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

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CHAPTER 7

SUMMARY AND GENERAL DISCUSSION

The studies in this thesis report on the outcomes of a double blind, randomized controlled trial (RCT) of light therapy in Hodgkin Lymphoma (HL) and Diffuse Large B-cell lymphoma (DLBCL) survivors with persistent moderate to severe fatigue since diagnosis. We evaluated the short- and long-term efficacy of light therapy on improving fatigue after cancer and associated symptoms including sleep quality, depression, anxiety, quality of life, cognitive complaints, cognitive functioning, and circadian rhythms of sleep-wake cycles, melatonin, and cortisol. In addition, we described a psychometric evaluation of one of the primary outcomes, the Multidimensional Fatigue Inventory (MFI) in the general Dutch population. We also reported on the associations of chronotype with cancer-related fatigue (CRF) and sleep quality with CRF. This chapter summarizes our main findings in part 1. In part 2, we discuss our results with respect to the current literature and report on methodological considerations, overall conclusions, clinical implications, and implications for future research.

PART 1: SUMMARY

Chapter 1 introduces the need for an effective treatment for cancer-related fatigue for HL and DLBCL survivors. In the Netherlands, the BETER consortium offers a healthcare infrastructure for survivorship care after a HL and DLBCL diagnosis. Within this consortium, survivors are informed about late adverse effects of treatment and offered screening and timely treatment. Cancer-related fatigue (CRF) is one of the most reported symptoms by HL and DLBCL survivors to radiation-oncologists and hematologists in this consortium. The prevalence rates range between 41 to 61 percent compared to a prevalence of moderate to severe fatigue of 23 to 28 percent in the general Dutch population. Although the etiology of CRF is unknown, it is suggested that CRF results from multiple factors covering demographic, medical, psychosocial, behavioral, and biological factors. An example of a biological factor is circadian rhythm disruptions. Despite its high prevalence, evidence-based treatments for CRF are limited (i.e. cognitive behavioral therapy or physical exercise) and are not effective for all survivors suffering from CRF (these therapies require a high motivation from patients). Therefore, it is important to investigate alternative treatments, for example light therapy. When the research described in this thesis started, two pilot studies in breast cancer patients receiving chemotherapy (n = 39) and cancer survivors (n = 36) showed promising effect of light therapy as a treatment for CRF. Moreover, secondary analyses indicated that light therapy affected symptoms associated with CRF including circadian sleep-wake cycles and quality of life. Therefore, it was hypothesized that light therapy reduced fatigue through a restorative effect on circadian rhythms. Despite the positive effects in these pilot studies, there were limitations including small sample sizes and short follow up times (up to three weeks post-intervention) and questions remained about the mechanisms of action that explain the positive effect of light therapy. Hence, replication of these results in a sufficiently powered randomized controlled trial and the investigation of possible mechanisms of action were necessary.

Chapter 2 describes the rationale and design of the SPARKLE study, where we aimed to examine the efficacy of light therapy on improving CRF. Participants were recruited from 10 community and academic hospitals. Eligible survivors were randomly assigned to exposure

to bright white light (BWL; intervention) or exposure to dim white light (DWL; control). Participants were instructed to use light therapy within 30 minutes after awakening for a duration of 30 minutes on 25 consecutive days. Primary outcomes included fatigue and work and social adjustments caused by this fatigue. Secondary outcomes included depression, anxiety, quality of life, sleep quality, circadian rhythms of sleep-wake cycles, melatonin, cortisol, cognitive complaints and cognitive functioning. Outcome measures were assessed at baseline (T0), immediate post-intervention (T1), and at three (T2) and nine (T3) months follow-up. Survivors in the DWL group were offered BWL after completion of the T3 assessment. Based on this study design, it was possible to replicate the promising effect of light therapy on CRF in a sufficiently powered trial, investigate the long-term effect of light therapy on CRF and explore potential mechanisms of action.

Chapter 3 reports the findings of the SPARKLE study. In total, 166 HL and DLBCL survivors with a mean age of 46 and a mean survivorship of 13 years participated. Compliance rates were high with a mean use of light therapy of 23 days. There were no significant differences between BWL and DWL in the reduction of fatigue over time. Both BWL and DWL significantly ($p < .001$) improved fatigue levels during the intervention which only slightly diminished during follow-up ($ES_{T0\text{-}T1} = -0.71$; $ES_{T1\text{-}T3} = 0.15$). Similar results were found for depression, sleep quality, and three aspects of quality of life (role limitations due to physical functioning, energy, and social functioning). Light therapy had no effect on anxiety, sleep-wake cycles (determined with actigraphy), and cortisol and melatonin levels. Subgroup analyses on participants who used: 1) light therapy on all 25 treatment days (n = 56); 2) Luminette glasses (n = 127); or 3) light therapy during autumn or winter (n = 88) showed similar results and did not change our conclusions. At the individual patient level, 35 to 63 percent of the survivors showed a clinically relevant reduction of fatigue at T1, irrespective of condition. This study demonstrates that BWL was not superior in reducing fatigue compared to DWL. Instead, both groups showed reduced fatigue levels. Future research is necessary to investigate which elements of the study protocol led to these condition-independent improvements.

Chapter 4 presents the effect of light therapy on cognitive complaints and cognitive functioning in long-term HL and DLBCL survivors with CRF. Over one-third of the participants showed cognitive dysfunction at baseline, specifically in verbal memory where deviant scores were observed for immediate recall in 34% and delayed recall in 27% of the participants compared to 16% in the norm population. Neither BWL nor DWL diminished cognitive complaints or improved cognitive functioning (range *p*-values .07 to .80; range effect sizes .04 to .29) in the total group of fatigued survivors nor in the subgroup suffering from cognitive dysfunction. These results indicate that approximately one-third of long-term HL and DLBCL survivors experience cognitive dysfunctioning. Light therapy does not appear to improve these complaints. Therefore, we suggest that other cognitive rehabilitation interventions should be made available to mitigate cognitive dysfunctioning in these survivors.

Chapter 5 presents the results of a psychometric evaluation of the Multidimensional Fatigue Inventory (MFI), which was one of the primary outcomes of the SPARKLE study. The original validation study suggested that the MFI measures five domains of fatigue, i.e. *general fatigue*, *physical fatigue*, *reduced activity*, *reduced motivation*, and *mental fatigue*, although

two four-factor structures also showed acceptable fit. Further validation studies showed inconclusive results on the factor structure of the MFI. The aim of this psychometric evaluation was to investigate the scale structure of the MFI in the general Dutch population (n = 2512). The results of a confirmatory factor analysis did not provide support for the original 5-factor structure (RMSEA = 0.120, CFI = 0.933, TLI = 0.920). Moreover, we were unable to replicate a four-factor structure that combined the general fatigue and physical fatigue subscales (RMSEA = 0.122, CFI = 0.928, TLI = 0.917). Adding a general factor to the five- and four-factor model to create a bi-factor model also did not show acceptable model fit (bi-4-factor: RMSEA = 0.151, CFI = 0.895, TLI = 0.873; bi-5-factor: RMSEA = 0.153, CFI = 0.894, TLI = 0.871). Exploratory factor analyses provided no alternative models with an acceptable model fit but seemed to show robustness in the loading of the original *general fatigue* items. These results did not provide empirical support for a four or five (bi-)factor structure of the MFI, nor for an alternative model. We propose that the most reliable scale of the MFI seems to be the *general fatigue* scale. This scale could be used as a general indicator of fatigue.

