraded after release from the synapse during neurotransmission, thus increasing the level of the neurotransmitter, which is strongly reduced in AD patients (Huang and Mucke, 2012). Antagonists of the NMDA-type glutamate receptors are used to prevent neuronal overstimulation by excess glutamate, which is thought to induce excitotoxicity and subsequent neuronal cell death (Wu *et al*., 2010; Stone *et al*., 2011). These interventions seem to have value in reducing symptoms of patients with mild-to-moderate cases of AD, but there is no convincing evidence that they can halt disease progression (Huang and Mucke, 2012). Moreover, clinical trials identified that sleep disorders were side effects of acetylcholinesterase (AChE)-inhibiting medication, like Donepezil and NMDA antagonists like Memantine, both used for treatment of cognitive problems in AD (Jarvis and Figgitt, 2003; Jackson *et al*., 2004). These sleep disorders are of concern because of the adverse effects they have on cognition. Therefore, they may even worsen AD cognitive problems in the long run (Stahl *et al*., 2003).

Most prescribed short term medication for circadian rhythm disorders in AD are sedative hypnotics, sedative antipsychotics and sedative antidepressants for sleep problems and stimulants for daytime sleepiness (Stahl *et al*., 2003). Sedative hypnotics increase the sleep quantity and decrease sleep latency, but lose their effectiveness after several weeks of constant use. Additionally, side effects include confusion, daytime sleepiness, forgetfulness and a deterioration in cognitive functioning (Glass *et al*., 2005). Sedating antipsychotics are the drugs mostly prescribed for sleep in agitated AD patients. A huge problem is that although they increase total sleep duration, they have a negative impact on the circadian rhythm. Moreover, they increase cognitive decline and are currently associated with mortality (Wu and Swaab, 2007). There is even recent evidence that their use may increase neurofibrillary tangles (Ballard *et al*., 2005). In cases where it is difficult to determine whether sleep disorders are associated with AD or depression, sedating antidepressants are often used. Selective serotonin reuptake inhibitors are antidepressants that are effective in decreasing

sleep latency, however they also cause drowsiness, sedation and poor concentration (Zhou *et al*., 2012). Finally, stimulants are given to decrease excessive daytime sleepiness. The adverse cardiovascular effects, increased agitation and greater chance of psychosis associated with these drugs should be taken into account (Dolder *et al*., 2010).

Altogether, the prescription of the previously mentioned drugs to AD patients should be done carefully. Although they may offer some short-term relieve, most of them have side effects that may have a negative impact on AD progression in the long run. Thus, new treatment options are essential. Approaches that act as modulators of the circadian timing system, such as bright light therapy, melatonin supplementation and electrical nerve stimulation, could offer a solution.

Alternative therapeutic interventions aimed at circadian rhythm disturbances

Interventions based on chronobiological principles have been suggested as a methodology for improving circadian rhythm disturbances in both non-AD elderly and AD patients. Bright light therapy, melatonin supplementation and transcutaneous electrical nerve stimulation are treatment options that may over a solution (Zhou *et al*., 2012)**.**

Bright light therapy

As described before, there are multiple AD related changes that contribute to a decreased SCN input. AD is associated with degenerative changes in the retina and the retino-hypothalamic pathway, which results in a decreased light input. A contributing factor is the reduced light exposure of most AD patients, as this aggravate circadian rhythm disturbances. In nursing homes the patients experience less environmental light during the day time and encounter more light exposure during the dark-phase due to corridor lights. The combination of these factors results in reduced synchronization of the biological clock to the 24-hour environmental cues (Hoogendijk *et al*., 1996; Zhou *et al*., 2012). Since less light exposure leads to dysregulation of the circadian rhythm, the solution for circadian rhythm disturbances may be bright light therapy.

Several studies have shown that treatment with bright light is able to improve disturbed sleep and rest-activity rhythms in AD patients. They showed improvements in total night time sleep, decreased night time awakenings and day time napping and increased stability of the rest-activity rhythm (McCurry *et al*., 2011; Riemersma-van der Lek *et al*., 2008; Mishima *et al*. 2000; Okumoto *et al*., 1998; Mishima *et al*., 1994). Others found that although there did not seem to be an effect of bright light on sleep, the rest-activity rhythms of the AD patients improved significantly (Dowling *et al*., 2005).Some of these studies observed that besides the positive effects of bright light therapy on sleep, there were improvements in agitation and sundowning as well (Burns *et al*., 2009; Khachiyants *et al*., 2011). Another study reported that although an increase in both morning and evening bright light exposure had no effect on total sleep time, it lengthened the time of sleep bouts. This decrease in night time disruptions probably has a positive effect on subjective sleep quality. In the same study it was shown that evening bright light led to more regular periods of rest-activity, suggesting improved circadian rhythmicity of the patients (Ancoli-Israel *et al*., 2003).

