Light therapy for cancer-related fatigue in (non-)Hodgkin lymphoma survivors

Starreveld, D.E.J.

CHAPTER 1

GENERAL INTRODUCTION

Cancer-related fatigue in (non-)Hodgkin lymphoma

Hematological cancers represent the fifth most prevalent cancer in the Netherlands[1]. A relatively rare type of hematological cancer is Hodgkin lymphoma (HL) with an absolute incidence of 532 in 2019[2]. This cancer develops in het lymphatic system; more specifically, it is an abnormal multiplication of B-lymphocytes. HL is most often diagnosed in younger individuals (age between 15 and 44 years). In the past decades, treatments for HL changed from large radiotherapy fields to the combination of chemotherapy and radiotherapy with smaller radiotherapy fields. Responses to these improved treatments are good, with a current overall 10-year survival rate of 78 percent[3].

The good prognosis leading to a higher number of survivors caused an increased interest towards the late effects experienced by HL survivors. For example, increased risks to develop secondary cancers and cardio-vascular diseases are reported in this group[4]. In the Netherlands, the BETER consortium (better care after HL: evaluation of long-term treatment effects and screening) offers a healthcare infrastructure aiming to inform, screen, and treat HL survivors for these late effects[5]. In 2021, the BETER consortium included 22 hospitals. Within this consortium, radiation-oncologists, hematologists, epidemiologists, and psychologists work together to formulate treatment guidelines and conduct research to improve care for these survivors. More recently, diffuse large B-cell lymphoma (DLBCL) survivors were added to the BETER-consortium because the late effects in this group are comparable to the late effects reported in HL survivors. DLBCL is the most prevalent hematological cancer with an incidence of 1.548 in 2019[2]. This aggressive non-Hodgkin lymphoma (NHL) is most often diagnosed in individuals 60 years of age or older and has a 10-year survival rate of 45 percent[1, 2, 6].

The screening within the BETER-clinics focuses on somatic and psychological late effects influencing the daily life of HL and DLBCL survivors. One of the symptoms often reported to radiation-oncologists and hematologists is cancer-related fatigue (CRF)[7]. A previous study within the BETER-consortium showed a prevalence of CRF in HL survivors of 41 to 43 percent compared to 23 to 28 percent in the general Dutch population. Moreover, a study with more than 800 NHL survivors (mean survivorship 4.2 years [SD = 2.7]) showed that 61 percent reported clinically relevant and persistent fatigue[8]. The National Comprehensive Cancer Network (NCCN) defines CRF as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning"[9]. Survivors suffering from fatigue report feeling tired despite resting, have difficulties to complete normal activities, and have problems concentrating[10]. It affects the quality of life of these survivors[11] and is often reported in a cluster of symptoms including sleep problems, depression, anxiety, and pain[12-16]. Moreover, higher levels of fatigue are associated with more problems in cognitive functioning[17-19], which are also reported by lymphoma survivors[20].

Etiology of cancer-related fatigue

Despite the high number of cancer survivors that suffer from CRF, relatively little is known about the etiology of CRF. There are several hypotheses for the etiology of CRF, covering demographic, medical, psychosocial, behavioral, and biological factors[21-24]. This section describes the current

knowledge on the influence of these factors on CRF based on four systematic reviews covering information from patients and survivors with different types of cancer[21-24]. If available, specific results for HL are reported separately[25].

Demographic factors

The majority of studies investigating the association between demographic factors and CRF suggest the absence of associations of gender, age, marital status, ethnicity, education, employment, or income to CRF[21-24]. Some studies suggested that fatigue was associated with gender, age, marital status, employment, and income[22]. Yet, there is an inconsistency in these studies as not all of these studies report associations into the same direction[22]. For example, it has been shown that higher levels of fatigue occur in younger patients in breast cancer patients receiving chemotherapy[22] while in HL survivors, it has been shown that higher levels of CRF were reported by older survivors[25].

Medical factors

In general, no associations were found of CRF with disease-related variables, including diagnosis, tumor size, tumor stage, the presence of metastases, and time since diagnosis in cancer survivors[22, 23]. Moreover, no associations were found between CRF and treatment-related variables, including treatment (e.g. chemotherapy, radiotherapy, tamoxifen), time since treatment completion and the length of hospital stay[22, 23]. This is also confirmed in 5-years HL survivors as there were no associations of CRF with HL specific factors or treatment-related variables[25]. There is a significant positive association between CRF and the number of self-reported comorbidities[12].

Psychosocial and behavioral factors

There are consistent findings showing that higher levels of fatigue are related to higher levels of anxiety, depression, sleep problems, dysfunctional coping behavior, lack of social support, and stressful life events[21-23, 26]. Moreover, higher levels of baseline fatigue prior to treatment are associated with higher levels of fatigue at follow-up in HL survivors[25]. It has been shown that higher levels of CRF are associated with lower levels of physical activity and increased body mass index[21-23].

Biological factors

Multiple biological factors have been studied in the context of CRF. For these biological factors, a difference is made between *central fatigue* that originates in the central nervous system and *peripheral fatigue* that reflects the inability of muscles to perform a task[27]. For *central fatigue*, the most studied mechanism is cytokine dysregulation[21, 26-28]. This is based on the principle that inflammatory cytokines can induce fatigue and other changes in behavior[29]. It is proposed that cancer and cancer treatment activate the production of pro-inflammatory cytokines[30, 31] that may persist after treatment as the host deals with persisting pathogenesis and changes in homeostasis[21]. Nonetheless, it should be noted that results on the association between different types of proinflammatory cytokines and CRF are inconclusive[21, 26-28]. Another biological factor linked to central fatigue is a dysregulation of the hypothalamic-pituitary-adrenal (HPA)

axis[21, 26-28]. The HPA-axis is responsible for the production of the hormone cortisol following a daily rhythm and in response to stress. There is some evidence that breast cancer survivors with fatigue had lower cortisol levels during the day and a blunted response to a stressor compared to breast cancer survivors without fatigue[32, 33] suggesting a dysregulation of the HPA axis. Similar results have been shown for women with ovarian cancer and advanced cancer patients[34, 35]. Animal studies suggested that this might be a consequence of chronic inflammation[36]. A third biological factor that may influence central fatigue is circadian rhythm disruption[21, 26-28], which is described in more detail below. Other hypothesized mechanisms related to central fatigue are serotonin dysregulation and vagal afferent nerve function, although these hypotheses are primarily based on animal studies[26, 27]. Hypotheses for *peripheral* mechanism include a muscle metabolism dysregulation caused by adenosine triphosphate dysregulation and contractile properties[26-28]. However, it should be noted that these hypotheses are based on small sample sized (animal) studies[26, 27].

It is important to mention that these biological factors relate to each other, making the pathophysiology of CRF very complex[26, 27]. Cytokine dysregulation seems to play a crucial role as cytokines influence other described mechanisms, including the HPA axis, circadian rhythms, serotonin metabolism and vagal afferent activation, via signaling pathways and feedback loops. The HPA axis regulates cortisol and cytokine production, while the HPA axis itself is also influenced by serotonin. Moreover, cortisol, inflammatory cytokines and serotonin influence circadian rhythms and disrupted circadian rhythms influence the HPA axis.