Chapter 6 reports on the results of a survey study, which was part of the recruitment for the SPARKLE study. Hence, it was completed by (non-)Hodgkin lymphoma survivors with and without fatigue. The rationale for this study was based on the ability of light to align internal circadian rhythms to external rhythm. Although several studies showed that circadian disruptions in the sleep-wake cycle (more awakenings during the night and more naps during the day) are associated with CRF in patients with cancer, it is unclear whether the timing of this rhythm is misaligned from the external rhythm in cancer survivors with CRF. Therefore, we investigated the associations of chronotype (someone's preference in the timing of sleep and wake, i.e. a morning or an evening type) with CRF, and sleep quality with CRF in a survey study. It was hypothesized that evening types would report higher levels of cancer-related fatigue compared to morning types. A total number of 458 survivors (50% female) with a mean age of 50 years completed a VAS fatigue-scale from 0 (no fatigue) to 10 (worst imaginable fatigue), the Munich Chronotype Questionnaire (MCTQ), and the Pittsburgh Sleep Quality Index (PSQI) between October 2018 and July 2019. The majority was diagnosed with a HL (71%) and the mean time since diagnosis was 12 years. Sixty-six percent of our sample reported moderate to severe fatigue. There was no statistically significant difference for average midsleep time, i.e. the midpoint between sleep onset and sleep offset that was used to determine chronotype, between survivors with and without fatigue symptoms. A hierarchical linear regression analysis was used to evaluate the associations between fatigue and chronotype (based on early, intermediate, or late average midsleep) in model 1, and fatigue and sleep quality in model 2. The results showed no indications for an association between chronotype and fatigue (all p-values ≥ .50). There were associations between two (out of seven) aspects of sleep quality and fatigue: subjective sleep quality ($p < .001$) and daily dysfunctioning ($p < .001$). Therefore, it is more likely that CRF in long-term HL and DLBCL survivors is associated with self-reported sleep quality rather than with chronotype.

PART 2: GENERAL DISCUSSION

This section describes a general discussion of the studies presented in this thesis. It is divided in two different parts. The first part covers light therapy for CRF and related symptoms. The second part covers circadian rhythms and CRF. The buildup of each part is as follows: first, we discuss our findings in the context of the current literature; thereafter follows a discussion of methodological limitations and an overview of overall conclusions; and finally, we reflect on the clinical implications and provide suggestions for future research.

LIGHT THERAPY FOR CANCER RELATED FATIGUE

Comparison with the literature

The rational for the SPARKLE study was based on two pilot studies from Ancoli-Israel et al.[1] in patients with breast cancer and Redd et al.[2] in cancer survivors that showed promising effects of light therapy as a treatment for CRF. Since then, several studies[3-13] on the effect of light therapy in cancer populations have been published. The sections below provide an overview of the results of these studies. First, studies that investigated the use of light therapy for CRF in cancer survivors with fatigue complaints are mentioned. Second, light therapy for cancer survivors with other symptoms are evaluated. Finally, light therapy for patients with cancer while receiving treatment are described. An overview of these studies is provided in Table 1.

Light therapy for cancer survivors with cancer-related fatigue

Two studies investigated the use of light therapy for cancer survivors with CRF as a treatment to reduce fatigue. The first study by Redd et al.[2] randomly assigned 36 survivors to exposure to BWL or dim red light (DRL) and used the FACIT-fatigue as primary outcome. The results showed superiority of BWL over DRL with an effect size of 0.98. The second study by Johnson et al. studied light therapy in 81 cancer survivorswho met ICD-10 criteria for CRF and compared exposure to BWL or DRL in a RCT[4]. Results showed superiority of BWL over DRL for reducing fatigue symptoms with an effect size of 0.30, indicating that the group exposed to BWL had a 17 percent larger reduction in fatigue complaints compared to participants exposed to DRL.

Our results showed no superiority of BWL over DWL on reducing fatigue but indicated that both groups, irrespective of light intensity, reported reduced fatigue (based on a VAS-scale for fatigue and the general fatigue subscale of the MFI) after completion of the light therapy protocol (**chapter 3**). This was an unexpected finding because both Redd et al.[2] and Johnson et al.[4] reported superiority of BWL. However, it is important to notice that Johnson et al. only observed superiority of BWL for the total score of the Multidimensional Fatigue Symptom Inventory - short form (MFSI-SF)[14]. In line with our results, Johnson et al.[4] showed no differences between survivors exposed to BWL or DRL for the effect of light therapy on the five domains of fatigue assessed with the MFSI-sf (general, physical, emotional, and mental fatigue, and vigor). The total group, irrespective of light intensity, reported clinically relevant improvements on general, physical, emotional, and mental fatigue. No effect was observed for vigor. This indicates that the only study showing a convincing superiority of BWL over DRL

Table 1. Overview of studies on the effect of light therapy in cancer populations

Study[a]	Study type[b]	Participants	Light therapy characteristics
CANCER SURVIVORS WITH CRF			
Redd et al. (2014)[2]	PS	Breast, gynecologic, and hematological cancer survivors Mean survivorship: 17 months	BWL (n=18) vs DRL (n=18) Litebook 1.2 30 min within 30 min upon waking, 4 weeks
Wu et al. (2018)[3]			BWL (n=25) vs DRL (n=19)
Johnson et al. (2017)[4]	RCT	Cancer survivors Mean survivorship: 28 months	BWL (n=42) vs DRL (n=39) Litebook Elite 30 min within 30 min upon waking, 4 weeks
Garland et al. (2020)[5]			
Johnson et al. (2020)[6]			
CANCER SURVIVORS WITH SYMPTOMS OTHER THAN FATIGUE			
Kronish et al. (2019)[7]	PT	Cancer survivors with at least mild depressive symptoms Mean survivorship: N/A	BWL vs DRL N=8 Litebook Advantage 30 min each morning, 3 weeks of BWL or DRL, crossover across 12 weeks

Outcome	Instrument	Conclusion
Fatigue	FACIT-fatigue	• BWL showed superiority over DRL for reducing fatigue (effect size Cohen's *d* = 0.98). • DRL did not reduce fatigue.
Sleep-wake cycles	Wrist actigraphy	• BWL showed superiority over DRL for improving sleep efficiency (partial η^2 = 0.28). • No effect on total sleep time and wake after sleep onset.
Sleep quality	PSQI	• No effect on sleep quality.
Fatigue	MFSI-SF	Total score: • BWL showed superiority over DRL for reducing fatigue (effect size Cohen's *d* = 0.30). • DRL did reduce fatigue (effect size Cohen's *d* = 0.93 compared to *d* = 1.20 in BWL). Subscales: • Improvements on general, physical, emotional, and mental fatigu over time in both groups. • No effect on vigor.
Mood	POMS-SF	• Improvement of mood disturbance over time in both groups.
Depression	CES-D	• Reduction of depressive symptoms over time in both groups.
Quality of Life	FACT-G	• Improvements of QoL over time in both groups.
Insomnia	ISI	• BWL showed superiority over DRL for improving insomnia.
Sleep quality	PSQI	• Improvements of sleep quality over time in both groups.
Sleep-wake cycles	Wrist actigraphy	• No effect on sleep onset latency, wake after sleep onset, sleep efficiency, and total sleep time.
Cortisol	Diurnal slope	• Increased cortisol slopes over time in both groups.
	Total cortisol output	• Increased cortisol output over time in both groups.
Depression	VAS-depression (daily)	• Two individuals reported a decrease, five reported no difference and one reported an increase of depressive symptoms after BWL compared to DRL.
Fatigue	VAS-fatigue (daily)	• One individual reported a decrease, six reported no differences, and one reported an increase of fatigue after BWL compared to DRL.

