Light, sleep, and circadian rhythms in older adults with Alzheimer's disease and related dementias

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Abstract: Individuals with Alzheimer's disease and related dementias (ADRD) may experience sleep problems, nocturnal wandering and daytime irritability, which in addition to being problematic for the ADRD patients themselves, may also place an increased burden on their family caregivers. As discussed in this review, light therapy has shown great promise as a non-pharmacological method to help regulate sleep in ADRD patients, with preliminary studies demonstrating that appropriately timed light exposure can consolidate and improve nighttime sleep efficiency, increase daytime wakefulness, and reduce evening agitation. Just as importantly, light therapy does not present the same adverse event profile as pharmacological treatments. Despite the promise of light therapy, a recent Cochrane review stated that there is not enough evidence to justify using light as a therapy to improve sleep and behavior in ADRD patients. There are two main barriers for the adoption of light therapy: (1) compliance to the light treatment; and (2) accurate measurement of light exposures during treatment. Recent research has shown that the circadian system is maximally sensitive to short-wavelength (blue) light. This finding opens the door for the potential application of lower, more targeted light intensities in therapeutic settings. Therefore, before light can be successfully implemented to treat circadian sleep disorders commonly found in ADRD patients, light delivery methods that maximize compliance and individualize light dose and timing need to be developed.

Keywords: Light, lighting, sleep, circadian rhythms, older adults, Alzheimer's disease, dementia, ADRD.

1. INTRODUCTION

Light is not just for vision. Light reaching the retina contributes not only to visual perception but also to non-visual responses, such as the resetting of the biological clock. Humans have a biological clock located in the suprachiasmatic nuclei (SCN) that generate and regulate circadian rhythms, which are biological rhythms that repeat approximately every 24 hours (h). These include cycles such as sleep-wake, body temperature, hormone production and alertness. The daily light-dark pattern reaching the retina is the main input to synchronize the biological clock to the solar day. If humans are not exposed to a sufficient amount of light of the right spectrum, for a sufficient amount of time, and with the right timing, the biological clock becomes desynchronized with the solar day and humans may experience decrements in physiological functions, neurobehavioral performance and sleep [1-4].

A person is more likely to experience a good night of sleep when the circadian and homeostatic systems, both of which influence the sleep-wake cycle, are aligned. Sleep homeostasis increases with time awake, contributing to high sleep pressure at night. The circadian system sends an alerting signal to the body during the day, counteracting the increase of sleep pressure with time awake, and a sleeping signal during the night, promoting a consolidated night of sleep. The circadian clock consolidates sleep and wake periods in part by driving two "gating" zones: (a) the wake maintenance zone, which occurs approximately 2-3 h prior to habitual sleep onset and (b) the sleep maintenance zone, which occurs approximately 2-3 h prior to habitual wake onset, close to the minimum core body temperature.

Another very well-known circadian rhythm is the cycle of melatonin production. Melatonin is a hormone produced by the pineal gland at night and under conditions of darkness. For diurnal species, such as humans, melatonin signals that it is time to sleep [5]. The timing of melatonin onset in the evening, referred to as dim light melatonin onset (DLMO), occurs approximately 2 h prior to natural bedtimes, and is used as a marker of the circadian clock [6].

2. LIGHTING CHARACTERISTICS AFFECTING THE CIRCADIAN SYSTEM

Lighting characteristics affecting the circadian system, as measured by acute melatonin suppression and phase shifting of DLMO, are different than those affecting visibility. Rods, cones and the intrinsically photosensitive retinal ganglion cells (ipRGCs) participate in circadian phototransduction, which is how the retina converts light signals into neural signals for the biological clock [7]. It is now known that lower levels of light, less than those originally demonstrated in the 1980s, can acutely decrease melatonin concentration and affect the timing of melatonin onset and offset; however, light levels needed to affect melatonin are still higher than those needed to affect vision [8,9]. For example, a warm color (correlated color temperature of 2700 K or lower) nightlight delivering 1 lux at the cornea will allow one to

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safely navigate in a space at night, but it will not suppress the hormone melatonin [9,10]. Humans are "blue sky detectors;" the peak sensitivity for acute melatonin suppression and phase shifting of DLMO is close to 460 nanometers (nm) [11-13].

