Circadian Lighting Research White Paper

About the Research

The Arrow Innovation Catalyst Project is part of Newcastle University and in 2021 they were asked by Circadacare to conduct thorough research into three broad areas relating to older adults and those living with dementia:

- What are the requirements for light intervention which will suit most older adults in care and will improve their health?
- What evidence is there to back up claims around the benefits of circadian lighting for older adults?
- What are the areas of future work and potential improvements in the area of circadian lighting?

The research was carried out by Dr Rebecca Hanna and Kasia Zmarzly pf Newcastle University's Arrow institution, under the supervision of Professor Anya Hurlbert, who is a world expert in visual neuroscience with a research focus on human visual perception of colour. In addition, research into published studies and reports was carried out by Naomi Gross, a PhD student supervised by Professor Hurlbert, who studies the effects of light on wellbeing and behaviour.

Key Findings

The importance of managing blue light for older eyes. There is a trade-off between providing stimulation to the non-visual pathway to optimise circadian rhythms and guarding against damage to the eye. Short-wavelength light at high doses damages the lens and the retina (the "blue light hazard"), yet short-wavelength light is also the most effective in activating melanopsin, the photopigment in the intrinsically photosensitive retinal ganglion cells (ipRGCs) that feed into the non-visual pathway that governs the sleep/wake cycle and other biological rhythms. In older people, accumulated light toxicity contributes to cataract formation, which in turn reduces the amount of short-wavelength light that reaches the retina. Cataracts – and the less extreme age-related yellowing of the lens - are therefore protective against further light-induced damage but also reduce visibility as well as the effectiveness of short-wavelength light stimulation of the non-visual pathway. Other age- related changes in the eye, such as restriction of pupil size, also reduce the overall amount of light that reaches the retina.

For older people, light during the day should be bright enough to ensure good vision, contain enough melanopic lux to ensure good sleep/wake cycles and sleep quality, but low enough in very short wavelength power to guard against further eye damage.

it is clear that the melanopic lux and photopic lux (brightness) of light needs to be personalised / tailored to each individual, depending on their eyes, their environment, and their personal biological rhythms. Lighting therefore needs to be tuneable both in spectrum and in overall irradiance. It is important to remember the amount of melanopic lux depends not only on the light spectrum and overall irradiance but also on the individual's eyes.

The effectiveness of good lighting in preventing falls. Poor vision and poor cognition both contribute to the likelihood of falls. The visual and non-visual effects of improved lighting may therefore also reduce the incidence of falls. Falls are more likely to occur at night, when there is poor lighting. Falls are also more likely to occur in people with disrupted circadian rhythms. Appropriately designed light delivery might therefore be a powerful therapeutic agent in helping to regulate and strengthen circadian rhythms as well as enable better vision at night without disrupting sleep.

Background Definitions

Bioadaptive lighting

Bioadaptive lighting is a culmination of the light spectrum (shape of spectral power distribution with reference to dominant wavelengths, and overall irradiance level), timing of light delivery, spatial distribution, and personalisation to an individual. Different spectral shapes and irradiance levels will have different melanopic lux- the power to activate the non-visual circadian system – which is distinct from photopic lux – the brightness seen by the visual system. It is now widely accepted that melanopic lux needs to be included in the specification of lighting. The aim is to regularise circadian phase to improve mood, alertness, performance and sleep-wake patterns.

Colour

Wavelength content and the shape of the spectral power distribution of light are colloquially referred to as colour, but it's important to use this term correctly. "Colour temperatures" are generally divided into "warm" (more orange/yellow) or "cool" (bluer) lights but note that Correlated Colour Temperature does not uniquely determine the chromaticity of light. Melanopic lux content (the level of stimulus to the non-visual pathway, or the circadian stimulus) can be altered without changing the visible colour (chromaticity) or brightness (photopic lux) of the light, therefore keeping the "colour temperature" the same. Such changes do, though, change the "colour rendering index" of the light spectrum.