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Table 1. *(continued)*

Study[a]	Study type[b]	Participants	Light therapy characteristics
Fox et al. (2020)[8]	FS	Ovarian and gynecologic cancer survivors with sleep disturbances Mean survivorship: N/A	Green BL (n=10) vs DRL (n=11) Re-Timer 45 min upon waking, 4 weeks
Rogers et al. (2020)[9]	FS	Adolescent cancer survivors Mean survivorship: 12 months	BWL (n=8) Litebook Elite 30 min upon waking, 4 weeks
PATIENTS WITH CANCER WHILE RECEIVING CANCER TREATMENT			
Ancoli-Israel et al. (2012)[1]	PS	Breast cancer patients receiving 4 cycles of chemotherapy	BWL (n=23) vs. DRL (n=16) Litebook 1.2 30 min upon waking, 8-12 weeks (4 cycles of chemotherapy)
Neikrug et al. (2012)[10]			
Jeste et al. (2013)[11]			

Outcome	Instrument	Conclusion
Sleep-wake cycles	Wrist actigraphy	• Tendency for superiority of BL over DRL on number of nighttime wakenings. • Tendency for an increase of total sleep time over time in both groups. • No effect on time in bed, sleep onset latency, wake after sleep onset, sleep efficiency.
Sleep quality	PSQI	• Tendency for superiority of BL over DRL on improving sleep quality.
Quality of life	FACT-G	• No effect on quality of life.
Fatigue	FACIT-fatigue	• Improvements of fatigue over time in both groups.
Cognitive function	FACT-Cognitive Function	• Tendency for superiority of BL over DRL on the comments from others subscale.
Depression	PROMIS-Depression Item Bank	• Tendency for superiority of BL over DRL on depressive symptoms.
Diurnal cortisol	Saliva	• No effect on cortisol.
Melatonin	Urine	• No effect on melatonin.
Sleep-wake cycles	Wrist actigraphy	• No effect on acrophase, amplitude, *F*-statistic, MESOR.
Fatigue	MFSI-SF	Total score: • BWL prevented the increase of fatigue that was seen after DRL. • Changes in fatigue were unrelated to changes in sleep or circadian rhythms. Subscales: • Both groups showed worse scores on general, physical, or mental subscales. • No change on the vigor subscale.
Sleep-wake cycles	Wrist actigraphy	• Both groups showed a dampened and less robust circadian rhythm during chemotherapy weeks compared to baseline. • The circadian rhythm returned to baseline or improved during the recovery week in the BWL group. This was not seen in the DRL group. • No effect on acrophase (time of day of the peak of the circadian rhythm, which is indicative for a phase advance or delay).
Quality of life	FACT-B	• No significant differences on change in QoL over time between groups. • The DRL group showed significantly lower QoL during chemotherapy weeks compared to baseline.

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Table 1. *(continued)*

Study[a]	Study type[b]	Participants	Light therapy characteristics
Valdimarsdottir et al. (2018)[12]	RCT	Patients with multiple myeloma during autologous stem cell transplantation hospitalization	BWL (n=23) vs DWL (n=21) Acuity Brands Programmed environmental illumination of hospital rooms between 7 and 10 AM
Crabtree et al. (2020)[13]	FS	AYA's undergoing cancer treatment	BWL (n=26) vs DRL (n=25) Litebook Advantage 30 min within 1 h upon waking, 8 weeks

AYA adolescents and young adults; **BL** bright light; **BWL** bright white light; **CES-D** Center for Epidemiologic Studies-Depression scale; **DRL** dim red light; **FACIT-fatigue** Functional Assessment of Chronic Illness Therapy-Fatigue; **FACT-B** Functional Assessment of Cancer Therapy-Breast; **FACT-G** Functional Assessment of Cancer Therapy-General; **FOSQ** Functional outcomes of Sleep Questionnaire; **ISI** Insomnia Severity Index **MFS** Multidimensional Fatigue Scale; **MFSI-SF** Multidimensional Fatigue Symptom Inventory-Short Form; **POMS-SF** Profile of Mood States-Short Form; **PROMIS** Patient-Reported Outcome Measurement Information System; **PSQI** Pittsburgh Sleep Quality Index; **VAS** Visual Analogue Scale.
[a] Authors in italics reported secondary analyses of the primary studies reported by the authors in normal font. [b] **FS** feasibility study; **PS** pilot study; **PT** personalized (within-subjects) trials; **RCT** Randomized controlled trial

was the pilot study by Redd et al.[2]. Both RCTs that followed after this pilot study showed that reductions of fatigue were also observed after exposure to a control condition.

It is relevant to have a closer look at the clinical importance of the positive effects observed after light therapy. Redd et al.[2] reported a clinically important distinction between survivors exposed to BWL compared to DRL since none of the cancer survivors experienced clinical levels of fatigue after exposure to BWL, while 55 percent of the survivors exposed to DRL still experienced CRF. The effect size of this difference was 0.98. Johnson et al.[4] reported a smaller effect size of 0.30 for the superiority of BWL on the total score of the MFSI-sf. Our results showed an effect size of 0.81 for general fatigue in all participants, irrespective of condition, at post intervention, which corresponds to clinical significant benefits for 60 to 63 percent in the BWL and DWL group, respectively (**chapter 3**). This is in line with effect sizes of 0.96 and 0.76 on general fatigue in BWL and DRL, respectively, reported by Johnson et al.[4]. The effect sizes of our study and the study by Johnson et al. suggest clinically relevant improvements in both groups

Outcome	Instrument	Conclusion
Quality of life	FOSQ	• Significant deterioration in sleepiness-related QoL in DRL compared to no change in BWL. • Changes in sleepiness-related QoL were related to changes in fatigue.
Depression	CES-D	• No significant differences on change in depression over time between groups. • The DRL showed significantly more depressive symptoms during chemotherapy weeks compared to baseline.
Depression	CES-D	• BWL prevented the increase of depressive symptoms that was seen after DRL ($\eta^2 = 0.08$).
Fatigue	PedsQL MFS	Total score: • BWL showed larger reductions of fatigue than the reduction seen after DRL. Subscales: • BWL showed a reductions on cognitive fatigue, which was not seen after DRL. • Both groups showed reductions on general and sleep/rest fatigue.

as effect sizes of 0.50 or larger are considered clinically relevant[15]. Moreover, these numbers are comparable to clinically significant improvements resulting from cognitive behavioral therapy (clinical improvement in 54 percent)[16] and physical exercise ($d = 0.53$)[17]. This suggests that all light therapies, either BWL, DWL, or DRL, led to clinically relevant improvements of fatigue in cancer survivors with CRF.

Our results further showed that both groups, irrespective of condition, showed improvements on subjectively reported sleep quality, depression, and three aspects of quality of life (**chapter 3**). No effects were observed for anxiety and other aspects of quality of life, nor for objectively assessed sleep-wake cycles and circadian rhythms of melatonin and cortisol (**chapter 3**). These results are partially in line with previous results. The pilot study[3] suggested that light therapy had no effect on subjective sleep quality but the RCT[5] showed, in line with our results, that both groups improved on subjective sleep quality over time. Moreover, results of the RCT[4] showed that both types of light therapy (BWL and DRL) led to improvements on depression and quality of life.

Light therapy is known for its entraining effect on circadian rhythms to the environmental rhythm (e.g. light-dark cycle). Redd et al.[2] suggested that the positive effect of light therapy might results from the entrainment of circadian activity rhythms. A secondary analysis of this study[3] suggested that BWL improved sleep efficiency in cancer survivors. However, this effect was small, clinically irrelevant and not replicated by our RCT (**chapter 3)** nor the RCT by Johnson et al.[5]. In fact, both RCTs showed no effect of light therapy on actigraphy derived sleep-wake cycles. We further investigated this hypothesis by looking at neuroendocrine correlates of the circadian rhythm (melatonin and cortisol). Our results showed that there was no effect on these

outcomes (**chapter 3**). This is partly in line with a secondary analysis of the RCT by Johnson et al.[6] showing that the diurnal cortisol slope and the total cortisol slope increased after completion of the light therapy in both groups (d = 0.57 and d = 0.49, respectively). This increase was not a mediator for the relationship between light therapy and fatigue levels.

Light therapy for cancer survivors with symptoms other than fatigue

Studies on light therapy in cancer survivors were not limited to CRF as an outcome. Three studies tested the efficacy for other symptoms in studies with small sample sizes.