The effects of light on the circadian system vary over the course of the 24-h day. Morning light, given after the trough of core body temperature that typically occurs in the second half of the night, will advance the timing of sleep in the following cycle, while evening light, given prior to the trough of core body temperature, will delay the timing of sleep [6].

Photic history, or the amount of light received during the previous day determines the effectiveness of light on acute melatonin suppression and on the phase shifting of the timing of DLMO [14-16]. For maximum results of light therapy, it is also important to accurately measure light exposures over the 24-h day, as opposed to taking just a "snapshot" measurement of light exposure at one certain place and time [17,18]. The circadian system seems to keep track of light exposure, and therefore, knowing an individual's light exposure history over the past 24 h can help determine the best light prescription for the next 24 h [18].

3. SLEEP AND CIRCADIAN DISRUPTION IN NORMAL AGING AND ADRD PATIENTS

Between 40-70% of older adults suffer from sleep disturbances or disorders, which are especially prevalent among Alzheimer's disease and related dementias (ADRD) patients [19]. Older adults, in particular, those with ADRD, exhibit reduced neuronal activity in the SCN, where the biological clock that governs circadian rhythms is located, along with reduced circadian rhythm amplitude due in part to the fact that at a molecular level, the SCN becomes less responsive to light for entrainment [20]. It has been demonstrated that fractal activity patterns, which are robust in healthy physiological systems, are governed by the SCN and are significantly altered in those with dementia [21,22]. Additionally, when discussing the effects of light on the aging population, it is important to keep in mind that the first stage of phototransduction, when light signals are converted into neural signals, is negatively affected in this population: older adults have reduced optical transmission at short wavelengths [23,24]. Less light reaches the back of the eye due to lens thickening, and reduced light on the retina allows circadian rhythms to get out of sync [25,26]. Moreover, older adults, especially those with ADRD typically lead a more sedentary indoor lifestyle, with less access to bright light during the day, potentially increasing the risk for circadian disruption [27-29]. Without exposure to a regular, daily pattern of light and dark, circadian rhythms can become irregular [30]. Circadian misalignment resulting from irregular light-dark patterns or from age-dependent changes in light sensitivity or in the circadian system response likely plays a role in poor sleep [25]. When the circadian system is disturbed, it can lead to poor sleep quality in older adults, even if they have no other significant health issues [31].

ADRD is the most common type of dementia diagnosed in older Americans. While individuals with ADRD can have similar sleep problems as healthy older adults, they tend to exhibit more random patterns of rest and activity rather than the consolidated patterns of healthy, older adults [32]. This lack of rest-activity pattern consolidation, along with related nocturnal wandering, is one of the main reasons why individuals with ADRD are transitioned from the home to more controlled environments.

Two studies using the Daysimeter [17] measured circadian light and circadian disruption among healthy older adults and those with dementia. Briefly, light sensing by the Daysimeter is performed with an integrated circuit (IC) sensor array (Hamamatsu model S11059-78HT) that includes optical filters for four measurement channels: red (R), green (G), blue (B), and infrared (IR). The R, G, B, and IR photo-elements have peak spectral responses at 615 nm, 530 nm, 460 nm, and 855 nm, respectively. The Daysimeter is calibrated in terms of orthodox photopic illuminance (lux) and of circadian illuminance (CL_A). CL_A calibration is based upon the spectral sensitivity of the human circadian system proposed by Rea *et al.* [33] From the recorded CL_A values it is then possible to determine the circadian stimulus (CS) magnitude, which represents the input-output operating characteristics of the human circadian system from threshold to saturation. Values of CS are numerically equal to the amount of expected melatonin suppression from the CL_A exposures according to the model by Rea *et al.* [13]