Circadian Stimulus (CS) versus Equivalent Melanopic Lux (EML) and Melanopic EDI

The term melanopic lux is a direct measure based on spectral sensitivity of the melanopsin pigment, and directly related to dose-response curves in biological systems, so is more widely used by biologists/colour scientists. Circadian Stimulus (CS) incorporates melanopic lux but transforms it non-linearly to predict the behavioural effectiveness of light. This

transformation/predictive power is not fully tested or empirically proved, so is generally considered to be an estimate rather than an exact prediction of effectiveness in any given situation. The CIE (2018) also recommends the use of Melanopic Equivalent Daylight Illuminance or Melanopic EDI, which is directly derived from melanopic lux, and is the photopic illuminance (photopic lux) of a 6500K daylight (D65) that provides the same melanopic illuminance as the specified light.

How the ageing brain and eyes affect circadian function

For successful interaction between the mammalian body and environment the brain has a master clock (circadian pacemaker) within the suprachiasmatic nucleus (SCN) of the hypothalamus. In anticipation of variations in the environment, it uses external cues to drive circadian rhythms in activity and rest (sleep), body temperature, feeding behaviour, and hormones, communicating in turn with other brain regions and body tissues.

It is well established that with advancing age the circadian timing system is progressively disturbed, and changes in the SCN have been described for hormonal rhythms, body core temperature, sleep–wakefulness and several other behavioural cycles.

Figure 1 *A simplified schematic of the circadian system taken from Videnovic et al. (2014). The timing of human biological rhythms is synchronized to the rotation of the Earth and is influenced by numerous external and internal time cues. These stimuli are known as 'zeitgebers' (German for 'time giver'). Light is the most important and potent zeitgeber. In addition to light, activity, feeding schedules, and the hormone melatonin also influence circadian timing. This loss of coordination of circadian rhythms can have negative consequences for sleep–wake cycles and numerous other biological functions.*

These changes are exacerbated in dementia, particularly Alzheimer's disease (AD) where the severe circadian dysfunction is one of the most important factors leading to institutionalisation. Indeed, some of the strongest evidence to link disruption of the circadian clock and sleep disturbance has come from studies in patients with dementia, and post-mortem brain tissue has revealed degeneration of neuronal populations within the hypothalamus SCN region. Numerous studies have used wrist worn actigraphy devices to clearly demonstrate differences in rest-activity patterns of patients with AD through the day and night, whereby the amount of circadian disruption correlates with disease progression.

A report by Wulff et al. (2010) summarised the wide-ranging health consequences of neurodegenerative disease (e.g., dementia) in Figure 2 - classified by emotional, cognitive and somatic responses.