First, Kronish et al.[7] used a different approach to study the efficacy of light therapy in cancer survivors with at least mild depressive symptoms. They used a crossover within-subject design for nine cancer survivors who were exposed to either BWL or DRL. The results of this study showed that the effect of light therapy is heterogeneous. Some survivors reported a decrease, the majority showed no difference, and some an increase on depression and fatigue after exposure to BWL compared to exposure to DRL. Whether depression and fatigue decreased during the study irrespective of condition was not reported.

Second, Fox et al.[8] studied the feasibility and preliminary efficacy of light therapy in ovarian and endometrial cancer survivors with sleep disturbances. Although not statistically significant, results showed a tendency towards superiority for green bright light (GBL) over DRL on the number of nighttime awakenings (actigraphy), subjective sleep quality, and depression. Furthermore, in line with our results, the results showed a statistically significant clinically relevant improvement (d = 1.19) of fatigue in all participants, irrespective of light condition. There was a tendency for a significant increase of total sleep time over time in both groups. No effects were found for other actigraphy-derived variables, quality of life, and cortisol and melatonin concentrations.

The study by Fox et al.[8] is the only study that also reported the effect of light therapy on subjectively assessed cognitive functioning, namely: perceived cognitive impairment, impact of perceived cognitive impairment on quality of life, comments from others, and perceived cognitive abilities. There was a nearly significant superiority of DRL over GBL for the comments from others domain since scores worsened in the GBL group and remained stable in the DRL group. However, the change in the GBL group was very small. No effects were found on the other domains. In **chapter 4**, we reported the effect of light therapy on cognitive impairment (assessed with questionnaires) and cognitive functioning (based on neuropsychological tests). Our results showed that light therapy, irrespective of light intensity, had no effect on these outcomes.

An important limitation of our study (**chapter 4**) and the study by Fox et al.[8] is that the samples were not recruited based on the presence of cognitive dysfunctioning but on the presence of sleep disturbances or CRF, respectively. A closer inspection of the baseline values in our study indicated that one-third of the survivors with CRF experienced cognitive dysfunctioning (**chapter 4**), which reduces the power of our study. The results of a sensitivity analysis in these survivors were in line with the intention-to-treat analyses, showing that light therapy had no effect on cognitive complaints or cognitive functioning (range p-values .05 to .78; range effect sizes .04 to .43). Based on these two studies, we suggest that light therapy is probably not effective for reducing cognitive complaints or improving cognitive functioning.

However, replication of these results in a sufficiently powered study in a sample with objectively assessed cognitive dysfunctioning at baseline is necessary to confirm this conclusion.

Finally, Rogers et al.[9] examined the feasibility of light therapy to improve circadian rhythms in eight adolescent cancer survivors. This was a convenience sample not selected on circadian disruptions a priori because the study primarily focused on the acceptability and adverse events and secondarily studied the effect of light therapy on circadian activity rhythms. The results showed that participants did not report an increased number of adverse events compared to healthy adolescents with no history of cancer. Moreover, there was no effect of light therapy on circadian activity rhythms. This might result from the selection of the sample, as the circadian activity rhythms of the participants were comparable to a healthy control group leaving small to no room for improvement.

Light therapy for patients with cancer while receiving cancer treatment

The interest for light therapy as a treatment for CRF stems from the pilot study of Ancoli-Israel et al.[1] that showed promising results. Exposure to BWL prevented the increase of fatigue and deterioration of circadian activity rhythms and quality of life compared to DRL in breast cancer patients receiving chemotherapy[1, 10, 11]. Since then, two more studies investigated the effect of light therapy in patients with cancer while receiving cancer treatment.

Valdimarsdottir et al.[12] investigated the effect of programmed environmental illumination of hospitals room on depressive symptoms in forty-four patients with multiple myeloma scheduled for autologous stem cell transplant. The results showed a significant difference between groups indicating that patients exposed to BWL showed a smaller increase of depressive symptoms during hospitalization compared to patients exposed to DWL.

Crabtree et al.[13] studied the acceptability and feasibility of light therapy to reduce fatigue in adolescent and young adults receiving treatment for cancer. Fifty-one participants with newly diagnosed solid tumors, including lymphoma, were randomized to BWL or DRL. Results showed that there were no differences between individuals exposed to BWL or DWL concerning the side effects reported due to light therapy and treatment of cancer. Moreover, results of self-reported fatigue showed that there were significant differences between groups for the effect of light therapy on cognitive fatigue and total fatigue, with larger reductions of fatigue after BWL compared to DRL. Improvements on general fatigue and sleep/rest fatigue were reported in both groups.

Summary of light therapy studies in cancer populations

In general, research on light therapy for cancer populations is limited. The majority of the published studies are pilot studies with methodological limitations, for example small sample sizes. Studies that primarily focused on light therapy for cancer survivors with CRF[2, 4] concluded superiority of exposure to BWL compared to DRL on fatigue, although a closer inspection of the RCT by Johnson et al.[4] indicates that both types of light therapy led to clinically relevant reductions in multiple domains of fatigue in cancer survivors with CRF. Moreover, light therapy, irrespective of condition, led to improvements on subjectively reported sleep quality, depression, and quality of life. It is unlikely that these positive effects result from an entrainment

of circadian rhythms as no effects were observed for light therapy on circadian rhythms of sleep-wake cycles, cortisol and melatonin.

Studies that included cancer survivors with symptoms other than CRF, also reported a reduction of fatigue after light therapy, irrespective of condition[8]. Moreover, results on the primary outcomes of these studies, including depressive symptoms or sleep disturbances were inconclusive. One study suggested superiority of exposure to BWL for the number of night time awakening, subjective sleep quality, and depression[8]. However, another study showed no effect on objectively assessed sleep-wake cycles[9]. This might be explained by individual differences on the effect of light therapy that was reported after a within-subject comparison of exposure to BWL and DRL[7].

Studies that investigated the use of light therapy in patients with cancer while receiving treatment seem more promising since all of them reported lower levels of fatigue and depression and better quality of life after exposure to BWL compared to DRL[1, 10-13]. One pilot study showed that exposure to BWL maintained the circadian rhythm at baseline while the group exposed to DRL showed deterioration of the circadian activity rhythm[10].

Unexpected improvement of fatigue irrespective of light intensity

Contrary to the results of Redd et al.[2], our study, as well as the RCT reported by Johnson et al.[4], reported clinically relevant improvements of fatigue after light therapy, irrespective of light intensity. There are multiple explanations for this improvement in both groups. First, the positive effect of light therapy on self-reported outcomes in both groups might be the consequence of non-specific treatment effects, i.e. the Hawthorne effect. The Hawthorne effect describes changes in the behavior and/or reporting by a participant simply because the participant is observed[18]. Examples of potential non-specific treatment effects in the SPARKLE study are positive attention from the research team, increased awareness that CRF is a common symptom, increased physical activity, and increased awareness on someone's sleep-wake cycle by the completion of a sleep diary for 10 days, which were all reported by the participants. Some participants also reported to enjoy the 30 minutes of "quiet time" in the morning while completing light therapy. These effects might resemble effective components of (internet-based) cognitive behavioral therapy (CBT) and mindfulness-based CBT (MBCT), which are shown to be effective as a treatment for CRF[16, 19, 20]. One module of CBT addresses the importance of a regular sleep-wake cycle and includes an assignment to track someone's sleep-wake rhythm for several days to gain insight into this rhythm. This assignment unintentionally became part of the study design of the SPARKLE study when we asked participants to complete a sleep diary for 10 days during each measurement point. Moreover, the 30 minutes of quiet time might resemble an assignment of MBCT. A closer evaluation of MBCT showed that an increase on *sense of control* was the most important working mechanism[21], which is in line with personal comments by some participants mentioning that they experienced an increased capability to change their fatigue.