Higgins *et al.* [34] measured light exposure and rest-activity patterns for an older adult with dementia and his caregiver spouse in a 7-day case study. The couple resided in an assisted living apartment with dim lighting; both wore Sleepwatch-L actigraphs to record rest-activity data and the caregiver also wore a Daysimeter. The data showed the patient with dementia slept 7.4 h at night, spent 1.6 h sleeping during the day and was awake almost 2 h each night; the caregiver slept 4.3 h at night after taking 1 h to fall asleep, slept 0.5 h during the day, and was awake almost 2 h at night. The patient spent most of his day in ambient light between 20-500 lux, with no exposure to bright light > 1000 lux; the caregiver spent 10.6 h/day in dim light and 8 min/day in bright light > 1000 lux. The caregiver had significantly less sleep and more fragmentation in activity than caregivers in other studies, and exhibited a high level of circadian disruption similar to that seen in rotating shift nurses [35]. In 2012 Figueiro *et al.* quantified light exposure and activity levels of healthy older adults compared to older adults with ADRD during summer and winter months [36]. Each of the 16 healthy older adults and 21 ADRD patients wore a wrist Daysimeter [17] to measure light and activity levels for 1 week. Results of the quantitative study show that individuals with ADRD experienced lower light levels, exhibited lower activity levels, and had greater disruption to their rest-activity patterns than healthy older adults. The findings also show that people with ADRD experience lower levels of light exposure and greater levels of rest-activity disruption during the winter than in summer. These results are consistent with earlier studies demonstrating that middle-aged adults are exposed to approximately 58 minutes (min) of bright white

light per day [28] while older adults in assisted living facilities were exposed to bright light for only 35 min per day [37]. Older adults with ADRD living in nursing homes experience as little as 2 min per day [38,39]. Given that current lighting in nursing homes and assisted living facilities is generally dim and constantly on, it is not surprising that sleep disturbances are common in this population [40].

Moe *et al.* [41] determined whether disrupted sleep-wake cycles could predict impaired cognition by observing 78 ADRD patients and 38 healthy control participants in an overnight lab study. Participants did not have any reported sleep problems. A stronger relationship was found between cognition and sleep with the ADRD patients; i.e., they found a negative correlation between nighttime waking and cognitive performance. Cognitive function decreased with more time awake and longer REM sleep latency, while more REM and slow-wave sleep were associated with better cognition.

These studies suggest that while circadian and sleep disturbances may be common in older adults, including those with ADRD, light, which is the strongest time giver for the circadian system, has a potential to promote entrainment and improve sleep in this population. Therefore, light has the potential to become a powerful treatment for mitigating poor sleep quality frequently found in the older population, including those with dementia. Medications, often prescribed for sleep problems, have low effectiveness [42,43] and are associated with adverse effects, such as worsening confusion, falls, and hip fractures [44-49]. A meta-analysis of sedative/hypnotic medications for older people with insomnia concluded that the benefits of sleep medication may not justify the increased risk [50]. Adverse side effects of light therapy may include eye strain and headaches [51] although other studies did not show any significant differences in side effects between light treatment and control experimental conditions [52]. The goal of this literature review was to identify studies that had used light as an intervention to improve sleep and behavior in patients diagnosed with ADRD.

4. LIGHT THERAPY FOR ADRD PATIENTS – A REVIEW OF THE LITERATURE

A search in Medline was performed in April-May 2015 using the terms: Alzheimer's disease, dementia, light therapy, phototherapy, sleep, and circadian rhythms. Studies from 1980 to 2015 that had used light as an intervention to improve sleep and/or behavior in ADRD patients were identified. The search yielded 304 results. After reading the abstracts, only those studies that discussed light as an intervention to reduce sleep disturbances and improve behavior (mood, depression and agitation) were selected, yielding a total of 24 articles. Table 1 details these studies and a summary of their findings is discussed below.

Fetveit *et al.* [53] demonstrated that exposure to 2 h of bright light (6000-8000 lux at the cornea) in the morning for at least 2 weeks substantially improved the sleep efficiency of 11 older adults with dementia. Alessi *et al.* [54] showed that 5 consecutive days of 30-min exposure to sunlight,

increased physical activity, structured bedtime, and control of light and noise at night resulted in a significant decrease in daytime sleeping in intervention participants compared to controls. Further, they showed that intervention participants had increased participation in social and physical activities as well as social conversation.