Circadian rhythms

Circadian rhythms[37] are internally generated rhythms that have a cycle of approximately 24-hours. The name stems from the Latin *circa* (about) and *dies* (day). These rhythms are necessary to optimize physiology and behavior in anticipation on the regular changes in environmental light, temperature, and food availability because of the earth's daily rotation. For example, in anticipation of sleeping, the production of cortisol is decreased and the production of melatonin, a hormone that stimulates sleep, is increased in dim light situations to optimize bodily conditions for sleep (Figure 1). It is essential that these internal rhythms synchronize to the external environment. For example, when we travel to the east or the west, we want our biological clock to adjust to the external environment in that situation. Our biological clock, based in the superchiasmatic nucleus (SCN) situated in the brain, uses signals from the environment to entrain internal circadian rhythms to external circadian rhythms. These entraining signals are called *zeitgebers*. The most important *zeitgeber* is light. Other *zeitgebers* are temperature, food availability and, for humans, social obligations[37].

Disruptions of circadian rhythms and the association with CRF have been studied using different methods. First, actigraphy can be used to assess rest-activity rhythms, i.e. sleep-wake cycles (Figure 2)[38]. An actigraph is a wrist-worn tri-axial accelerometer. Based on movements, each epoch (for example, a period of 60 seconds) is categorized as being asleep or being awake. Together with information on bed times provided by the individual who wore the actigraph, it is possible to calculate sleep and circadian variables[38, 39], e.g. total time in bed, actual sleep time, and mid-sleep (the time between sleep onset and sleep offset). Results of actigraphy studies in patients with cancer showed that patients with higher levels of CRF showed more disruptions

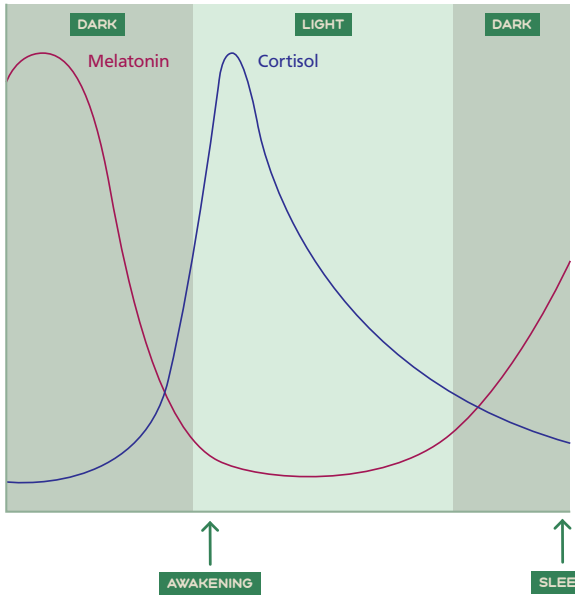

Figure 1. Circadian rhythm of cortisol and melatonin. Cortisol shows a strong increase in the early morning with a decrease during the day that reaches its lowest point during the night. Melatonin shows an increase in the evening in dim light conditions with the highest point during the night and a steep decrease in the early morning.

in their sleep-wake cycle, i.e. they had more awakenings during the night and were less active during the day[40-43].

A second method to study circadian rhythms is via the assessment of the secretion of hormones that follow a circadian rhythm, specifically melatonin and cortisol. Melatonin is the best marker of the internal rhythm in dim light conditions[44]. Its circadian rhythm shows increasing levels during the evening (in dim light conditions) that reaches its top during the night followed by a decrease that reaches its lowest point during the day[44]. To the best of our knowledge, there are currently no published results on the association between melatonin secretion and CRF. Cortisol shows a circadian rhythm with a steep increase after awakening followed by a gradual decline during the day that reaches its lowest point during the night. Besides the lower secretion of cortisol and the smaller response to stressors[32-35], some studies suggested that a disruption in this circadian rhythm is associated with CRF[34, 35, 45]. For example, it is shown that a smaller morning/night ratio of cortisol is associated with higher levels of CRF[34].

A third approach to study circadian rhythms is via self-reported questionnaires that include items on the sleep-wake rhythm. Examples of these questionnaires are the Munich Chronotype Questionnaire (MCTQ)[46], the Morningness Eveningness Questionnare (MEQ)[47], and the Composite Scale of Morningness (CSM)[48]. The outcome of these questionnaires is someone's chronotype, which describes an individual's preference in the timing of sleep and wake, also known as morning or evening types[46]. Morning types, or *larks*, tend to get up early and prefer to complete tasks in the morning, while evening types, or *owls*, tend to wake up later and prefer to complete tasks in the afternoon or evening. Individual differences in chronotype are