Second, the improvement of fatigue in the DWL group can be the result of a placebo response, which could be the case for the BWL group as well. Placebo responses to treatments for CRF have been reported and a recent meta-analysis based on 29 studies showed that 29 percent (with a range between 3 to 77 percent[22, 23]) of the participants showed a decrease in

fatigue after placebo treatment in patients with cancer and cancer survivors[24]. The included studies mostly investigated pharmacological treatment for CRF compared to placebo pills, but other placebo treatments were sham acupuncture (n = 3), control telephone calls (n = 1), sesame seed oil injections (n = 1), and sham infrared laser (n = 1). Hoenemeyer et al.[25] showed that this placebo response also occurs when it is clearly mentioned to participants that they receive placebo pills. Twenty-nine percent of the participants who received open-label placebo pills reported clinically relevant and statistically significant improvements with a moderate effect size (*d* = 0.63) compared to treatment as usual. This effect remained stable during a follow-up period of three weeks. Another meta-analyses on the effect of placebo treatment for insomnia symptoms showed that participants who received a placebo treatment (pharmacological and psychological) reported significant changes in self-reported sleep outcomes but not in objective outcomes[26].

To the best of our knowledge, a placebo response for light therapy has not been described but the findings of the SPARKLE study suggest this might be the case. Both BWL and DWL led to improvements in self-reported outcomes with effect sizes comparable to those found after open-label placebo pills treatment[25] in the absence of a response on objectively assessed circadian rhythms of sleep-wake cycles, cortisol, and melatonin. However, we should be careful to conclude that light therapy in the SPARKLE study did not elicit a biological response. We primarily focused on the assumption that light therapy works via entrainment of circadian rhythms because light is the most important *zeitgeber* for the circadian rhythm. Nonetheless, it has been shown that the intrinsically photosensitive retinal ganglion cells responsible for this biological response are not only connected to the superchiasmatic nucleus but also to other brain regions involved in sleep regulation, cognitive functioning, and mood[27]. For example, a recent study[28] showed that sleep quality measured with polysomnography was associated with light exposure on the preceding day in healthy participants. These results suggested that light exposure not only affects circadian driven aspects of sleep but also homeostatic sleep pressure. The homeostatic sleep pressure was not assessed in the SPARKLE study. Therefore, there might be other mechanisms of action, independent from circadian entrainment, explaining the effect of light therapy that have not been studied in the SPARKLE study.

Finally, the positive effect of light therapy in both groups might not be related to light therapy or study participation but could simply be the consequence of a natural improvement of fatigue. Although we did not include a waiting list control condition to test this hypothesis, we believe that the chance of spontaneous natural improvement of CRF in our participants is very small. The mean time since diagnosis of our sample was almost 13 years, indicating that these survivors suffered from CRF for many years. A natural improvement of CRF is likely to occur in the first two years after diagnosis but stable levels, or even increasing levels, are reported after this period[29]. Specifically, two longitudinal studies in long-term cancer survivors showed that fatigue levels remained stable during follow-up[30, 31]. Therefore, we expect that a spontaneous improvement of fatigue in our sample during a period of 3,5 weeks is unlikely.

Methodological limitations

Our intervention study had several methodological strengths, including the double-blind, randomized controlled design, the assessment of self-reported, behavioral, and biological

outcomes, a large sample size, multicenter participation, and a relatively long follow-up period of nine months. However, there were also some methodological limitations concerning the light therapy characteristics, the assessment of fatigue, and the assessment of melatonin and cortisol.

Light therapy characteristics

Light therapy protocol

The first study in breast cancer patients receiving chemotherapy instructed participants to use light therapy for 30 minutes in the morning, upon awakening, during the first four cycles of chemotherapy (approximately eight to twelve weeks)[1, 10]. These instructions were based on the guidelines for light therapy for seasonal affective disorder (SAD)[32, 33]. The studies that followed used similar instructions, although the duration was shortened to four weeks (28 days)[2, 4, 8, 9] or three weeks[7] in cancer survivors. Only the Instructions for the study by Valdimarsdottir et al.[12] differed as light sources were on between 7 AM and 9 AM while the participant was hospitalized for autologous stem cell transplant. Although this seems like a much longer time frame, the authors made this choice to ensure that participants were exposed to light therapy for at least 30 minutes each morning as participants were allowed to leave their room. In line with these studies, we instructed participants to use light therapy for 30 minutes within half an hour after wakening. Only the duration of light therapy was slightly shorter (25 days). We preferred this duration, as we wanted to collect saliva at the end of a workweek (i.e. on Friday) to decrease the circadian shift effect due to changing sleep-wake rhythms on weekend days compared to weekdays. The shorter duration of light therapy could potentially explain the lack of superiority of BWL over DWL. However, we believe this is unlikely, as the guideline of light therapy for SAD describe that light therapy usually shows improvements within the first two weeks with a full clinical response after four weeks[33]. Therefore, the duration of 25 days should have been enough to elicit an initial clinical response.

Compliance to light therapy

A compliance rate of 47 to 49 percent was reported in adult patients receiving chemotherapy[1], which was slightly smaller than the compliance rate of 57% reported in AYA's receiving cancer treatment. In adult cancer survivors[3, 4, 8], the compliance rate ranged from 67 to 95 percent compared to 61 percent in adolescent cancer survivors[9]. The subjective report of compliance in the SPARKLE study showed that light therapy was used on 91 percent of the required days. Hence, the compliance rate in our study was high compared to previous studies. When we look at the compliance on an individual basis, we see that 37 percent of the participants completed light therapy on all 25 treatment days. The majority, 56 percent, used light therapy for 14 to 24 days. Based on the light therapy guidelines for seasonal affective disorder[32], we expect that these individuals would have experienced a first response to the light therapy but might not have reached a full response. We did not include an objective measurement of light exposure in our study. Therefore, we could not confirm the compliance to light therapy nor correct for daily light exposure. However, sensitivity analyses corrected for season did not change the conclusions.

Spectral aspects of light therapy

Most studies that investigated light therapy in cancer populations used a light therapy device from the Litebook Company (i.e. *Litebook 1.2*[1, 2], *Litebook Elite*[4, 9], or *Litebook Advantage*[7, 13]). One study used light therapy glasses, i.e. the *Re-Timer*[8] and one study used lights from *Acuity Brands*[12] that could be placed in hospital rooms. The first 37 participants of the SPARKLE study used of *Litebook Edge*. However, spectral measurements established a light spectrum enriched around 450 nm of 351 lux at eye level for the device used in the BWL condition. This is comparable to office lighting and not sufficient for light therapy. Therefore, we changed to *Luminette glasses*. Table 2 gives an overview of the technical aspects of these devices.

Table 2: Overview of technical aspects of light therapy devices[a].

Light source	Condition	LEDs	Light intensity	Peak light spectrum
Litebook 1.2	BWL	60, white	1.350 lux	464 nm and 564 nm
	DRL	60, red	< 50 lux	N/A
Litebook Elite	BWL	25, white	1.250 - 1.500 lux	465 nm
	DRL	25, red	< 400 lux	633 nm
Litebook Advantage	BWL	24, red	10.000 lux	N/A
	DRL	24, red	N/A	N/A
Re-Timer	BGL	4, red	506 lux	N/A
	DRL	4, red	N/A	N/A
Acuity Brands	BWL	N/A	1.300 lux	N/A
	DWL	N/A	90 lux	N/A
Litebook Edge	BWL	15, white	10.000 lux	480 nm
	DWL	15, white	< 20 lux	480 nm
Luminette glasses	BWL	8, white	1.013 lux	465 nm
	DWL	8, white	8 lux	465 nm

LED light-emitting diode, **BWL** bright white light, **DRL** dim red light, **BGL** bright green light, **DWL** dim white light, **nm** nanometer

[a] These technical aspects were retrieved from the methodological sections of the studies using these devices. The technical aspects of the Luminette glasses used in our study are based on spectrometric measurements.