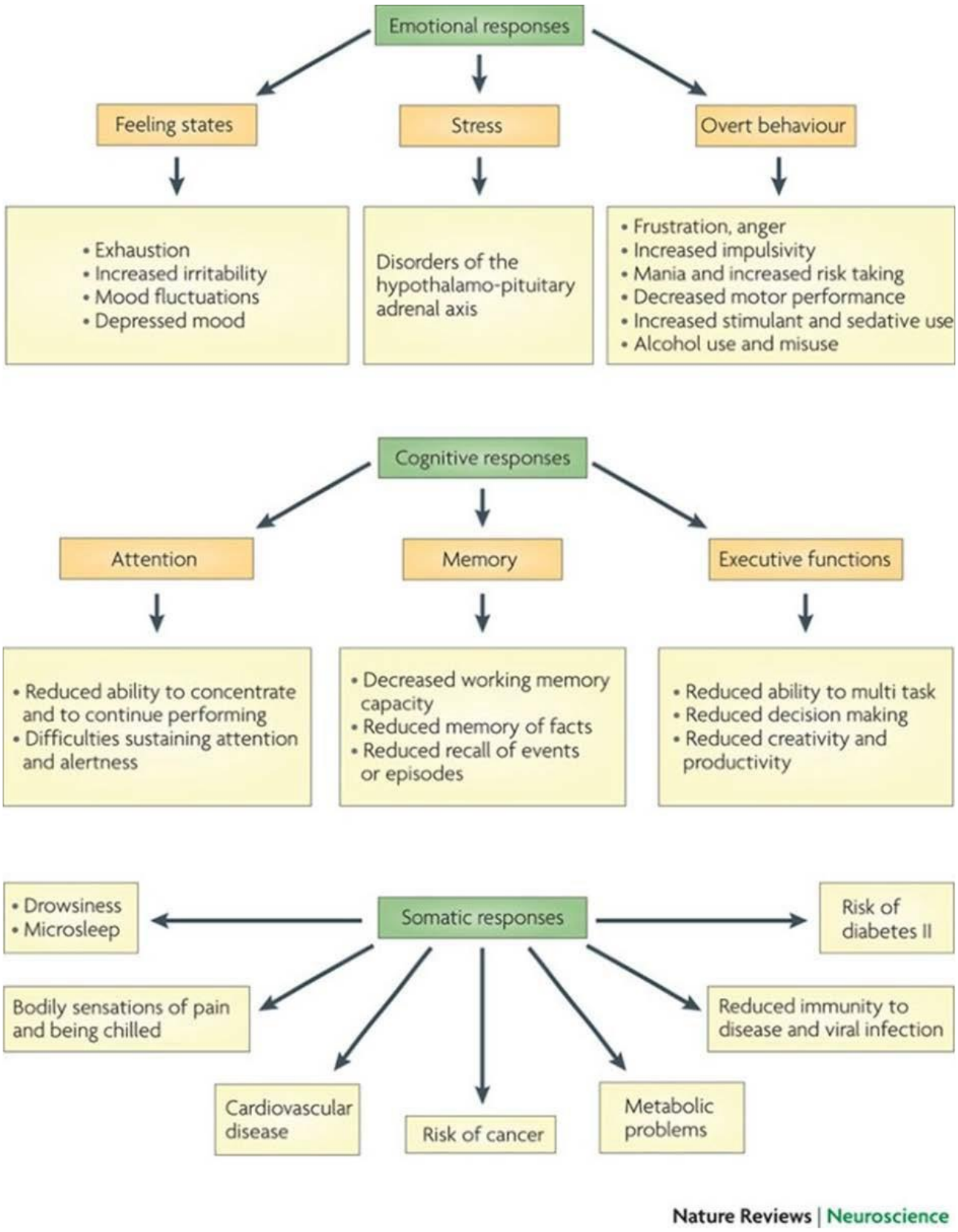

Figure 2 *The health consequences of shortened or reduced sleep and desynchronized circadian rhythms, classified by emotional, cognitive and somatic responses. (Wulff et al., 2010)*

The Ageing Eye

In addition to the brain, age-related ageing of the eye and eye conditions have an impact on circadian function. Asides from eye function in relation to vision, whereby cones allow us to see colour, spatial detail and motion at light levels typical for daytime, the eyes deliver non-visual environmental light cues from the retina to the SCN. It is well established that short wavelength (446-477nm) light induces melatonin suppression/phase shifting/increased alertness, but natural ageing of the human lens and decrease in pupil size (pupillary miosis) reduces transmission of those wavelengths to the retina. Age-related changes in the eye include changes in both number and function of the classical photoreceptors (rods and cones). Furthermore, age-related eye conditions and retinopathies impair ocular light transmission (particularly short wavelength blue light) to the SCN even further, e.g., cataracts, macular degeneration, glaucoma. It is also of relevance that a large study of 632 visually impaired older adults (>60yrs), found they were significantly more likely to have a depression or anxiety disorder than their non- visually impaired peers, with the most prevalent anxiety disorders being agoraphobia and social anxiety.

However, it is recognised that light can also damage the eyes, induce and exasperate eye conditions. There is a view that the amount of cumulative short-wavelength light exposure throughout life could be a factor behind age-related macular degeneration. One study argues that LEDs with peak emission of 470-490m are safer for ocular health than those of 400-460nm range.

Studies investigating lighting with the older adult and older adults with dementia

The therapeutic use of light to affect our health and well-being (e.g., sleep, mood) is an ever- changing field that can be broadly thought of as before and after the discovery of the photopigment melanopsin, which has a peak spectral sensitivity around 480nm. The culmination of this discovery and the technological advancement of LED technology which can fine-tune light spectra has led to some very recent positive clinical trials/intervention studies that are summarised here briefly.