Analyzing actigraph data, Van Someren *et al.* [55] found that increased illumination in the living environment of 22 ADRD patients increased the stability of their rest-activity rhythm following 4 weeks of treatment. A ceiling-mounted light fixture containing high-intensity white fluorescent tubes was installed in the common areas where the patients spent most of their waking time. Patients received an average of 1136 ± 89 lux at the cornea from the new lighting, although the amount of light received ranged from 790-2190 lux at the cornea depending on the patient's position relative to a window. Bright light treatment was most effective in patients with relatively unimpaired vision, as opposed to those with severe visual deficits. Interdaily stability, which is a measure of the consistency in rest-activity patterns over the course of many days, increased (i.e., coupling of the rhythm to environmental *Zeitgebers*, such as time of meals) indicating a more steadfast organization of the circadian rest-activity rhythm. This was the first field study demonstrating that unattended light during the daytime could improve rest-activity rhythms in ADRD patients.

Satlin *et al.* [56] examined whether evening light exposure (1500-2000 lux at the cornea) would improve sleep-wake patterns and reduce agitation in ADRD patients, and found an increase in circadian amplitude and improvement in intradaily variability but not in interdaily stability. They also found that evening light exposure decreased nighttime activity and sundowning symptoms. Lyketsos *et al.* [57] administered 1 h of light (10,000 lux at the cornea) each morning for 2 weeks to ADRD patients with agitated behaviors and found that these individuals with agitated behaviors slept more hours at night, when exposed to bright light in the morning.

Mishima *et al.* [58] exposed 14 patients with dementia to 2 h of light (3000-5000 lux at the cornea measured at a distance of 1 meter) each morning for 4 consecutive weeks and observed a significant increase in nighttime sleep duration and a significant reduction in agitated behavior. In a later study Mishima *et al*. [59] examined the therapeutic effects of 2 weeks of morning bright light (5000-8000 lux at the cornea) on rest-activity rhythm disorders in 12 patients with vascular dementia and 10 ADRD patients. The 2 weeks of morning bright light induced a significant reduction in both nighttime activity and percentages of nighttime activity to total activity compared with the pre-treatment period, and compared with the dim light condition in the vascular dementia group, but not in the ADRD group.

Ancoli-Israel *et al.* [60] administered light (2500 lux at the cornea) for 2 h in the morning or the evening for 10 consecutive days and found both groups of ADRD patients (those who received morning and those who received evening light) exhibited more consolidated sleep at night, as measured by average length of maximum nocturnal sleep bouts. Using the same data set, Ancoli-Israel *et al.* [61] evaluated the effect of the lighting intervention on agitated

behavior in these patients. Morning light delayed the acrophase of agitation by 1.5 h but there was no significant effect on observational ratings of agitation. Yamadera *et al.* [62] found that 4 weeks of morning bright light (3000 lux at the cornea) administered to 27 ADRD patients resulted in improved mental status scores, decreased percentage of daytime naps/naptime, increased percentage of nighttime sleep time, and decreased percentage of nighttime awakenings.

Skjerve *et al.* [63] investigated sleep-wake rhythm disturbances and behavioral symptoms in subjects with severe dementia. Bright light treatment was given daily for 45 min in the morning to 10 patients with severe dementia, sleep-wake rhythm disturbances, and significant behavioral symptoms. Light treatment consisted of 5000-8000 lux at the cornea measured at a distance of 0.3-0.5 m. The patients' behavioral symptoms improved with treatment, but no changes in sleep-wake measures were found. The results suggested that short-term bright light improves behavioral symptoms and aspects of sleep-wake rhythm disturbances, even in severely demented patients.

Dowling *et al.* [64] tested the effects of morning versus evening light, hypothesizing that morning bright light (≥2500 lux at the cornea) should result in the most improvement with a phase advance in the rest-activity rhythm of ADRD patients. Conversely, afternoon light exposure would phase delay the rhythm. No significant differences in actigraphy-based measures of nighttime sleep or daytime wake were found. However, both groups evidenced a significantly more stable rest-activity rhythm acrophase over the 10-week treatment period compared to the controls. The study concluded that 1 h of bright light exposure may provide sufficient additional input to the circadian pacemaker to facilitate entrainment to the 24-h day. When examining morning light therapy treatment, their results indicated that subjects with the most impaired rest-activity rhythm responded significantly and positively to the 1-h light intervention [65].