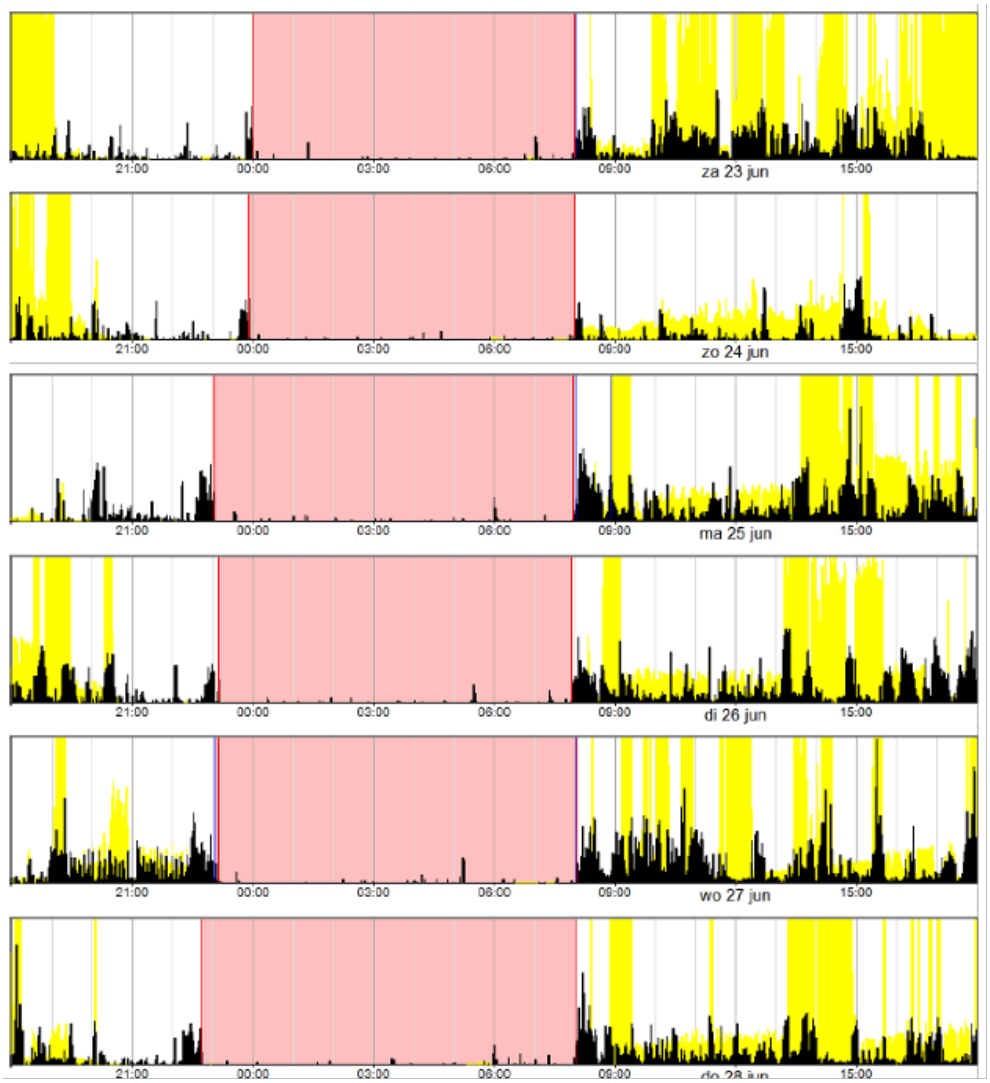

Figure 2. Example of an actigraphy measurement of six days. The black spikes represent activity as measured with the tri-axial accelerometer. The yellow spikes show when the light sensory detected light and at which intensity. The red area is the period during which the participant reported to be asleep. To determine this period, the participant pushed a button on the actigraph. These periods are used to calculate sleep variables like time in bed, sleep onset, sleep offset, got-up time, and sleep efficiency. The activity of the complete days are used to calculate non-parametric outcomes concerning the circadian rhythm like interdaily stability and intradaily variability.

the result of genetic variation (genes affect the temporal relationship between a zeitgeber and the biological clock[49-51]), weaker zeitgeber signals in the current society (the introduction of artificial light increases exposure to light in previously dim light situations), and age (adolescents are more likely to have later chronotypes, which shifts to earlier chronotypes after adolescence)[52]. Some studies showed that evening types reported higher levels of fatigue

compared to morning types in individuals with irritable bowel symptoms[53] and students[54]. As far as we know, the association between chronotype and fatigue in cancer populations has not been studied.

Assessment of cancer-related fatigue

Originally, the general concept of fatigue was conceptualized as a unidimensional construct but increased research interest for fatigue changed this view to a multidimensional concept of fatigue since the 1990s[55]. The first distinction was made into physical and mental components of fatigue[56, 57]. Nowadays, different views exist on the multidimensionality of fatigue. For example, Vercoulen et al. propose four domains: subjective experience of fatigue, reduced concentration, reduced motivation, and reduced physical activity[58]; while Schwartz et al propose three domains: situation-specific fatigue, consequences of fatigue, and response to rest/sleep[59].

The distinction between unidimensional and multidimensional fatigue is also reflected in the number of instruments that are available to measure CRF. Several review studies[60-62] identified a range of 14 up to 40 different questionnaires, although the validity and reliability for most of these questionnaires is questionable. Taken together, these reviews suggest that a 10-point numeric rating scale is the best screening tool for CRF[61, 62]. For the unidimensional construct, the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) fatigue subscale[63] and the Functional Assessment of Cancer Therapy-Fatigue subscale (FACT-F)[64] were suggested as questionnaires with excellent psychometric properties[60-62]. The Multidimensional Fatigue Symptom Inventory short form (MFSI-30)[65] and the Chalder Fatigue Scale (FQ)[66] were highly recommended for the assessment of multiple dimensions of fatigue [60-62].

Another assessment of fatigue recommended for measuring multiple dimensions of CRF is the Multidimensional Fatigue Inventory[67]. This scale aims to measure five dimensions of fatigue, including general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. After the initial validation[67, 68], the questionnaire became one of the most widely used fatigue assessments in Europe[69]. It has been translated and validated in multiple languages[70-83]. However, the original validation study did not only show an acceptable fit for the five-factor structure but also for two four-factor structures. One in which the dimensions of general fatigue and physical fatigue were combined and one in which the general fatigue items were removed[67]. Therefore, the authors suggested that additional research was necessary to investigate the additional value of the separate use of the general fatigue and physical fatigue subscales.

Treatment for cancer-related fatigue

Even though there is a high prevalence of cancer-related fatigue, radiation-oncologists and hematologists of the BETER-consortium have no standard treatment to offer HL and DLBCL survivors suffering from CRF. The NCCN guidelines[84] mention high-level evidence for non-pharmacological interventions, including physical activity, psychosocial interventions, and cognitive behavioral therapy for insomnia, which could be offered to cancer survivors to

reduce CRF. Lower-level evidence is available for pharmacologic treatments, including psychostimulants, for CRF. A recent meta-analysis[85] evaluated which intervention type is most effective in reducing cancer-related fatigue. A total number of 113 studies were included. The majority of the studies (n=69) investigated physical activity (including aerobic, anaerobic, or the combination of aerobic and anaerobic modes of exercise), followed by psychological interventions (n=34; including cognitive behavioral therapy, psychoeducation, or an eclectic method), pharmaceutical interventions (n=14; including paroxetine hydrochloride, modafinil or armodafinil, methylphenidate hydrochloride or dexymethylphenidate, dexamphetamine, or methylprednisolone) and the combination of physical activity and psychosocial interventions (n=10). Results showed that the largest improvement in CRF was seen after physical activity interventions, which are associated with a general weighted moderate effect size of 0.33. Psychological interventions and the combination of physical activity and psychological interventions showed similar improvements, with weighted effect sizes of 0.27 and 0.26, respectively. Pharmaceutical interventions led to significant improvements but these were associated with a smaller weighted effect size of 0.09. Therefore, it was concluded that physicians should prescribe physical activity and psychological interventions to reduce fatigue in patients suffering from CRF.

Despite the high number of studies showing promising results for physical activity and psychological interventions, these type of interventions are still not implemented as standard treatments for CRF. This might be due to limitations of these interventions. For example, fatigue has the characteristic to be a barrier to start physical activity meaning that not all fatigued survivors will be motivated to participate[86]. Moreover, most of the studied interventions are labor intensive, as they require professional guidance during the intervention. Therefore, it is interesting to seek for other interventions that are easy to deliver and have low costs and a low burden to complete. An example of such an intervention is light therapy, which is also mentioned in the NCCN guidelines based on lower-level evidence with consensus that the treatment is appropriate[84].

Light therapy

The history of light therapy is well described by Choukroun and Geoffroy[87]. Briefly, the importance and therapeutic effect of the sun, and thus light, was already mentioned by Hippocrates in his book *On Airs, Waters, Places*[88] at 400 BC. The modern use of light therapy stems from the 1980s when doctor Rosenthal described Seasonal Affective Disorder (SAD) and the antidepressant effect of light therapy on these depressive symptoms during autumn and winter[89]. Since then, many studies followed to test the efficacy of light therapy on reducing depressive symptoms[90, 91] and other symptoms like circadian rhythm disturbances and sleep disorders[92, 93]. While it has been shown to be effective to improve sleep and circadian problems[92, 93], the results for the efficacy of light therapy on mood disorders is promising but less conclusive[90].