Some studies failed to find any effect of bright light treatment in patients with AD (Ohashi *et al*. Morita, 1999; Colenda *et al*., 1997). An explanation for the mixed results could lie in the heterogeneity of the studies. Currently there is no consensus regarding light intensity and duration of the applied bright light. It is possible that specific light intensities are necessary in AD patients because of the deterioration of both the visual and circadian system. Furthermore, the patients in the trial were in various stages of AD. The specific AD stage at which bright light treatment is started, is probably crucial in the success of the treatment. It is likely that light loses its ability to improve circadian rhythmicity once a patient is in an advanced stage of AD due to irrevocable neuronal damage in the timing system (Van Someren *et al*., 1993). Besides the effects on sleep and circadian rhythmicity, Riemersma-van der Lek *et al*. (2008) found that bright light treatment was associated with improved cognitive function and a decrease in symptoms of depression in residents of group

care facilities. 87% Of these residents were diagnosed with AD. All studies report little or no adverse effects of the treatment on the subjects' health or wellbeing.

There are some hypotheses about the mechanisms by which bright light therapy is able to improve circadian rhythmicity and sleep. Bright light therapy may be effective by means of amplifying the circadian input and thereby enhancing photic entrainment of the SCN and its outputs. This hypothesis is supported by a number of findings. Increased light intensities have proven to improve firing rates of SCN neurons in rats (Meijer *et al*., 1998). Another study carried out on rats showed that increasing illumination levels led to an enhanced sleep-wake cycle amplitude of aged rats to levels similar to young rats. In humans, increased amplitude of slow wave activity has been observed as a result of bright light treatment (Van Someren *et al*., 1993). Another possibility is that the increased exposure to light may actually enhance the function of the various components of the circadian system. In this case, the improvements following increased light exposure should show a slower development and termination of the treatment would not result in an immediate relapse. Evidence for this is seen in a study investigating the effect of both bright light and exercise on circadian rhythm disturbances in AD patients. Six month after treatment, the positive effects were still present. Although the exact mechanism behind the positive effects of bright light therapy is still unclear, it seems that the both pathways described above are involved (Van Someren *et al*., 1993).

In summary, stimulation of the SCN by bright light intervention seems to have a positive impact on circadian rhythm disturbances in AD patients in most cases and may therefore be an alternative treatment option with less adverse side effects compared to the conventional medication. Patients in the earlier stages of AD will likely benefit the most from the therapy. Further studies should be directed at determining the optimal exposure time, duration and level of bright light in treating circadian rhythm disturbances in AD patients.

Melatonin supplementation

Light input tends to be the strongest Zeitgeber of the biological clock. Nevertheless, melatonin is also a potent synchronizer of the biological clock. The SCN regulates melatonin secretion by the pineal gland in a timely manner, which in turn gives feedback to the SCN (Dibner *et al*., 2010). This feedback system is weakened in AD patients, since they not only exhibit reduced levels of melatonin, but also irregular melatonin pattern compared to healthy individuals. This suggests that the melatonin rhythm has a reduced signal strength in clock synchronization as well as a reduced reliability as an internal synchronizing time cue. At the moment, melatonin is already used as a therapeutic agent for circadian rhythm disruptions in jet lag and shift work related sleep disorders, delayed sleep phase syndrome and circadian disorders in blind people (Rios *et al*., 2010). Because of the positive impact of melatonin in these disorders, several studies investigated whether the substance was able to improve circadian rhythm disturbances in AD patients as well.