McCurry *et al.* [66] tested the effects of walking, light exposure and a combination intervention (walking, light and sleep education) on total wake time and subjective sleep quality in ADRD patients living in independent community settings. Participants in the walking, light and combination intervention showed significant improvements in total wake times and sleep efficiency, and the effect was larger in those who had greater adherence to the experimental protocol.

Sloane *et al.* [67] showed a statistically significant improvement in nighttime sleep with morning or all-day light (>2500 lux at the cornea), with greater improvement among persons with severe dementia. The authors claim that the effect size was greater than has been reported using prescription sleep medicines in long-term care populations. Using the same data set, Hickman *et al.* [68] showed that, compared to all day and evening light exposures, morning light had the greatest effect on both sexes. Depressive symptoms were decreased in women and increased in men after morning light exposure.

To determine whether the progression of cognitive and non-cognitive symptoms may be ameliorated by individual or combined long-term application of bright light and melatonin, Riemersma-van der Lek *et al.* [69] conducted a long-term, double-blind, placebo-controlled study with 189 elderly patients with dementia living in nursing homes. Light alone was found to attenuate both cognitive deterioration by as much as 5%, as determined by the Mini Mental Status Examination and the increase in functional limitations, as determined by the Activities of Daily Living Scale. Oral melatonin alone shortened sleep onset latency and increased sleep duration, but also increased withdrawn behavior. The light and melatonin treatment increased sleep efficiency and improved nocturnal restlessness, thus indicating that the adverse effect of melatonin on mood can be counteracted when administered as part of treatment with light for cognitive and non-cognitive function.

However, not all studies to date have shown a positive effect of light on sleep disturbances or rest-activity rhythms of those with dementia. In the study by Ancoli-Israel *et al.* [70], bright light exposure (2500 lux at the cornea) did not produce significant improvement in nighttime sleep and daytime alertness. The authors suggested that these negative results were due to level of dementia. They did, however, find that increasing the exposure to morning light made the circadian rhythm of rest-activity significantly more robust in this population. Dowling *et al.* [71] found no effect of light treatment alone on nighttime sleep, daytime wake, or rest-activity rhythms, but were able to demonstrate an increase in daytime wakefulness and activity levels with concurrent administration of oral melatonin. Sloane *et al.* [72] showed a positive effect of a tailored light treatment (bluish white light, correlated color temperature = 13,000 K) designed to deliver 400 lux at the cornea, in self-reported sleep in caregivers of ADRD patients living at home, but not in sleep and behavior of the patients themselves. Van Hoof *et al.* [73] did not find a significant effect on behavior and tympanic temperature rhythms in dementia patients after they were exposed to 500 lux at the cornea of a 17,000 K light source. Burns *et al.* [74] exposed dementia patients to either 10,000 lux at the cornea (treatment condition) or 100 lux at the cornea (control) of light for 4 consecutive weeks and measured agitation and depression scores as well as actigraphy. Results showed very little effect of light treatment on agitation and depression and only a slight indication that sleep was improved, especially in the winter months. Colenda *et al.* [75] used light visors to deliver 2000 lux of light at the cornea each morning for 10 days to community-dwelling AD patients and found no consistent biological effect of the light treatment on sleep, noting that perhaps light visors may be an inadequate means of providing light treatment.

Given that not all of the published studies yielded positive outcomes, it is not surprising that a Cochrane review conducted in 2004, which included only 5 studies that met their inclusion criteria (relevant, randomized controlled trials in which bright light treatment was compared to a control group for the effect on managing sleep, behavioral, mood or cognitive disturbances), concluded that there was not enough evidence to assess the value of light treatment for people with dementia [76]. A recent Cochrane review conducted in 2014 included 8 studies that met their inclusion criteria and that had available data for their analyses. Authors, again,

concluded that there is not enough evidence to justify the use of light therapy to improve sleep and behavior in ADRD patients [77].