The current guidelines on the treatment of SAD prescribe a standard protocol for light therapy[94, 95]. This protocol mentions that individuals should be exposed to bright light of at least 2.500 lux of white, fluorescent light without ultra-violet wavelengths. The preferred starting 'dose' is exposure to a light intensity of 10.000 lux for a duration of 30 minutes in the morning.

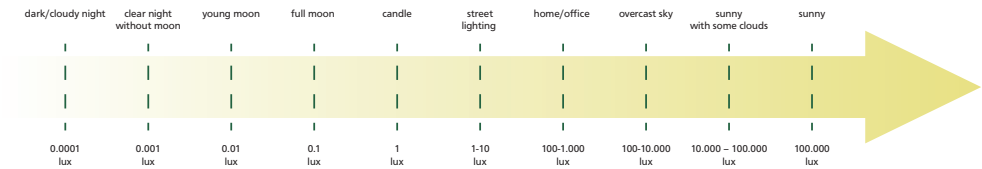

Figure 3. Overview of light intensities for different situations.

Figure 3 shows a comparison of this light intensity to daily situations. Individuals should position the light source closely to their eyes (no more than 50-80 centimeters apart) and the eyes should be open. Based on this protocol, patients with SAD usually show improvements within one week, which can take up to four weeks to achieve a full response[94].

Physiology of light

The exact mechanism of light therapy to improve mood, sleep and circadian rhythm disorders are not completely understood. To understand more about this mechanism it is important to learn more about the information processing of light by the retina and brain, which can be identified in two categories[87]. First, and best known, is *visual* information: light that falls on the retina is transferred to the visual cortex. This is primarily done by rods and cones, which are photoreceptors that transmit their signals via ganglion cells to the optic nerve for further processing in the visual cortex. The second type of information is *non-visual* and results primarily from light information processed by the intrinsically photosensitive retinal ganglion cells (ipRGC)[96, 97]. These cells transmit their signals via the production of melanopsin to non-image forming centers of the brain that are involved in the regulation of pupillary light reflex, sleep, arousal, and circadian rhythms[87, 96-99].

The mechanism of light therapy is attributed to this non-visual information processing. So far, the most studied pathway that explains the effect of light therapy is the influence of light on circadian rhythms[100, 101]. The link between light and circadian rhythms is strong, as light is the most important *zeitgeber* for circadian rhythms[37, 102]. This is the result of a direct association between of the ipRGCs via the retinohypothalamic tract to the superchiasmatic nucleus (SCN)[96, 97]. The SCN is the pacemaker of circadian rhythms, i.e. the human biological clock, that ensures entrainment of circadian rhythms to the environment via the secretion of hormones to signal circadian rhythms to other structures in the body[96, 97, 102]. The most important example is the secretion of melatonin by the pineal gland, which is inhibited in bright light conditions[103]. The effect of light therapy in the morning on melatonin is shown in figure 4. Exposure to light in the morning results in a phase advance of the circadian rhythm, i.e. the biological night, causing someone to feel alert earlier in the morning and sleepy earlier in the night. Light therapy in the evening prolongs the environmental day and therefore delays the biological night, causing someone to feel alert later in the morning and sleepy later in the night.

The rods, cones, and ipRGC have different photo pigments, which makes them most sensitive to light with different wavelengths, i.e. different colors. The rods are most sensitive to light of 492 nm (blue-greenish) and are necessary to process visual information in dim light circumstances[104]. Cones are necessary for distinguishing colors in normal lit situations with different sensitivity peaks for short (S, 420 nm, blue), medium (M, 533 nm, green color) and long (L, 562 nm, red color) wavelengths[104]. The ipRGCs are most sensitive for blue light (around

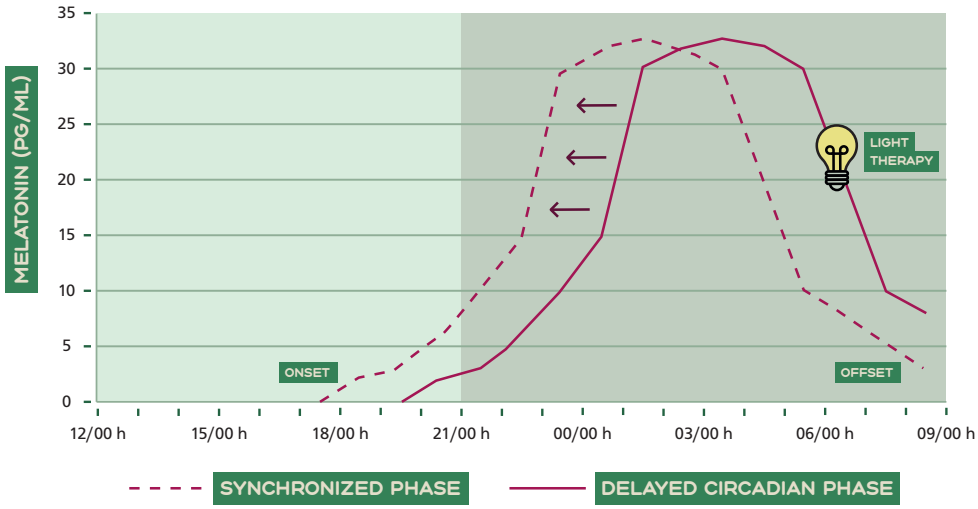

Figure 4. The effect of morning light therapy on the circadian rhythm of melatonin. In this case, the solid line shows a circadian rhythm of someone who has a delayed circadian rhythm, i.e. has problems to fall asleep during the night and difficulties to stay awake in the morning because the biological night is not synchronized to the environmental night. Light therapy in the morning cause a phase advance of light therapy. As a result, the onset of melatonin production is at an earlier time point, inducing sleepiness at an earlier time point.

460 nm) and therefore the circadian response is most strongly affected by blue light[98, 105]. Hence, the type of light used in light therapy is mostly enriched around these wavelengths.

Light therapy in cancer populations

At the start of the study described in this thesis, two pilot studies tested the efficacy of light therapy as a treatment for CRF in cancer populations[106, 107]. The first study was conducted by Ancoli-Israel et al in women with breast cancer undergoing chemotherapy to test the effect of light therapy during treatment[106]. Thirty-nine participants were randomized to a bright white light condition (BWL, intervention)or a dim red light condition (DRL, control). Results showed that the usual increase in CRF during chemotherapy (from baseline to the recovery week after a fourth cycle of chemotherapy) was present in the DRL condition but not in the BWL condition. This indicates that light therapy protected against a deterioration of fatigue during treatment. Secondary analyses with actigraphy data indicated that light therapy prevented circadian rhythm desynchronization[108]. More specifically, the group exposed to DRL showed circadian rhythm deterioration during the first and fourth chemotherapy treatment week, which did not return to baseline during the recovery weeks. However, the group exposed to BWL showed some deterioration of the circadian rhythm during the chemotherapy weeks but also showed statistically significant improvements of the circadian rhythm during the recovery weeks. Moreover, it has been shown that BWL prevented a quality of life deterioration, while individuals exposed to DRL showed lower levels of quality of life after chemotherapy[109].