Summary conclusions of some recent clinical trials and intervention studies looking at the use of bioadaptive lighting in elderly and elderly with dementia

1. Figueiro et al. (2020) USA, Clinical Trial : 6-month care-home based clinical trial (24 weeks with lighting intervention, 32/47 participants completed study) found regular daytime tailored lighting intervention (TLI) improved night-time sleep and reduced agitation/depression in elderly with Alzheimer's and related dementias (ADRD). Aim was to provide daily dose of 0.4 CS. Effects were cumulative over time, and effect differences found between sexes and severity/progression of dementia. The TLI were the same as Figueiro et al. (2019) and well tolerated. This study expands on the findings of Figueiro et al. (2019) with two key differences - participants are receiving the lighting intervention for 24 weeks instead of 4 weeks, and this study does not have a placebo group or cross-over design. Clinical trial number not provided in paper.

2. Figueiro et al. (2019) USA, Clinical Trial: 14-week care-home based clinical trial (4 weeks with lighting intervention, 46 participants) found regular daytime tailored lighting intervention (TLI) improved night-time sleep and reduced agitation/depression in elderly with Alzheimer's and related dementias (ADRD). Aim was to provide daily dose of 0.4 CS. The TLI were the same as Figueiro et al. (2020) and well tolerated.
3. Rubiño et al. (2020) Spain, Research Intervention Study: 3-week care-home based study (1 week lighting intervention, 37 participants), found 90 mins daily morning Bright Light Therapy (BLT) had positive effects on the cognition and circadian cycles (sleep/wake and temperature) of elderly residents. Participants sat at a worktable performing daily tasks (e.g., reading, writing, social activity). During weeks 1 and 3 they were exposed to habitual light levels, but during week 2 the table lighting provided BLT (7000-10000 lux, 350-750nm, at 40-60cm from the eyes).
4. Bromundt et al. (2019) Switzerland, Clinical Trial: 5-month care-home based study (8 weeks of lighting intervention, 20 participants) investigated the effects of a dawn-dusk simulation (DDS) prototype (above resident bed) on circadian rest-activity cycles, sleep, mood and well-being in dementia patients. DDS was well tolerated, although only significant findings were a better mood and cheerfulness upon awakening (subjective data from caregivers). Clinical trial number not provided in paper.
5. Hopkins et al. (2017) UK, Research Intervention Study: 12-week care-home based study (4 weeks of lighting intervention, 69/80 participants completed study) investigated the effects of a high colour temperature blue-enriched white communal lighting intervention (versus control white lighting) on mood, alertness, rest-activity rhythms and sleep of elderly. Blue-enriched lighting produced some positive (increased daytime activity, reduced anxiety) and negative (increased night-time activity, reduced sleep efficiency and quality) effects in older people. They don't comment on how well tolerated the light was.

Summary of recent clinical trial and research studies assessing circadian-effective lighting (published 2017-20)

1. Clinical Trial, USA -New York District, Figueiro et al. (2020)

Research question: What are the effects of a tailored lighting intervention (TLI) on sleep quality, rest–activity, mood, and behaviour in older adults with Alzheimer's disease and related dementia (ADRD)?

Study details: 47 ADRD patients across 9 care facilities (data analysed for n=32, 27 females (mean age 88.8yrs), 20 males (mean age 80yrs)), 6-month trial, TLI were timer activated and continuous between ≈06 : 00–08 : 00 to 18 : 00, with habitual waking time tailored to the individual. The existing facility lighting, delivering a CS < 0.1 at eye level, was used in all spaces after18:00. Participants had a private bedroom and spent daytime in communal areas, with devices located where individual spent most time.

Key findings and emerging questions:

- Pittsburgh Sleep Quality Index (PSQI) results significantly decreased from baseline mean 11.89 to mean 5.36 by week 24, whereby score >5 indicates threshold of sleep disturbance
- Depression mean Cornell Scale for Depression in Dementia (CSDD) scores significantly decreased from baseline mean 10.89 to mean 5.65 by week 25, whereby total scores >12 indicate probable major depression
- Agitation mean Cohen-Mansfield Agitation Inventory (CMAI) Agitation CMAI scores significantly decreased from baseline mean 45.06 to mean 37.21 by week 25, whereby scores >45 indicate clinically significant agitation
- Regular daytime tailored lighting intervention improved night-time sleep and reduced agitation/depression – authors attribute this to long exposure duration
- Outcomes appear cumulative over time – unknown what long-term adaptation to stimulus would be
- Differences in data between males and females despite this not being an aspect of the study design

2. Clinical Trial, USA, Figueiro et al. (2019)

Research question: Does Long-Term, All-Day Exposure to Circadian-Effective Light Improve Sleep, Mood, and Behaviour in Persons with Dementia?