One explanation for the mixed results may be that current light therapy approaches for sleep disturbances in older adults are not formalized in terms of intensity, spectrum, timing, distribution and duration, leading, in some cases, to a weakening of the therapeutic effects of light. In fact, Forbes *et al.* in their latest Cochrane review [77] analyzed studies that used a variety of light therapy approaches. None of the studies included in their analyses controlled or measured actual light dose received by participants. Pooling data from these studies where the various light delivery methods were used without any control of how much light subjects were actually being exposed to during the intervention may have affected the outcomes of their analyses. This is an important point to consider, because in studies where carefully controlled light stimulus was delivered, a positive impact of light on sleep quality of those with ADRD was in fact found [78,79].

In general, the only formalized recommendations of light treatment (intensity, spectrum, and duration) are those used for treating symptoms of seasonal affective disorder (SAD). Sufferers of SAD are expected to be exposed to 10,000 lux at the cornea of white light for 30 min or 2500 lux at the cornea of the same white light for 2 h. Those recommendations were developed based on studies conducted by Lewy *et al.* [80] nearly 30 years ago, when the knowledge of non-visual effects of light on circadian regulation was very limited. While this recommendation has been successful in treating symptoms of SAD, clinicians often find that patients have a difficult time complying with the recommendations because the high light levels of white light can be very uncomfortable, resulting in squinting and gaze aversion. Since much more is now known about the retinal phototransduction mechanisms that drive the circadian system, there is a much higher likelihood that more modest and more comfortable light doses can be used as a reliable, non-pharmacological treatment for circadian sleep disturbances so commonly found in those with ADRD. In fact, Figueiro *et al.* [78] recently showed a positive effect of a more comfortable lighting intervention designed to maximally affect the circadian system in ADRD patients living in long-term care facilities. The same principle can be used in any population suffering from circadian sleep disorders.

5. MOVING FORWARD

Although there is not a complete understanding of the effects of light on the aging circadian system outside laboratory conditions, it is clear that a distinct, repeated pattern of light and dark is needed to help maintain the synchrony between the aging circadian system and the solar day [81]. With that in mind, it is important to design separate lighting systems for daytime and nighttime activities. Lighting in the built environment should provide (a) high circadian light stimulation during the day and low circadian stimulation at night, (b) good visual performance (e.g., reading) during waking hours, and (c) low-level nightlights that enable safe navigation through the space and that minimize sleep disruption.

During daytime hours, light levels in indoor environments should be high enough to activate the circadian system. This can be accomplished with the use of daylight or electric lighting systems. Care should be taken to avoid introducing glare in the space. The combination of high levels of "cool" light sources (a minimum of 400-600 lux at the cornea and CCT >6500K) during the day and "warm" light sources (no more than 80-100 lux at the cornea; CCT <2800K) in the evening promotes circadian entrainment better than current lighting system designs (i.e., constant dim light). As detailed in Figueiro [81], the cool light source at that light level for a 1 h duration will provide good circadian stimulation. A similar lighting specification was shown to improve restless behavior in patients with dementia [82].

In addition to impacting the aging circadian system, light can also impact the aging perceptual system. Sight and visibility are important for good perception; therefore, it is important to provide light that will support the perceptual system. At night, light levels should be dim and allow for safe navigation, especially in bedrooms and bathrooms [81,83-85]. It is also important to encourage older people to increase their exposure to light-dark patterns as part of their wellness program. Daylight can be added into the home environment, especially in long-term care settings, by adding skylights, clerestory windows, and sunrooms.

Future clinical research should focus on testing these new lighting schemes that are designed to specifically deliver a strong daytime circadian stimulation to ADRD patients. But, it is imperative that the light dose that subjects are receiving be measured. It is also important to point out that light therapy that promotes better sleep may not only improve the quality of lives of those with ADRD and their caregivers, but it may also have an important clinical relevance. Recent research suggests that sleep quantity and quality may be directly linked to ADRD [86,87]; therefore, studies should be designed to remove barriers to the use of effective non-pharmacological therapies that increase sleep efficiency. Finally, when assessing the effect of light on sleep and behavior in ADRD patients, it is important to also consider other environmental factors and comorbidities (e.g., ophthalmological diseases [88]) and other therapies, such as cognitive behavior therapy and exercise [66]. Future studies should investigate if the light can be more effective at treating sleep and behavior disturbances if combined with some of these other therapies.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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