Based on the positive effects of light therapy in cancer patients receiving treatment, Redd et al investigated the efficacy of light therapy on CRF in survivors of different types of cancer[107].

Thirty-six participants with a mean time since diagnosis of 1.4 years were randomized to a BWL of DRL condition and used light therapy for four consecutive weeks. The results were promising. Both groups showed an equal improvement in fatigue during the first two weeks, but during the last two weeks a clear difference was seen between the two groups. Participants exposed to BWL showed further improvements in fatigue that continued until three weeks post intervention, while the fatigue levels of participants exposed to DRL returned to baseline levels. The effect size of the difference in change of fatigue over time between BWL and DWL was large (d = 0.98). On an individual level, all participants in the BWL condition had fatigue levels below the cut-off score of clinically relevant fatigue, while 55 percent of the participants in the DRL condition still showed clinically relevant fatigue after four weeks of light therapy. A secondary analyses on sleep parameters showed that subjectively reported sleep quality and actigraphy derived sleep efficiency, total sleep time and wake after sleep onset improved for participants in the BWL condition and remained stable in participants exposed to DRL[110].

These first studies[106, 107] showed that light therapy is feasible and potentially effective as a treatment for CRF and symptoms related to CRF like depression, quality of life, sleep quality and sleep disturbances. However, sample sizes of both studies were small and the follow-up time was relatively short (until 3 weeks post intervention). Moreover, the effect of light therapy on biological outcomes, e.g. the circadian rhythms of cortisol and melatonin, has not been described. This information could provide new insights into the mechanism of action of light therapy and the etiology of CRF.

Light therapy and cognitive functioning

CRF is associated with cancer-related cognitive impairments[17-19]. Hence, it is clinically relevant to investigate whether light therapy also leads to improvements in cognitive functioning. Two types of studies can be identified. First, studies that investigate the direct effect of light on someone's cognitive functioning[111-115]. Results of these studies provide information on light settings in which individuals function best, for example, what type of lights in the office leads to the most optimal work environment for employers. Second, studies that investigate long-term exposure to light therapy (daily use of at least two weeks). So far, these studies have been reported for patients with dementia and mild traumatic brain injury with inconclusive results. Some showed positive effects[116-118], while other studies showed no effects[119, 120]. As far as we know, the effect of light therapy on cognitive functioning in cancer populations has not been studied before.

Thesis outline

In this thesis, we report on the SPARKLE study: a multicenter, double blind, randomized controlled trial (RCT) evaluating the effect of light therapy on CRF and related symptoms including sleep quality, psychosocial functioning, and circadian rhythms in HL and DLBCL survivors with CRF. **Chapter 2** describes the study rationale, design and methods of the SPARKLE study. In **Chapter 3**, we report the efficacy of light therapy on improving CRF, sleep quality, depression, anxiety, health-related quality of life, and objectively assessed circadian rhythms of sleep, cortisol, and melatonin. **Chapter 4** describes the efficacy of light therapy on subjective and objective cognitive functioning. **Chapter 5** reports on a cross-sectional study to evaluate the factor

structure and the optimal scoring algorithm of the Multidimensional Fatigue Inventory in the general Dutch population, which has been used as a primary outcome in the SPARKLE study. In **chapter 6**, we investigated the associations of CRF with chronotype and CRF with sleep quality in (non-) Hodgkin lymphoma survivors with and without CRF to learn more about potential working mechanisms of light therapy as a treatment for CRF. This thesis ends with an overall summary and a general discussion of the research and outcomes in **chapter 7**.

REFERENCES

1. Netherlands Comprehensive Cancer Organisation (IKNL). Incidentie hematologische kanker (2021) [January 2021]. Available from: https://www.iknl.nl/kankersoorten/hemato-oncologie/registratie/incidentie.
2. Netherlands Comprehensive Cancer Organisation (IKNL). Cijfers over kanker (2021) [January 2021]. Available from: https://www.cijfersoverkanker.nl/.
3. Favier O, Heutte N, Stamatoullas-Bastard A, Carde P, van't Veer M B, Aleman B M, et al. (2009). Survival after Hodgkin lymphoma. *Cancer*, 115(8):1680-91.
4. Aleman B M, van den Belt-Dusebout A W, Klokman W J, van't Veer M B, Bartelink H, van Leeuwen F E (2003). Long-term cause-specific mortality of patients treated for Hodgkin's lymphoma. *J Clin Oncol*, 21:3431-9.
5. Dekker N, Aleman B, Raemaekers J (2015). The BETER survivorship care initiative for Hodgkin lymphoma; tailored survivorship care for late effects of treatment. *Ned Tijdschr Geneeskd*, 159:A9269-A.
6. Pfreundschuh M, Trümper L, Österborg A, Pettengell R, Trneny M, Imrie K, et al. (2006). CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *The lancet oncology*, 7(5):379-91.
7. Aleman B M, van Leeuwen F E (2007). Are we improving the long-term burden of Hodgkin's lymphoma patients with modern treatment? *Hematol Oncol Clin North Am*, 21(5):961-75.
8. Oerlemans S, Mols F, Issa D E, Pruijt J, Peters W G, Lybeert M, et al. (2013). A high level of fatigue among long-term survivors of non-Hodgkin's lymphoma: results from the longitudinal population-based PROFILES registry in the south of the Netherlands. *Haematologica*, 98(3):479-86.
9. Mock V, Atkinson A, Barsevick A, Cella D, Cimprich B, Cleeland C, et al. (2000). NCCN Practice Guidelines for Cancer-Related Fatigue. *Oncology (Williston Park, NY)*, 14(11A):151-61.
10. Curt G A, Breitbart W, Cella D, Groopman J E, Horning S J, Itri L M, et al. (2000). Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *The oncologist*, 5(5):353-60.
11. Bower J E, Bak K, Berger A, Breitbart W, Escalante C P, Ganz P A, et al. (2014). Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol*, 32(17):1840-50.
12. Daniëls L, Oerlemans S, Krol A, Creutzberg C, van de Poll-Franse L (2014). Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity. *Br J Cancer*, 110(4):868-74.
13. Agasi-Idenburg S, Thong M, Punt C, Stuiver M, Aaronson N (2017). Comparison of symptom clusters associated with fatigue in older and younger survivors of colorectal cancer. *Support Care Cancer*, 25(2):625-32.
14. Kwekkeboom K L, editor Cancer symptom cluster management. Semin Oncol Nurs; 2016: Elsevier.
15. Barsevick A M (2007). The elusive concept of the symptom cluster. *Oncol Nurs Forum*, 34(5).
16. Gehrman P R, Garland S N, Matura L A, Mao J J P, care s (2017). Insomnia in breast cancer: Independent symptom or symptom cluster? *Palliative & supportive care*, 15(3):369-75.
17. Ganz P A, Kwan L, Castellon S A, Oppenheim A, Bower J E, Silverman D H, et al. (2013). Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance. *J Natl Cancer Inst*, 105:791-801.
18. Vardy J L, Dhillon H M, Pond G R, Rourke S B, Bekele T, Renton C, et al. (2015). Cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: a prospective, longitudinal, controlled study. *J Clin Oncol*, 33(34):4085.
19. Schilder C, Seynaeve C, Linn S, Boogerd W, Beex L, Gundy C, et al. (2012). Self-reported cognitive functioning in postmenopausal breast cancer patients before and during endocrine treatment: findings from the neuropsychological TEAM side-study. *Psycho-Oncology*, 21(5):479-87.
20. Wouters H, Baars J W, Schagen S B (2016). Neurocognitive function of lymphoma patients after treatment with chemotherapy. *Acta Oncol*, 55(9-10):1121-5.
21. Bower J E (2014). Cancer-related fatigue: mechanisms, risk factors, and treatments. *Nature Reviews Clinical Oncology*, 11(10):597-609.
22. Prue G, Rankin J, Allen J, Gracey J, Cramp F (2006). Cancer-related fatigue: a critical appraisal. *Eur J Cancer*, 42(7):846-63.