A number of open-label studies, case report and double-blind, randomized controlled trials tested the effects of melatonin on circadian rhythm disturbances in AD patients. Four out of six randomized controlled trials supported the potential positive effects of melatonin. The observed effects included improved sleep quality and rest-activity rhythm, reduced variability of sleep onset time and reduced sundowning. However, two of them, of which one was a multicenter cilinical trial in 31 AD centres in the US, failed to find any effects (Cardinali *et al*., 2010). Moreover, although some of these studies individually reported improvements of cognitive functions as well, a meta-analysis by Jansen *et al*. (2006) concluded that melatonin did not improve cognitive impairments. An explanation for the ambiguous results may be that melatonin's ability to entrain circadian rhythms depends on the time of administration relative to the internal circadian phase of the individual. Different responses to the treatment may thereby be due to differences in circadian phase between patients (Wulff *et al*., 2010). Another good possibility for explaining why no effects were found may lie in the strong reduction in SCN MT1 receptors observed in AD patients. Patients in advanced stage of the disease only have about 10% of the MT1 receptors left compared to healthy individuals and this may not be enough to elicit an effect (Wu *et al*., 2007). Starting melatonin treatment in earlier stages of AD may therefore be useful in improving circadian rhythm disturbances. Support for this is the fact

that individuals with mild cognitive impairment seem to respond well to melatonin treatment. Improvements in rest-activity rhythm, sleep quality, sundowning and cognitive functioning are reported (Cardinali *et al*., 2010).

It is thought that therapeutic effects of melatonin are likely due to replacement of the depleted melatonin levels seen in AD patients. Melatonin levels are significantly lowered in AD patients, a consequence of lowered melatonin production. Increasing their melatonin levels to regular levels may therefore be adequate in resynchronizing the clock (Srinivasan *et al*., 2010). Beneficial effects may also relate to the antioxidant, mitochondrial and antiamyloidogenic effects of melatonin that were outlined before. These effects may interfere in the progression of AD. It is possible that as a consequence, long-term melatonin treatment slows down the neurodegeneration of brain areas associated to both the circadian timing and cognitive system.

The question as to whether melatonin abnormalities contribute to or are a result of AD pathology remains unanswered. Despite controversial results there are indications that melatonin can be effective in reducing circadian rhythm disturbances, especially in the early stages of AD. Benefits of melatonin are that is it easily administered, it is relatively inexpensive and it seems to have only few side effects (Wu and Swaab, 2007). The moment the treatment is started however, is probably the factor which determines whether the treatment is effective. In particular administration during the early stages, rather than in fully developed AD, provides relief.

Transcutaneous electrical nerve stimulation

According to the 'use it or lose' principle of Swaab neuronal degeneration can be reduced or even restored by increased stimulation. Supporting this are the observations that activated neurons are better able to protect themselves from AD related degeneration (Swaab *et al*., 2002). Transcutaneous electrical nerve stimulation (TENS) is suggested as a means to (re)activate the biological clock. Electrical pulses are applied to the skin and further transmitted through afferent nerve fibers of the peripheral nervous system to the spinal cord. The pulses ultimately end in the brain, including the SCN (Van Someren *et al*., 1998).

Some studies indicate improved circadian rest-activity rhythms in AD patients as a result of TENS. One of them observed a reduction in night time restlessness as well. (Van Someren *et al*., 1998; Scherder *et al*., 1999; Van Dijk *et al*., 2002). A study conducted by Van Dijk *et al*. (2006) only partially supported the hypotheses that TENS improves the rest-activity rhythm. They found near-significant effects of treatment on circadian rhythmicity in AD patients. Interestingly, further analysis revealed treatment effects for those patients who did not take cholinesterase inhibitors. This indicates that studies concerning interventions aimed at circadian rhythm disturbances in AD, including TENS, should take the prescription of additional medication into account. Moreover, a large number of the patients in this study were either in an advanced stage of AD or suffered from early onset AD, which was not the case in the other studies. These factors are likely to have a large impact on the effectiveness of the treatment (Ho *et al*., 2002; Le Bars *et al*., 2001). In relation to other AD associated symptoms it is relevant to mention that various studies also report positive effects of electrical nerve stimulation on cognitive functioning (Van Dijk *et al*., 2002). These effects may be either a result of improved circadian rhythm disturbances, or entirely different mechanisms.