Study design: 46 ADRD patients across 8 care facilities (30 females (mean age 85.3), 16 males (mean age 83.1)), 14-week trial, all other details as for Figueiro et al. (2020) except this was a randomized, placebo-controlled, crossover design (1 week baseline, 4 weeks of active/control intervention, 4-week washout, 1 week baseline, 4 weeks of active/control intervention).

Key findings and emerging questions:

- Sleep mean Pittsburgh Sleep Quality Index (PSQI) scores were significantly lower after the active intervention (from 10.3 baseline to 6.67), than control (from 9.8 baseline to 8.41), whereby score >5 indicates threshold of sleep disturbance
- Depression mean Cornell Scale for Depression in Dementia (CSDD) scores were significantly lower after the active intervention (from 10.3 baseline to 7.05), than control (from 10.73 baseline to 9.61), whereby total scores ~7 indicate no depression, ~10 indicate mild depression >12 indicate probable major depression
- Agitation mean Cohen-Mansfield Agitation Inventory (CMAI) scores were significantly lower after the active intervention (from 42.65 baseline to 37.14), than control (from 42.71 baseline to 41.21), whereby scores >45 indicate clinically significant agitation
- There were no differences between groups for Minimum Data Set Activities of Daily Living Scale (MDS-ADL)
- The light was also well tolerated by the participants, which is crucial for the effective delivery of a lighting intervention in real-world application

3. Research Intervention Study, UK – England, Hopkins et al. (2017)

Research question: Is a colour temperature (17000 K; ≈ 900 lux) blue-enriched white light better than a low colour temperature (4000 K; (≈ 200 lux) white light better for older peoples' mood, alertness, rest-activity rhythms and sleep?

Study design: 80 residents (69 females, mean age 85.8yrs) across 7 care homes. Inclusion criteria was >60yrs who spend time each day in communal rooms where lights were installed. The study design had different levels of participation that allowed residents to complete as much as they wished or were capable of. A general health questionnaire was completed (vision, mobility) and medications noted for each participant at the beginning of the study. 40% were taking antidepressants, 16.3% were taking hypnotics, 12.5% were taking anti- psychotics and 12.5% were taking glaucoma medication. 65% had mild cognitive decline, but none had diagnosed dementia. A 12-week study of randomised cross-over design which included 1 baseline week (normal lighting), 4 weeks of active/control lighting, 3 weeks washout (normal lighting), and 4 weeks of active/control lighting. Lights were installed in communal lounges and dining rooms (n = 20) used frequently by the residents. The light luminaires were suspended overhead from free-standing Dexian frames, built specifically for each room. The two light conditions differing in colour temperature and spectral power distribution (see spectra)

Key findings and emerging questions:

- Blue-enriched (17000 K) light increased wake time and activity during sleep, decreasing actual sleep time, sleep percentage and sleep efficiency
- Blue-enriched 17000 K lighting significantly advanced the timing of participants' rest- activity rhythm, increased daytime and night-time activity, reduced subjective anxiety and sleep quality (PSQI).
- Blue-enriched lighting produced some positive (increased daytime activity, reduced anxiety) and negative (increased night-time activity, reduced sleep efficiency and quality) effects in older people

4. Pilot Study – USA, California, Konis et al. (2018)

Research question: effects of indoor daylight exposure on depression and other neuropsychiatric symptoms in people living with dementia in long-term care communities

Study design: 12-week study across 8 dementia care homes, whereby 4 care homes were an intervention group and the other 4 a control group. 46 participants completed the lighting intervention, and 31 participants completed the control. Mean age of 85.3yrs, 92.2% were white ethnicity, 72.7% were female.

Intervention: staff increased the daylight exposure of participants by taking them to the perimeter zone of a daylit room from 8:00 to 10:00 AM for socialization over a period of 12 weeks. The perimeter zone was defined to be the region of the room within 3 m from the windows. The intervention was administered each day (7 days/week) over the duration of the study.