23. Servaes P, Verhagen C, Bleijenberg G (2002). Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. *Eur J Cancer*, 38(1):27-43.
24. Donovan K A, Stein K D, Lee M, Leach C R, Ilozumba O, Jacobsen P B (2015). Systematic review of the multidimensional fatigue symptom inventory-short form. *Support Care Cancer*, 23(1):191-212.
25. Kreissl S, Mueller H, Goergen H, Mayer A, Brillant C, Behringer K, et al. (2016). Cancer-related fatigue in patients with and survivors of Hodgkin's lymphoma: a longitudinal study of the German Hodgkin Study Group. *The Lancet Oncology*, 17(10):1453-62.
26. Ryan J L, Carroll J K, Ryan E P, Mustian K M, Fiscella K, Morrow G R (2007). Mechanisms of cancer-related fatigue. *Oncologist*, 12.
27. O'Higgins C, Brady B, O'Connor B, Walsh D, Reilly R (2018). The pathophysiology of cancer-related fatigue: current controversies. *Support Care Cancer*, 26(10):3353-64.
28. Saligan L N, Olson K, Filler K, Larkin D, Cramp F, Sriram Y, et al. (2015). The biology of cancer-related fatigue: a review of the literature. *Support Care Cancer*, 23(8):2461-78.
29. Dantzer R, O'Connor J C, Freund G G, Johnson R W, Kelley K W (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews neuroscience*, 9(1):46-56.
30. Aggarwal B B, Vijayalekshmi R, Sung B (2009). Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. *Clin Cancer Res*, 15(2):425-30.
31. Coussens L M, Werb Z (2002). Inflammation and cancer. *Nature*, 420(6917):860-7.
32. Bower J E, Ganz P A, Aziz N, Fahey J L (2002). Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom Med*, 64(4):604-11.
33. Bower J E, Ganz P A, Aziz N (2005). Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. *Psychosom Med*, 67(2):277-80.
34. Weinrib A Z, Sephton S E, DeGeest K, Penedo F, Bender D, Zimmerman B, et al. (2010). Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer. *Cancer*, 116(18):4410-9.
35. Innominato P F, Mormont M-C, Rich T A, Waterhouse J, Lévi F A, Bjarnason G A (2009). Circadian disruption, fatigue, and anorexia clustering in advanced cancer patients: implications for innovative therapeutic approaches. *Integr Cancer Ther*, 8(4):361-70.
36. Shanks N, Harbuz M, Jessop D, Perks P, Moore P, Lightman S (1998). Inflammatory disease as chronic stress. *Ann N Y Acad Sci*, 840(1):599-607.
37. Foster R, Kreitzman L (2017). Circadian Rhythms: A 24-hour phenomenon, in Foster R, Kreitzman L (eds): Circadian rhythms: a very short introduction. Oxford, United Kingdom: Oxford University Press. p. 1-12.
38. Ancoli-Israel S, Martin J L, Blackwell T, Buenaver L, Liu L, Meltzer L J, et al. (2015). The SBSM guide to actigraphy monitoring: clinical and research applications. *Behav Sleep Med*, 13(sup1):S4-S38.
39. Van Someren E J, Swaab D F, Colenda C C, Cohen W, McCall W V, Rosenquist P B (1999). Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. *Chronobiol Int*, 16(4):505-18.
40. Mormont M-C, Waterhouse J (2002). Contribution of the rest–activity circadian rhythm to quality of life in cancer patients. *Chronobiol Int*, 19(1):313-23.
41. Payne J K (2011). Altered circadian rhythms and cancer-related fatigue outcomes. *Integr Cancer Ther*, 10(3):221-33.
42. Rich T A (2007). Symptom clusters in cancer patients and their relation to EGFR ligand modulation of the circadian axis. *J Support Oncol*, 5(4):167-74.
43. Innominato P F, Roche V P, Palesh O G, Ulusakarya A, Spiegel D, Lévi F A (2014). The circadian timing system in clinical oncology. *Ann Med*, 46(4):191-207.
44. Cajochen C, Kräuchi K, Wirz-Justice A (2003). Role of melatonin in the regulation of human circadian rhythms and sleep. *J Neuroendocrinol*, 15(4):432-7.
45. Schrepf A, Clevenger L, Christensen D, DeGeest K, Bender D, Ahmed A, et al. (2013). Cortisol and inflammatory processes in ovarian cancer patients following primary treatment: relationships with depression, fatigue, and disability. *Brain Behav Immun*, 30:S126-S34.
46. Roenneberg T, Wirz-Justice A, Merrow M (2003). Life between clocks: daily temporal patterns of human chronotypes. *J Biol Rhythms*, 18(1):80-90.
47. Horne J A, Ostberg O (1975). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol*, 4(2):97-110.