The (re)activation of the SCN neurons may proceed through four pathways. The first is the spinohypothalamic tract, which goes from spinal cord directly to the master clock. The second is the spino-septal-hypothalamic tract, an indirect pathway from the spinal cord to the SCN via the septal nuclei. The third is the spino-brainstem-hypothalamic tract, a projection from the spinal cord to the locus coeruleus (LC) in the brainstem and subsequently to the SCN. The last pathway goes from the spinal cord to the brainstem dorsal raphe nuclei (DRN) and further to the SCN (Van Dijk *et al*., 2006). In other words, TENS may (re)activate the biological clock through pathways that originating in the peripheral nervous system and thereby have its positive effect of circadian rhythm disturbances and subsequent cognitive skills. Another possible manner of explaining the improvements in cognitive function concerns the functional connection of the LC and DRN with the cortical cholinergic system, by means of acting on the nucleus basalis of Meynert (NBM). This area is important in cognitive

functioning and memory. It is possible that stimulation of the NBM via the LC and DRN results in the observed cognitive improvements after TENS treatment (Cooper *et al*., 2005).

Whether TENS has any clinical relevance as an effective treatment for circadian rhythm disturbances in AD patients should be further investigated. In all trials the TENS therapy was tested for a relative short period of time and it may be that long-term daily stimulation results in a stronger effect by way of improving SCN functionality. Future studies should also take the time of onset and stage of AD into account. The number of studies investigating TENS in AD patients is currently low, thereby making firm conclusions difficult.

Mixed modality

The combination of different treatments, known as mixed modality, may be even more effective in reducing circadian rhythm disturbances in AD patients. It is possible that the combination of individual interventions produce an additive effect that results in a better treatment outcomes.

Since both light and melatonin are an input to the SCN and involved in synchronizing the biological clock, combining the two may strengthen circadian rhythms. Two studies investigated the combination of bright light therapy and melatonin administration. As a result circadian rhythm disturbances were reduced, with strengthened rest-activity rhythms, improved sleep efficiency, decreased daytime sleepiness and a reduction in sundowning behaviour (Riemersma-van der Lek *et al*., 2008; Dowling *et al*., 2008).

The combination of TENS with either light or melatonin has unfortunately never been investigated. It would be very interesting, since it is suggested that TENS is able to (re)activate the SCN and strengthening the input signal by means of bright light or melatonin as well, may therefore even have a stronger influence.

Increased physical activity as an stand-alone treatment for circadian rhythm disturbances has only been tested twice. The results of the two studies with regard to rhythmicity contradict each other (Zhou *et al*., 2012). Therefore it is not clear whether physical activity as an isolated treatment is strong enough to synchronize the biological clock. However, in combination with bright light therapy it seems to be promising. A randomized controlled trial by (McCurry *et al*.2011) demonstrated a decrease in number of night time awakenings, total time awake at night, and depression in AD patients treated with bright light therapy in combination with daily exercise. After 6 months, the positive effects were still observed and there was even an additional decrease in night awakenings and daytime sleepiness. Several other studies support this finding (Zhou *et al*., 2012). Despite of these promising results, it should be taken into account that increasing daily physical activity in order to improve circadian rhythm disturbances may be difficult in patients with AD. These patients are often limited in their mobility and have difficulties understanding instructions and will therefore need caregiver assistance when doing the exercises (Suttanon *et al*., 2012).

The investigated mixed modality treatments seem to yield better results than individual interventions. Treatment strategies should probably be individualized according to the individual conditions of the patients in order to achieve the best results.

Evaluation

To date, there is still no treatment that is able to cure or stop progression of AD. In combination with the expected growth of new patients, the costs of healthcare will rise enormously. Furthermore, the disease is a huge emotional burden on both patients and their caretakers. Therefore it is of the utmost importance to keep patients independent as long as possible in order to limit the cost of clinical care. Circadian rhythm disturbances are often the primary reason for institutionalization of AD patients and current treatments are far from optimal. The drugs that are currently used in the treatment of AD patients should be prescribed with caution. They have proven to be only minimally effective and there are a lot of side effects associated with their use that may even have negative consequences for AD progression in the long run. Drug dependency and tolerance are likely consequences and adverse effects such as worsened cognitive functioning, is something that is

particularly problematic in this group of patients. The implementation of alternative interventions aimed at improving circadian rhythm disturbances can therefore be a valuable option to improve quality of life of both patient and caregivers and postpone institutionalization. Bright light therapy, melatonin supplementation and transcutaneous electrical nerve stimulation are three options based on chronobiological principles that may fit this description. The new treatments for AD might decrease the costs of medical care, especially the costs of social care in the long run (Wimo and Prince, 2010).