Based on the details of the light spectra used in the different studies, we want to address three issues. First, there appears to be a difference of the intensity of the *Litebook Advantage* (10.000 lux) compared to the *Litebook 1.2* and *Litebook Elite* (1.250 to 1.500 lux). However, it is very likely that the intensity of the *Litebook Advantage* is the intensity reported by the distributor, which is described as an equivalent of 1.500 lux at eye level. Second, the guidelines for light therapy use in seasonal affective disorders propose that the starting "dose" for light therapy is 10.000 lux for 30 to 40 minutes a day. An alternative dose is exposure to 2.500 lux for 2 hours a day[33]. This indicates that the intensity of light therapy used in the described trials might have been too low or the duration too short. However, we suspect that the guidelines mean that light therapy devices used for light therapy should elicit an intensity of 10.000 lux, which is equivalent to 1.500 lux at eye level. If this is the case, than the light therapy protocols in these

studies follow the guidelines. Third, the description of the light spectra lacks details in most studies. Most details were mentioned by Johnson et al.[4] who described the peak wavelength and intensity of both conditions, while other studies[9, 13] only reported the intensity of the BWL condition without details on the peak wavelength or the light spectrum of the DRL condition. There is also an example of different light spectrum reports within the same research team, as Ancoli-Israel et al.[1] reported no information on the BWL condition, Neikrug et al.[10] mentioned an intensity of 1.500 lux, while Jeste et al.[11] described an intensity of 10.000 lux. Therefore, we want to underline the importance of a standard description based on standardized estimations of light spectra in light therapy studies. In our study, we used the Irradiance Toolbox by Lucas et al. to describe light spectra[34]. More recently, the International Commission on Illumination (CIE) introduced an Equivalent Daylight Illuminance Toolbox that can be used to convert light spectra into absolute α-opic irradiance in mW/m^2, which is in line with the seven units of the basic International System of Units (SI units)[35]. More details on minimum reporting guidelines for light exposure are reported by Spitschan et al.[36].

There were differences between the light spectra of the control conditions used in the studies on light therapy in cancer patients or cancer survivors. Most studies used DRL with intensities of less than 50 lux[1, 2] or 400 lux[4], or intensities were not reported[8, 9, 13]. In the SPARKLE study, we used DWL with an intensity of less than 20 lux. This light might have been able to elicit a biological response. Nonetheless, several studies showed that polychromatic light, as used in the SPARKLE trial, needed an intensity of 393 lux or higher to induce an effect on circadian rhythms[37, 38]. This is supported by the study of Valdimarsdottir et al.[12] that showed significant differences in individuals exposed to BWL (1.300 lux) and DWL (90 lux). Moreover, one study[39] compared the effect of dim white light (50 lux, 460 nm) and dim red light (50 lux, 633 nm) on mood and fatigue in a within-subjects design. The results, based on five cancer survivors who completed primary cancer treatment, showed that two participants had significantly lower fatigue symptoms after DRL while this was not seen after exposure to DWL. The remaining participants showed no differences of the effects of exposure to DRL or DWL. These results suggests that the between group differences in the SPARKLE study could be similar or even larger compared to previous studies using DRL.

Assessment of cancer-related fatigue

Different instruments were used to assess fatigue in studies investigating the efficacy of light therapy as a treatment for CRF. Redd et al.[2] used the FACIT-fatigue[40], Johnson et al.[4] the MFSI-SF[14] and we used the MFI[41] as one of the primary outcomes. We decided to use the MFI for four reasons. First, this scale measures five different domains of fatigue and therefore, it was possible to investigate whether light therapy has an effect on some aspects of fatigue and not on other domains of fatigue. Second, the MFI has been widely used to assess CRF[42]. Third, several review studies suggested that the MFI is a valid and reliable assessment for CRF with acceptable psychometric properties[43-46]. Finally, norm data from a German population was available to determine the clinical significance of fatigue in eligible HL and DLBCL survivors[42].

While the SPARKLE study was ongoing, we wanted to publish norm data of the MFI from a Dutch population and had a closer look into the validation studies of the MFI. At that moment, we realized that replication of the original five-factor structure was scarce and decided to

perform a psychometric evaluation of the MFI. The results of our confirmatory factor analyses, reported in **chapter 5**, showed no empirical support for the original 5-factor structure of the MFI, nor for the alternative 4-factor structure reported in the original validation study or a bi-5-factor and bi-4-factor structure that also included a general factor for fatigue. We performed additional exploratory factor analyses to examine whether an alternative factor structure could describe the different dimensions of fatigue assessed with the MFI. The results showed no reliable and valid alternative factor structure. Therefore, we suggest that results of the subscales of the MFI should be interpreted with caution. It is preferred that conclusions are based on the general fatigue subscale as this subscale showed the most robust results and the highest correlations with a visual analogue scale from 0 (no fatigue) to 10 (worst imaginable fatigue).

Consequently, we only reported results of the MFI general fatigue scale in our studies. This could potentially explain why we were unable to detect superiority of BWL over DWL because Redd et al. and Johnson et al. showed superiority of BWL over DRL for the total fatigue score from the FACIT-fatigue and the MFSI-SF. The results on the general fatigue scales in both RCTs were conclusive, showing improvements over time in both groups. When we repeated our analysis for the total score of the MFI and the remaining scales of the MFI (unpublished), we were still unable to detect statistically significant differences in change over time between BWL and DWL. An improvement over time was seen in the total group, irrespective of light intensity, for the total score of the MFI and physical fatigue, reduced activity and reduced motivation. No effect was seen on mental fatigue, which contradicts the finding of Johnson et al. where mental fatigue improved in both groups.

Another aspect of the fatigue instruments used in these studies is whether fatigue was assessed as a unidimensional or a multidimensional construct. The FACIT-fatigue measures fatigue as a unidimensional construct. The MFSI-SF measures multiple dimensions of fatigue. The MFI aims to assess five dimensions of fatigue but the lack of a reproducible factor structure and the presence of high correlations between the original factors (**chapter 5**) suggests that the MFI might not be successful in the assessment of different dimensions of fatigue. The correlations between factors indicate an overlap in variation, which makes it questionable that these factors represent unique domains of fatigue. Instead, it might be that the MFI measures a unidimensional general fatigue dimension and that the other scales cover other constructs that can, but may not necessarily be, influenced by fatigue. For example, the mental fatigue domain covers cognitive functioning and physical fatigue covers physical functioning. Therefore, we only reported the results of general fatigue and considered this a unidimensional assessment of fatigue. Remarkably, Johnson[47] reported that results from the FACIT-fatigue in their RCT showed no significant difference between groups but improvements over time for the total sample. Taken together, the inconsistency for the superiority of BWL compared to a comparison condition is also not explained by the choice to assess fatigue as a unidimensional or multidimensional construct.

It is important to note two important methodological aspects when interpreting the lack of a factor structure in our psychometric evaluation of the MFI while other studies were able to identify certain factor structures. First, the samples used to examine the factor structure of the MFI. Our study was conducted in a sample of the Dutch general population, while other

studies tested the factor structure in samples of patients with somatic disorders. Consequently, the reported factor structures might be sample specific. Second, the sample size should be considered. A rule of thumb states that at least five participants per estimated parameter need to be included to perform confirmatory factor analysis[48]. This means that at least 350 participants are necessary to confirm the factor structure of the MFI. Our study included the largest sample size so far for a confirmatory factor analysis of the MFI (n = 2512). Most of the validation studies in the past did not reach this bare minimum, which might have led to unjustified conclusions in the past.