48. Smith C S, Reilly C, Midkiff K (1989). Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. *J Appl Psychol*, 74(5):728-38.
49. Jones C R, Campbell S S, Zone S E, Cooper F, DeSano A, Murphy P J, et al. (1999). Familial advanced sleep-phase syndrome: A short-period circadian rhythm variant in humans. *Nat Med*, 5(9):1062-5.
50. Jones S E, Tyrrell J, Wood A R, Beaumont R N, Ruth K S, Tuke M A, et al. (2016). Genome-wide association analyses in 128,266 individuals identifies new morningness and sleep duration loci. *PLoS Genet*, 12(8):e1006125.
51. Xu Y, Padiath Q S, Shapiro R E, Jones C R, Wu S C, Saigoh N, et al. (2005). Functional consequences of a CKIδ mutation causing familial advanced sleep phase syndrome. *Nature*, 434(7033):640-4.
52. Roenneberg T, Pilz L K, Zerbini G, Winnebeck E C J B (2019). Chronotype and Social Jetlag: A (Self-) Critical Review. *Biology*, 8(3):54.
53. Chrobak A A, Nowakowski J, Zwolińska-Wcisło M, Cibor D, Przybylska-Feluś M, Ochyra K, et al. (2018). Associations between chronotype, sleep disturbances and seasonality with fatigue and inflammatory bowel disease symptoms. *Chronobiol Int*, 35(8):1142-52.
54. Martin J S, Hébert M, Ledoux É, Gaudreault M, Laberge L (2012). Relationship of chronotype to sleep, light exposure, and work-related fatigue in student workers. *Chronobiol Int*, 29(3):295-304.
55. Michielsen H J, De Vries J, Van Heck G L, Van de Vijver F J, Sijtsma K J E J o P A (2004). Examination of the dimensionality of fatigue. 20(1):39-48.
56. Grandjean E (1979). Fatigue in industry. *Occup Environ Med*, 36(3):175-86.
57. Rockwell D, Burr B (1977). The tired patient. *The Journal of family practice*, 5(5):853-7.
58. Vercoulen J (1999). The checklist individual strength. *Gedragstherapie*, 32:131-6.
59. Schwartz J E, Jandorf L, Krupp L B (1993). The measurement of fatigue: a new instrument. *J Psychosom Res*, 37(7):753-62.
60. Minton O, Stone P (2009). A systematic review of the scales used for the measurement of cancer-related fatigue (CRF). *Ann Oncol*, 20(1):17-25.
61. Fisher M I, Davies C, Lacy H, Doherty D (2018). Oncology section EDGE task force on cancer: measures of cancer-related fatigue—a systematic review. *Rehabil Oncol*, 36(2):93-105.
62. Seyidova-Khoshknabi D, Davis M P, Walsh D (2011). A systematic review of cancer-related fatigue measurement questionnaires. *American Journal of Hospice and Palliative Medicine®*, 28(2):119-29.
63. Aaronson N K, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez N J, et al. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*, 85(5):365-76.
64. Yellen S B, Cella D F, Webster K, Blendowski C, Kaplan E (1997). Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*, 13(2):63-74.
65. Stein K D, Martin S C, Hann D M, Jacobsen P B J C p (1998). A multidimensional measure of fatigue for use with cancer patients. *Cancer Pract*, 6(3):143-52.
66. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. (1993). Development of a fatigue scale. *J Psychosom Res*, 37(2):147-53.
67. Smets E, Garssen B, Bonke B d, De Haes J (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*, 39(3):315-25.
68. Smets E, Garssen B, Cull A, De Haes J (1996). Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. *Br J Cancer*, 73(2):241.
69. Schwarz R, Krauss O, Hinz A (2003). Fatigue in the general population. *Oncology Research and Treatment*, 26(2):140-4.
70. Wintermann G-B, Rosendahl J, Weidner K, Strauß B, Hinz A, Petrowski K (2018). Fatigue in chronically critically ill patients following intensive care-reliability and validity of the multidimensional fatigue inventory (MFI-20). *Health and quality of life outcomes*, 16(1):37.
71. Buss T, Kruk A, Wiśniewski P, Modlinska A, Janiszewska J, Lichodziejewska-Niemierko M (2014). Psychometric Properties of the Polish Version of the Multidimensional Fatigue Inventory-20 in Cancer Patients. *J Pain Symptom Manage*, 48(4):730-7.
72. Gentile S, Delaroziere J, Favre F, Sambuc R, San Marco J (2003). Validation of the French 'multidimensional fatigue inventory'(MFI 20). *European journal of cancer care*, 12(1):58-64.
73. Song S-W, Kang S-G, Kim K-S, Kim M-J, Kim K-M, Cho D-Y, et al. (2018). Reliability and validity of the Korean version of the multidimensional fatigue inventory (MFI-20): a multicenter, cross-sectional study. *Pain Research and Management*, 2018.

74. Baptista R L R, Biasoli I, Scheliga A, Soares A, Brabo E, Morais J C, et al. (2012). Psychometric properties of the multidimensional fatigue inventory in Brazilian Hodgkin's lymphoma survivors. *J Pain Symptom Manage*, 44(6):908-15.
75. Saffari M, Naderi M K, Piper C N, Koenig H G (2017). Multidimensional Fatigue Inventory in People With Hepatitis B Infection: Cross-cultural Adaptation and Psychometric Evaluation of the Persian Version. *Gastroenterol Nurs*, 40(5):380-92.
76. Chandel P, Sultan A, Khan K A, Choudhary V, Parganiha A (2015). Validation of the Hindi version of the Multidimensional Fatigue Inventory-20 (MFI-20) in Indian cancer patients. *Support Care Cancer*, 23(10):2957-64.
77. Tian J, Hong J-S (2012). Validation of the Chinese version of Multidimensional Fatigue Inventory-20 in Chinese patients with cancer. *Support Care Cancer*, 20(10):2379-83.
78. Chung K-F, Yu B Y-M, Yung K-P, Yeung W-F, Ng T H, Ho F Y-Y (2014). Assessment of fatigue using the Multidimensional Fatigue Inventory in patients with major depressive disorder. *Compr Psychiatry*, 55(7):1671-8.
79. Lin J-M S, Brimmer D J, Maloney E M, Nyarko E, BeLue R, Reeves W C (2009). Further validation of the Multidimensional Fatigue Inventory in a US adult population sample. *Population health metrics*, 7(1):18.
80. Chilcot J, Guirguis A, Friedli K, Almond M, Davenport A, Day C, et al. (2017). Measuring fatigue using the Multidimensional Fatigue Inventory-20: a questionable factor structure in haemodialysis patients. *Nephron*, 136(2):121-6.
81. Goodchild C E, Treharne G J, Booth D A, Kitas G D, Bowman S J (2008). Measuring fatigue among women with Sjogren's syndrome or rheumatoid arthritis: a comparison of the Profile of Fatigue (ProF) and the Multidimensional Fatigue Inventory (MFI). *Musculoskeletal Care*, 6(1):31-48.
82. Meek P M, Nail L M, Barsevick A, Schwartz A L, Stephen S, Whitmer K, et al. (2000). Psychometric testing of fatigue instruments for use with cancer patients. *Nurs Res*, 49(4):181-90.
83. Lundh Hagelin C, Wengström Y, Runesdotter S, Johan Fürst C (2007). The psychometric properties of the Swedish Multidimensional Fatigue Inventory MFI-20 in four different populations. *Acta Oncol*, 46(1):97-104.
84. Berger A M, Mooney K, Aranha O, Banarjee C, Breitbart W S, Carpenter K M, et al. (2020). Cancer-related fatigue, version 1.2021. *NCCN Guidelines*.
85. Mustian K M, Alfano C M, Heckler C, Kleckner A S, Kleckner I R, Leach C R, et al. (2017). Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. *JAMA oncology*, 3(7):961-8.
86. Craike M J, Hose K, Courneya K S, Harrison S J, Livingston P M (2013). Perceived benefits and barriers to exercise for recently treated patients with multiple myeloma: a qualitative study. *BMC Cancer*, 13(1):1.
87. Choukroun J, Geoffroy P A (2019). Light therapy in mood disorders: a brief history with physiological insights. *Chronobiol Med*, 1:3-8.
88. Hippocrates H ippocrates on Airs, Waters and Places. London: Messrs. Wyman and Sons; 1881.
89. Rosenthal N E, Sack D A, Gillin J C, Lewy A J, Goodwin F K, Davenport Y, et al. (1984). Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry*, 41(1):72-80.
90. Mårtensson B, Pettersson A, Berglund L, Ekselius L (2015). Bright white light therapy in depression: a critical review of the evidence. *J Affect Disord*, 182:1-7.
91. Al-Karawi D, Jubair L (2016). Bright light therapy for nonseasonal depression: meta-analysis of clinical trials. *J Affect Disord*, 198:64-71.
92. Åkerstedt T, Landström U, Byström M, Nordström B, Wibom R (2003). Bright light as a sleepiness prophylactic: a laboratory study of subjective ratings and EEG. *Percept Mot Skills*, 97(3):811-9.
93. van Maanen A, Meijer A M, van der Heijden K B, Oort F J (2016). The effects of light therapy on sleep problems: A systematic review and meta-analysis. *Sleep Med Rev*, 29:52-62.
94. Lam R, Levitt A (1999). Canadian Consensus Guidelines for the treatment of SAD. *A summary of the report of the Canadian Consensus Group on SAD Clinical and Academic Publishing, Vancouver, Canada*.
95. Bauer M, Bschor T, Pfennig A, Whybrow P C, Angst J, Versiani M, et al. (2007). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders in primary care. *The World Journal of Biological Psychiatry*, 8(2):67-104.