Key findings and emerging questions:

- Participants in the daylight intervention experienced an average decrease over the trial in the Neuropsychiatric Inventory Nursing Home Version (NPI-NH) scores and the Cornell Scale for Depression in Dementia (CSDD) scores. It was statistically reduced in CSDD only. These trends weren't found in the control group.

- Overall, the mean average melanopic illuminance (mLuxAVG) level measured in the daylight intervention spaces (159.3) was 3.8 times greater than the mean value for the control spaces (42.3)
- The mLuxAVG measures were found to be significantly inversely correlated with the change in CSDD over the trial , suggesting that greater levels of melanopic illuminance are associated with a greater reduction in depression symptoms

Risk factors for falls – direct/indirect role of age, vision, sleep and cognition

Attribution of the causes of falls is multifactorial and could be ascribed to the following types of causes: intrinsic (due mainly to medical conditions) and extrinsic (largely arising due to environmental factors). Extrinsic factors are related mainly to environmental situations (eg, inadequate lighting, presence of obstacles, slippery surfaces, absence of handrails, among others).8 In addition, Montero-Odasso (2018) highlights the importance of cognitive impairments such as lack of attention that compromises postural and gait stability and executive functions such as impairment of attention, inhibitory control, working memory and cognitive flexibility thus leading to falls. Ageing is associated with weakening of the circadian system. Poor vision and poor cognition are contributing factors to the likelihood of falls.

Vision and falls

The WHO-funded LARES study looked at the relationship of residential light and risk of depression or falls in 6017 European residents (Brown and Jacobs, 2011). They found that participants reporting inadequate natural light in their dwellings were 1.4 times as likely to report depression and 1.5 times as likely to report a fall compared with those satisfied with their dwelling's light. Those who reported falling were more likely to be female; in poor health; divorced/widowed/ separated; older than 70 years; have low income; have a self-reported handicap; work less than full time; and were likely to have fallen due to tripping over a structure (e.g., stairs, floor cracks). It's also well established that those with dementia, and those who are socially isolated are at greater risk of falls.

Circadian disruption, sleep and falls

In a recent study the link between fall risk, circadian rhythms and the role of melatonin was examined by Nandu Goswami (Falls Risk, Circadian Rhythms and Melatonin: Current Perspectives Goswami et al. 2020). The review seeks to assess the relationships between fall risk and the potential role circadian rhythms and melatonin play in mitigating this risk. The following are key extracts from the research review.

Melatonin is a hormone that is naturally made by the body, and its production is closely tied to light. In response to darkness, the pineal gland in the brain initiates production of melatonin, but light exposure slows or halts that production. Melatonin is an important physiological sleep regulator in humans. The sharp increase in sleep propensity at night usually occurs around two hours after the onset of endogenous melatonin production in humans.

The circadian amplitude of melatonin decreases as a function of age, raising the questions whether such a decrease in the circadian amplitude of melatonin relates to a higher risk of falls (Figure 3) and, if so, whether melatonin supplementation may be an effective countermeasure. Indeed, a direct link between sleep quality, falls risk and melatonin has been shown. For instance, sleep disturbances have been shown to be associated with increased risk of falls in older men. By improving sleep in older persons, the regulation of melatonin could play an important role in falls prevention in older persons.

One of the most relevant circadian rhythms is the sleep-wake cycle since it encompasses and orchestrates many other bodily rhythms. In aging, circadian rhythms become more fragmented, slow wave sleep (SWS) is reduced (which plays a key role in memory consolidation) and there is an increase of wakeful periods during the night and of inactivity intervals during the day (naps), which represents