Assessment of melatonin and cortisol

One of the strengths of our study is the inclusion of the assessment of circadian rhythms of melatonin and cortisol. It is known that these neuroendocrine correlates of the circadian rhythm are affected by multiple factors, e.g. drinking of caffeinated drinks, eating bananas or chocolate. Moreover, it is important for the determination of the dim light melatonin onset (DLMO) that the evening saliva samples were collected in dim light situations. Therefore, we planned to collect the melatonin samples only during autumn and winter and asked participants to close the curtains during the collection of these samples. Despite our efforts, 15 out of 57 participants collected evening saliva samples for DLMO determination in the spring or the summer. These participants were asked to wear orange glasses to block blue light during the evening sample collection. Although we provided clear instructions, we don't know whether all participants followed these instructions. Some participants self-reported that they did not comply with some of the instructions and were removed from the analyses. Specifically for the DLMO, non-adherence to the dim light saliva collection could have masked a true effect of light therapy.

Overall conclusions

The following conclusions can be drawn from the light therapy study presented in this thesis:

- There is insufficient evidence to recommend light therapy as a treatment for cancer-related fatigue in long-term cancer survivors.
  - There was no superiority for exposure to BWL compared to DWL on reducing fatigue in long-term HL and DLBCL survivors with chronic-cancer related fatigue (**chapter 3**).
  - Both groups, irrespective of light intensity, showed clinically relevant improvements of fatigue (**chapter 3**).
  - Both groups, irrespective of light intensity, showed improvements on subjective sleep quality, depression and some aspects of quality of life (i.e. role limitations due to physical functioning, energy, and social functioning) (**chapter 3**).
  - Light therapy had no effect on objectively assessed circadian activity rhythms (**chapter 3**).
  - Light therapy had no effect on the circadian rhythms of cortisol and melatonin (**chapter 3**).
- One-third of long-term HL and DLBCL survivors with persistent fatigue experience cognitive dysfunctioning.

- Cognitive dysfunctioning especially occurs in the verbal memory domain (**chapter 4**).
- Light therapy had no effect on cognitive complaints and cognitive functioning in long-term HL and DLBCL survivors with chronic cancer-related fatigue (**chapter 4**).

❖ The multidimensional fatigue inventory has a questionable factor structure.

- A psychometric evaluation of the Multidimensional Fatigue Inventory in the Dutch general population (n = 2512) did not confirm the original 5-factor structure, nor an alternative 4-factor nor a 5- and 4-bifactor model (**chapter 5**).
- The lack of a clear factor structure makes it questionable whether the MFI measures multiple dimensions of fatigue (**chapter 5**).
- The conceptual and structural issues with the MFI question whether conclusions based on the five scales of the MFI are reliable (**chapter 5**).
- The *general fatigue* scale showed robust loadings and showed the highest correlation with a fatigue rating from 0 (no fatigue) to 10 (worst fatigue) suggesting that the *general fatigue* scale could be a good measure to assess fatigue (**chapter 5**).

Clinical implications

The guidelines of the National Comprehensive Cancer Network (NCCN) currently recommend the use of light therapy for CRF in cancer survivors. This recommendation is based on lower-level evidence from the pilot study by Redd et al.[2] and the RCT by Johnson et al.[4] and uniform consensus that the intervention is appropriate. The study described in this thesis does not support this recommendation for long-term cancer survivors. However, there was a clinically relevant and statistically significant improvement for fatigue in approximately sixty percent of our participants, irrespective of light intensity, which should not be ignored as these survivors suffered from fatigue for an average duration of 13 years. For some participants, this effect was life changing, as can be seen in the comment of one participant describing how light therapy influenced her life nine months after light therapy use:

> *"I can't describe the feeling that I got my life back. No longer a walking zombie. Sleeping for max. 2 to 3 hours a night is over. During the last 10 years, my life was disrupted because of insomnia. Continuously fatigued. Now, people in my environment see a sparkle in my eyes. They see changes in my behavior. I also feel this. I am more active. More outgoing. Enjoying trips and vacations. I can go on for hours. The light therapy was offered to me at the right time in my life. It felt like a complete reset. Shortly, I feel reborn. I became a new human."*
> (Female participant, 58 years, 9 years since DLBCL diagnosis, exposed to DWL)

At this moment, it remains unclear what caused this positive effect reported by the majority of the participants. Therefore, the interpretation of these results for clinical implications can be twofold. On the one hand, we can conclude that we cannot advice the radiation-oncologists and hematologists of the BETER consortium to prescribe light therapy as a treatment for CRF. Within our RCT, we compared a biologically active light intensity with a light intensity

that is currently considered to be biologically inactive. As there were no differences between individuals exposed to the intervention or the control light, there is no proof for the efficacy of light therapy. Instead, the improvement might be caused by other factors, for example life style changes, the Hawthorne effect or a placebo response. Therefore, it is necessary to further investigate which elements of the light therapy study protocol are responsible for the clinical relevant improvements before implementation of light therapy as a treatment for cancer survivors with CRF.

On the other hand, one could argue that light therapy could be made available for cancer survivors with CRF. As described by Kaptchuk and Miller[49], the goal of medicine is to heal. This includes curation, controlling a disease, and *relieving* symptoms. The results described in this thesis suggest that light therapy is able to relieve fatigue in a substantial part of cancer survivors that are suffering. Moreover, it is easy to deliver and requires almost no supervision from clinical staff. As the mechanisms of action are currently unclear, and a placebo response cannot be excluded, light therapy could be implemented according to the recommendations for implementation of placebo treatments in clinical practice[50]. These recommendations mention that placebo effects should be optimally used in clinical practice while informing patients optimally about placebo effects. For light therapy, this would mean that physicians acknowledge that the positive effects for light therapy are not yet understood and might stem from placebo effects. If a patient remains enthusiastic about light therapy, they could try if it works for them. Expectations play an important role in placebo effects[50]. Hence, we advise to only offer light therapy to cancer survivors who have a positive attitude towards it. Previous studies showed that the prescription of an open-label placebo treatment in cancer survivors with CRF[25], irritable bowel syndrome[51], chronic pain[52, 53], and migraine[54] led to reduced symptoms.

However, while our study was ongoing, the evaluation of an internet-based cognitive behavioral therapy (ICBT) for CRF was published[19]. Severely fatigued breast cancer survivors were randomized to ICBT or care a usual (CAU; mean time since diagnosis of 44 and 39 months, respectively). Results showed that survivors randomized to ICBT reported significantly reduced fatigue levels compared to survivors who received CAU with an effect size of 1.0. On an individual level, 73% of the survivors in the ICBT group reported a clinically relevant reduction compared to 27% of the survivors in the CAU group. Therefore, it can be suggested that this internet-based function was as successful (or even more successful) that the face-to-face version of CBT for CRF, which led to a clinical improvement in 54% of the participants[55]. Moreover, the internet-based version has additional advantages, for example lower costs and it is easier accessible for survivors. Therefore, it might be more interesting for the radiation-oncologists and hematologists of the BETER-consortium to explore the efficacy and implementation of ICBT for CRF in clinical practice.

Another important clinical finding described in this thesis is the finding that approximately one-third of the long-term HL and DLBCL survivors with persistent CRF experienced cognitive dysfunctioning, predominantly in the verbal memory domain. This can be very disturbing for survivors as it can influence their daily life, e.g. they might have trouble in their professional life. Therefore, physicians of the BETER consortium should be aware of these problems. Survivors

might benefit from early detection, for example via the Amsterdam Cognition Scan[56], and referral to cognitive rehabilitations programs, e.g. internet-based cognitive rehabilitation[57].

Directions for future research

Multiple questions for the use of light therapy as a treatment of CRF remain. For example, it could be further investigated which elements of light therapy study protocols are responsible for the clinically relevant improvements observed in a small majority of our participants. The section "Unexpected improvement of fatigue irrespective of light intensity" gives an overview of potential elements, including non-specific treatment effects or a placebo response. Moreover, the dataset collected during this project can be used to further investigate several research questions. First, actigraphy data collected during the day can be used to investigate whether the positive effect of light therapy was associated with increased physical activity during the intervention. Second, exploratory analyses can be performed to investigate individual differences between individuals who experienced reduced fatigue levels after light therapy, irrespective of condition, compared to survivors who did not experience this effect. Third, blood samples collected at baseline and post intervention can be used to investigate the influence of light therapy in inflammatory biomarkers related to CRF. These blood samples can also be used to investigate associations between a response to light therapy and the genetic profile, for example with clock genes.