96. Hattar S, Liao H-W, Takao M, Berson D M, Yau K-W (2002). Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science*, 295(5557):1065-70.
97. Berson D M, Dunn F A, Takao M (2002). Phototransduction by retinal ganglion cells that set the circadian clock. *Science*, 295(5557):1070-3.
98. Lucas R J, Peirson S N, Berson D M, Brown T M, Cooper H M, Czeisler C A, et al. (2014). Measuring and using light in the melanopsin age. *Trends Neurosci*, 37(1):1-9.
99. Schmidt T M, Chen S-K, Hattar S J T i n (2011). Intrinsically photosensitive retinal ganglion cells: many subtypes, diverse functions. *Trends Neurosci*, 34(11):572-80.
100. Tsai J W, Hannibal J, Hagiwara G, Colas D, Ruppert E, Ruby N F, et al. (2009). Melanopsin as a sleep modulator: circadian gating of the direct effects of light on sleep and altered sleep homeostasis in Opn4−/− mice. *PLoS Biol*, 7(6):e1000125.
101. LeGates T A, Fernandez D C, Hattar S (2014). Light as a central modulator of circadian rhythms, sleep and affect. *Nature Reviews Neuroscience*, 15(7):443-54.
102. Blume C, Garbazza C, Spitschan M (2019). Effects of light on human circadian rhythms, sleep and mood. *Somnologie*:1-10.
103. Lewy A J, Wehr T A, Goodwin F K, Newsome D A, Markey S (1980). Light suppresses melatonin secretion in humans. *Science*, 210(4475):1267-9.
104. Bowmaker J K, Dartnall H (1980). Visual pigments of rods and cones in a human retina. *The Journal of physiology*, 298(1):501-11.
105. Brainard G C, Sliney D, Hanifin J P, Glickman G, Byrne B, Greeson J M, et al. (2008). Sensitivity of the human circadian system to short-wavelength (420-nm) light. *J Biol Rhythms*, 23(5):379-86.
106. Ancoli-Israel S, Rissling M, Neikrug A, Trofimenko V, Natarajan L, Parker B A, et al. (2012). Light treatment prevents fatigue in women undergoing chemotherapy for breast cancer. *Support Care Cancer*, 20(6):1211-9.
107. Redd W H, Valdimarsdottir H, Wu L M, Winkel G, Byrne E E, Beltre M A, et al. (2014). Systematic light exposure in the treatment of cancer-related fatigue: a preliminary study. *Psychooncology*, 23(12):1431-4.
108. Neikrug A B, Rissling M, Trofimenko V, Liu L, Natarajan L, Lawton S, et al. (2012). Bright light therapy protects women from circadian rhythm desynchronization during chemotherapy for breast cancer. *Behav Sleep Med*, 10(3):202-16.
109. Jeste N, Liu L, Rissling M, Trofimenko V, Natarajan L, Parker B A, et al. (2013). Prevention of quality-of-life deterioration with light therapy is associated with changes in fatigue in women with breast cancer undergoing chemotherapy. *Qual Life Res*, 22(6):1239-44.
110. Wu L M, Amidi A, Valdimarsdottir H, Ancoli-Israel S, Liu L, Winkel G, et al. (2018). The effect of systematic light exposure on sleep in a mixed group of fatigued cancer survivors. *J Clin Sleep Med*, 14(01):31-9.
111. Huiberts L, Smolders K, De Kort Y (2017). Seasonal and time-of-day variations in acute non-image forming effects of illuminance level on performance, physiology, and subjective well-being. *Chronobiol Int*, 34(7):827-44.
112. Smolders K C, De Kort Y A, Cluitmans P J P, Behavior (2012). A higher illuminance induces alertness even during office hours: findings on subjective measures, task performance and heart rate measures. *Physiol Behav*, 107(1):7-16.
113. Gabel V, Maire M, Reichert C F, Chellappa S L, Schmidt C, Hommes V, et al. (2015). Dawn simulation light impacts on different cognitive domains under sleep restriction. *Behav Brain Res*, 281:258-66.
114. Phipps-Nelson J, Redman J R, Dijk D-J, Rajaratnam S M (2003). Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance. *Sleep*, 26(6):695-700.
115. Smolders K C, de Kort Y A (2014). Bright light and mental fatigue: Effects on alertness, vitality, performance and physiological arousal. *J Environ Psychol*, 39:77-91.
116. Riemersma-Van Der Lek R F, Swaab D F, Twisk J, Hol E M, Hoogendijk W J, Van Someren E J (2008). Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *JAMA*, 299(22):2642-55.
117. Royer M, Ballentine N H, Eslinger P J, Houser K, Mistrick R, Behr R, et al. (2012). Light therapy for seniors in long term care. *J Am Med Dir Assoc*, 13(2):100-2.
118. Killgore W D, Vanuk J R, Shane B R, Weber M, Bajaj S (2020). A randomized, double-blind, placebo-controlled trial of blue wavelength light exposure on sleep and recovery of brain structure, function, and cognition following mild traumatic brain injury. *Neurobiol Dis*, 134:104679.

119. Burns A, Allen H, Tomenson B, Duignan D, Byrne J (2009). Bright light therapy for agitation in dementia: a randomized controlled trial. *Int Psychogeriatr*, 21(4):711.
120. Forbes D, Blake C M, Thiessen E J, Peacock S, Hawranik P (2014). Light therapy for improving cognition, activities of daily living, sleep, challenging behaviour, and psychiatric disturbances in dementia. *Cochrane database of systematic reviews*, (2).