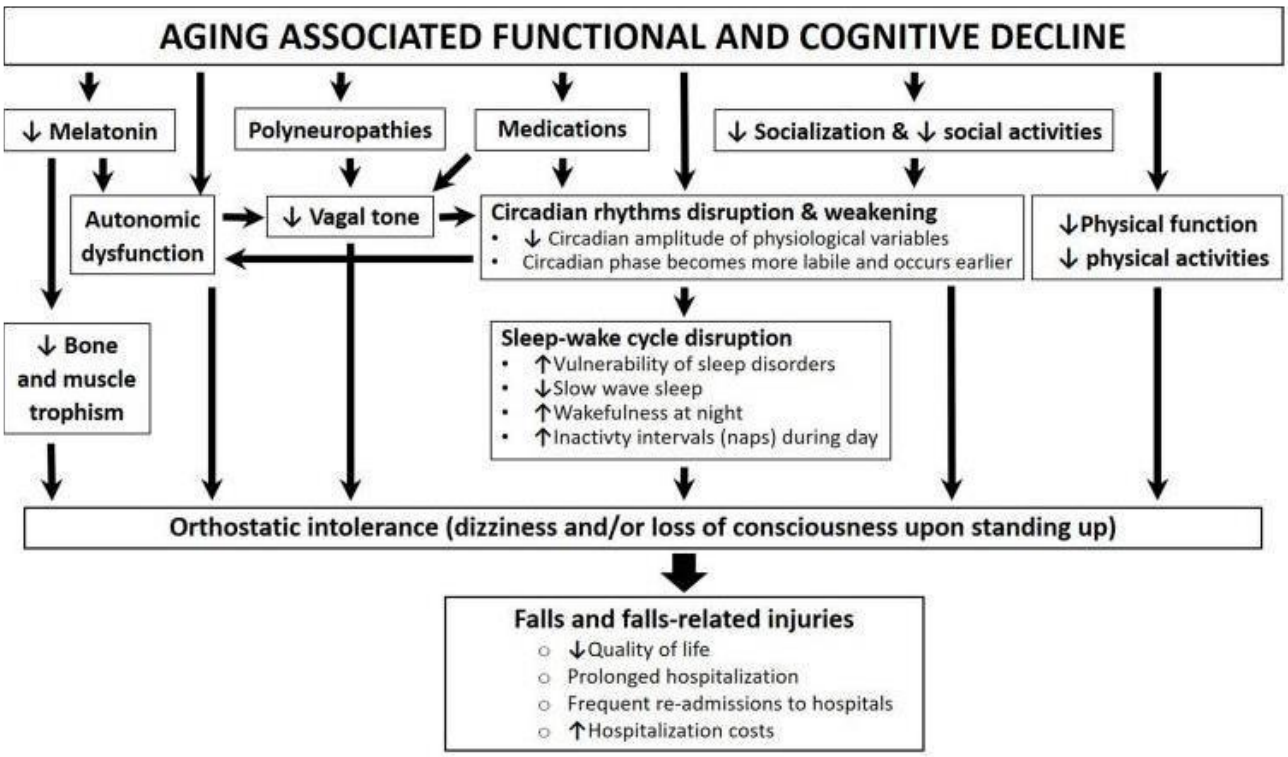

Figure 3 *Aging-associated functional and cognitive decline and its relationship with autonomic function, circadian rhythms, melatonin and falls (orthostatic intolerance). (Goswami et al. 2020)*

an age-related vulnerability to sleep disorders. In turn, sleep disorders exacerbate cognitive symptoms in subjects with increased risk of developing neurodegenerative diseases, accelerating the rate of cognitive decline in such patients. In addition, sleep

disorders have been reported to exacerbate behavioural, pathophysiological manifestations of dementia and changes in the circadian rhythm of activity are associated to higher risk of mild cognitive impairment and dementia.

Whether one is concerned with disease prediction and prevention or maintenance of healthy aging, the study of circadian rhythms and the broader time structure underlying physiopathology is helpful in terms of screening, early diagnosis and prognosis, as well as the timely institution of prophylactic and/or palliative/curative treatment. Timing the administration of such treatment as a function of circadian rhythms also could lead to reduction of falls in older persons.

There is no literature on the study of the circadian rhythm of the ANS yet given the existing research on the subject and the fact that HRV is a fast, non-invasive, affordable and easily implemented technique, a 24hr HRV assessment presents an attractive and promising approach to the study of frailty and falls in older persons.

Finally, a prominent circadian rhythm characterizes melatonin, which peaks during the night. The circadian amplitude of melatonin decreases as a function of age, raising the questions whether such a decrease in the circadian amplitude of melatonin relates to a higher risk of falls.