In light of the current data, the three alternative interventions differ in several areas. Bright light therapy is the best studied one and shows the most promising results. Although the studies differ in size and made use of different methods, almost all report improvement in circadian rhythm disturbances. Despite the fact that it is not possible to test for placebo effect, bright light therapy should be seriously considered as a treatment option. The effectiveness of melatonin supplementation remains unclear. The results are ambiguous and it may well be that additional melatonin only has its effects when treatment is initiated in the early stages of AD. Another option may be a combined treatment with melatonin and bright light. The combination of these two interventions seems to offer possibilities in decreasing circadian rhythm disturbances and subsequently improve independence and life quality. The explanation for this may lie in the complex and multifaceted nature of the disease, which includes not only the various neurodegenerative changes associated with AD, but also the environment of the patients. Intervening on different levels, might thus improve the timing system as a whole. At the moment there is not enough data about TENS as a treatment option for circadian rhythm disturbances. TENS has never been tested clinically on large scale and the precise mechanism by which it would improve rhythm disturbances remains unclear. Although theoretically promising, further investigations with regard to TENS are much needed. What distinguishes all three alternative treatments discussed in this review from the conventional therapies is that they all act on the circadian system. They not only improve just one of the symptoms, but they contain both day and night effects, which supports the idea that they actually have an effect on the circadian timing system. The exact relationship between AD and the circadian system remains unclear and it is uncertain to what extend these treatments are able to reactivate the timing system. However, reported improvements in circadian rhythm disturbances as a result of these interventions suggest that there is a connection between AD and rhythmicity and there may still be some plasticity in the timing system of AD patients. Altogether it seems that treatments directed at the circadian system can be promising in the treatment of circadian rhythm disturbances and they appear to have little or no adverse side effects. Hence, they are mentioned in several reviews as good candidate treatments (Van Someren *et al*.1993; Wu and Swaab, 2007; Weldemichael and Grossberg, 2010; Zhou *et al*., 2012). Utilizing alternative interventions to stimulate the clock system, especially the earlier stages of AD, deserves further research. Once there is profound neurodegeneration in advanced stage AD patients, it may well be too late to intervene. Multicentre randomized and placebo controlled trials are a way to investigate both individual and combinations of these interventions aimed at improving circadian rhythm disturbances.

Something that needs to be worked out in further research is standardization of treatment guidelines. At the moment there is no consensus on the various aspects of the different interventions. An example of this is found in light therapy, where light intensities, duration and time of exposure differ between the various studies. At the moment however, it is common to use relatively high light intensities, which may need to be revised. Melanopsin, the photopigment primarily responsible for circadian photo-entrainment, is a shortwavelength light-sensitive receptor. It has been hypothesized that short-wavelength light with low intensities is possibly better in stimulating the melanopsin-containing ganglion cells in the retina and is thereby more effective in entraining the circadian system (Pail *et al*., 2011). This and similar issues must be solved in order to come up with the most effective treatment.

In addition, evidence is piling up that the relationship between AD, circadian rhythms and sleep is more complicated than previously thought. Not only do the neurodegenerative changes associated with AD affect the components of the timing system and thereby sleep, there is an

influence of sleep and circadian related mechanisms on AD pathology as well. Because of this, the distinction between cause and effect has been blurred. On the one hand, this means that we have to alter our current ideas of AD pathology, as well as potential treatment options. On the other hand, it may also be seen as a possibility to intervene. By improving circadian rhythms it may be possible that the progression of AD is delayed. Furthermore, better rhythmicity does not only reduce the burden of both patient and caregivers, sleep disorders associated with circadian rhythm disturbances exacerbate memory impairments. Cognitive functioning, which is already affected in AD patients will further deteriorate due to these disturbances. Thus not only can these interventions be valuable in symptomatic treatment, they may even be disease-modifying. Optimization in the treatment of these disturbances in AD patients is for these reasons of the utmost importance.

Additionally, it would be interesting to investigate the relationship between the circadian system and AD in alternative manners. For instance, examine whether a correlation between total daylight exposure during lifetime and AD prevalence exists. Similarly, it would be valuable to see if people with an irregular lifestyle, such as people who work in shifts, develop more often Alzheimer's than people with a more structured lifestyle. Due to confounding variables no causal link can be established, but it would give some clues with regard to the relationship between circadian rhythmicity and AD.

In conclusion, despite the fact that there are still many uncertainties about the mechanisms and effectiveness of alternative interventions, the chronobiological approach seems to be a promising option in reducing circadian rhythm disturbances in AD patients and is in that way improving independency and quality of life of patient suffering from AD.

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