A two-year study conducted by investigators at Brigham and Women's Hospital and the Midwest Lighting Institute in the US and published in August 2022, showed a significant 43 percent reduction in the rate of falls in residents at long-term care facilities that utilised a tunable LED lighting system compared to control facilities that maintained standard lighting. The lighting was operated on a schedule that implements specific spectrum and intensity levels timed to regularize sleep-wake cycles and boost the daytime alerting effects of light, in a similar way to the Circadacare approach. The results were published in the Journal of the American Medical Directors Association.

"Falls among care home residents have major health and economic implications, and this study is the first of its kind to translate the known beneficial effects of tunable lighting on neurocognitive responses into a real-world setting and examine if changes in lighting spectrum and intensity throughout the day can reduce the risk of falls in the elderly," said Shadab Rahman, Ph.D. MPH, Investigator in the Division of Sleep and Circadian Disorders at Brigham and Women's Hospital and Assistant Professor of Medicine at Harvard Medical School. "We found that upgrading ambient lighting is a safe, effective, low-cost, low-burden preventative strategy to reduce fall risk in long-term care settings, one that has tremendous potential to save lives and improve patients' health and well-being."

The study was designed to assess the impact of a tunable lighting schedule on the rate of falls in long-term care home residents. The observational study examined two pairs of care homes (four sites total) with 758 residents. One site from each pair was selected for a solid-state tunable lighting system upgrade throughout the facility, while the other site served as a control.

At the experimental sites, the intensity and spectrum were changed throughout the day to increase exposure to short-wavelength (blue light) during the day (6 a.m. to 6 p.m.) and decrease it overnight (6 p.m. to 6 a.m.). Intensity and spectrum did not change throughout the day at the control sites with standard lighting. The number of falls was aggregated from medical records covering approximately 126,000 resident days to

compare the rate of falls per 1,000 resident days between the experimental and control conditions.

Results indicated a similar rate of falls between experimental and control sites before the lighting upgrade, whereas following the upgrade, the rate of falls was significantly reduced by 43 percent at the experimental sites compared to the control sites.

What remains unknown or unclarified within the field?

The Arrow study identified a number of areas which remain unresearched or lacking in evidence. A number of these will be the basis of further and future research.

- There are no studies looking at the effects of light on sleep/behaviour, whilst specifically considering environmental factors, co-morbidities (e.g., eye-disease, obesity, menopause), and lighting combined with other therapies or lifestyle changes (e.g., CBT, exercise, diet – example of DREAMS-START clinical trial for those with dementia (Livingston et al., 2019)).
- It is unclear if bioadaptive lighting is best suited as a preventative treatment to delay onset/progression of mild cognitive decline or dementia, rather than an intervention for the symptoms of established disease.
- No intervention studies were found that looked specifically at the non-visual effects of improved lighting as a means to reduce the incidence of falls
- Studies should include caregivers as well as elderly/elderly with dementia in their design, as it is recognised that caregivers (especially family) of those with dementia have chronic sleep problems which affects all aspects of their health and care capacity (Gao et al., 2019).
- Personalised circadian-effective dosing regimens are yet to be elucidated, which account for individual light exposure, lifestyle/behaviour, home environment, medical health (cognition, mobility, mental health, co-morbidities etc.), socio-economic background etc. Differences between males and females is an emerging interest in the field.
- Duncan (2020) recently reviewed unanswered questions related to the role of circadian rhythms in Alzheimer's (AD). Some examples include - Does sex influence the effects of aging on clock gene expression and overt circadian rhythms in the elderly or in AD patients or in individuals at risk of AD? Which physiological /environmental factors mediate the effects of aging on expression of clock genes in the SCN/hippocampus/cerebral cortex? Are aging changes exacerbated in humans by modern lifestyles that include light exposure at night, sleep restriction, and Western diets with a high fat and sugar content? If strategies to maintain or enhance robust circadian rhythms are implemented during young adulthood or middle age, will the risk of AD or its onset and progression be attenuated?
- Natural eyesight deterioration affects confidence performing independent tasks – is there a possible application for lighting technology with personal appliances e.g., washing machine, or memory prompts for dementia e.g., to drink water, use bathroom.

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