It is a difficult issue to investigate whether a placebo response led to the positive effects observed in our light therapy trial, as there are still gaps in our knowledge on the mechanisms of action for light therapy. The literature describes several control conditions for light therapy trials, including DRL, DWL, negative ions at a low or high flow rate, or the use of a deactivated negative air ionizer[58]. We choose to use white light with a low intensity as a control condition because we assumed the lower intensity would cause no, or a very limited, biological response. However, we cannot rule out that the DWL had some biological effects. Therefore, future studies should investigate whether the DWL spectrum of our study had any biological effects. More fundamental research on the projections of intrinsically photosensitive retinal ganglion cells might unravel pathways sensitive for blue-enriched white light of low intensities. This research should not be limited to circadian responses but should also investigate projections to other brain regions (for example emotion regulation and sleep regulation). New insights into these pathways will make it easier to determine the characteristics of a true placebo light therapy.

On a more general level, it would be interesting to explore whether the combination of light therapy with other treatments for CRF, for example ICBT, leads to additive treatment effects. For example, in insomnia patients it has been shown that the combination of chronobiologic treatment, e.g. light therapy, and internet-based CBT for insomnia (ICBTI) led to a longer sustained effect of ICBTI[59]. The design of a similar study in breast cancer patients receiving chemotherapy was recently published by Bean et al.[60] and data collection is ongoing. To the best of our knowledge, this is currently not under investigation in cancer survivors. An alternative approach might be a design in which participants first complete four weeks of light therapy followed by a physical exercise or CBT intervention based on the hypothesis that an initial response to light therapy might increase motivation to participate in these interventions.

The discussion on light therapy studies in cancer populations in this chapter described a discrepancy for the effect of light therapy in cancer survivors compared to patients with cancer receiving treatment. The evidence for superiority of BWL over a control condition in the treatment of CRF in cancer survivors is not convincing. However, several studies in patients with cancer receiving treatment suggest a protective effect of BWL compared to DRL for the increase of negative symptoms like fatigue and depression and desynchronization of circadian rhythms during treatment. As these studies had methodological limitations, we would advice to perform a RCT to test the protective effect of light therapy for the occurrence of fatigue and related symptoms in patients with cancer undergoing treatment. This trial should include long-term follow-up assessments to investigate whether this initial intervention prevents the occurrence or reduces the levels of these symptoms in cancer survivors.

The results of our critical evaluation of the psychometric properties of the MFI shows the importance of psychometric evaluations of scales that have been widely used in research. Even though multiple review studies mentioned the MFI as a valid and reliable scale to measure multiple dimensions of fatigue, our results suggest otherwise. Based on the lack of a clear distinction between multiple dimensions of fatigue, we suggest that results from the MFI should be interpreted with caution. The general fatigue subscale seems to be the most reliable scale. For future studies, we would advice to primarily use a valid and reliable assessment of the unidimensional concept of fatigue. This advice is in line with previous recommendations[61, 62]. Moreover, it is questionable whether it is clinically relevant to distinguish different dimensions of fatigue[45]. In case of specific hypotheses on subdomains of fatigue, a multidimensional assessment of fatigue can be added. This recommendation is in line with current guidelines of an independent working group, the ASCPRO (assessing symptoms of cancer using patient-reported outcomes)[63]

CIRCADIAN RHYTHMS AND CANCER RELATED FATIGUE

Comparison with the literature

The studies described in this thesis strongly focused on the effect of light on circadian rhythms. This was based on the rationale that light is the most strongest *zeitgeber* for circadian rhythms and the findings that higher levels of CRF are consistently associated with disruptions in circadian rhythms in patients with cancer[64-69]. Studies based on circadian activity rhythms, assessed with actigraphy, concluded that patients with cancer with higher levels of fatigue showed less daytime activity, more daytime sleep, and night awakenings. Studies that investigated the association between neuroendocrine correlates of circadian rhythms and fatigue after cancer showed that a flatter diurnal slope was associated with higher levels of CRF[70, 71]. However, when we started this study, it was unclear whether a misalignment between the environmental rhythm and endogenous circadian rhythms is associated with CRF. We hypothesized that the endogenous circadian rhythms of cancer survivors with CRF might be delayed compared to the environmental rhythm.

To test this hypothesis, we performed a survey study in which we compared the chronotype and sleep quality of long-term HL and DLBCL survivors with and without CRF (**chapter 6**). Our results showed that there was no association between chronotype and CRF, suggesting that the

preference for morningness or eveningness did not differ between survivors with and without fatigue. Our results are in line with the finding that chronotype was not associated with fatigue in patients with rheumatoid arthritis[72]. However, our results contradict a previous study that reported that breast cancer survivors who reported to be an evening type suffered from higher levels of fatigue compared to survivors who reported to be a morning type[73]. Studies in other populations also showed that evening types reported higher levels of fatigue compared to morning types (e.g.in individuals with irritable bowel symptoms[74] and students[75]).

Since chronotype is not only correlated with circadian phase but also with the homeostatic sleep drive, we also assessed sleep quality in the survey study. Results showed that two aspects of sleep quality, i.e. subjective sleep quality and daily dysfunctioning, were associated with CRF (i.e. worse scores on these aspects were associated with higher levels of fatigue). These findings are in line with the baseline values of the objective assessment of circadian sleep-wake cycles in the light therapy study (**chapter 3**) suggesting that cancer survivors with CRF showed disrupted sleep patterns compared to healthy populations, while circadian variables were within the normal range[76-78].

Remarkably, the number of studies on the association between circadian disruptions and CRF in long-term cancer survivors (at least two years after diagnosis) is very limited. To the best of our knowledge, only two recent studies are available[79-81]. One study compared circadian activity rhythms, assessed with actigraphy, between 15 breast cancer survivors (5 years post-diagnosis) to 13 age and BMI-matched healthy controls[79, 80]. Results showed no differences in the timing of the sleep-wake cycle between both group but there were differences between groups for activity levels. Breast cancer survivors showed lower activity levels during the total 24-hour cycle compared to healthy controls. There was no report on the association between circadian activity rhythms and fatigue. The other study assessed circadian activity rhythms with actigraphy in 29 adolescents within 5 years after cancer treatment and 30 healthy controls[81]. There were no differences between survivors and healthy controls on circadian activity rhythms and fatigue scores between adolescent cancer survivors and healthy controls. Notably, there was an association between circadian activity disruptions and fatigue in early survivors, which was not seen in long-term survivors, suggesting that disruptions in circadian activity rhythms experienced shortly after treatment recovered within the first 5 years after treatment for adolescent cancer.

Taken together, disruptions in circadian rhythms have been associated with fatigue in patients with cancer. However, studies on this association in cancer survivors are scarce and suggest the absence of an association between disruptions in circadian rhythms and CRF in long-term cancer survivors. Replication of these results is necessary in sufficiently powered studies including objective assessments of circadian rhythms.

Methodological considerations

This survey study (**chapter 6**) had several strengths, including the large sample size, multicenter participation and the use of average midsleep as an indicator for chronotype instead of the original indicator of chronotype from the Munich Chronotype Questionnaire (MCTQ). However, several methodological issues need to be considered when interpreting the results.

The inconclusive results on the association between chronotype and fatigue in the studies described above might result from the use of different questionnaires to assess someone's chronotype. The two studies that showed no association between chronotype and fatigue, including our study, used the MCTQ[82]. This questionnaire assesses actual sleep times on work and free days to determine chronotype. The studies suggesting an association between chronotype and fatigue used other questionnaires, for example the Morningness Eveningness Questionnaire (MEQ)[83] or the Composite Scale of Morningness (SCM)[84]. An advantage of these questionnaires is the availability of cutoff scores to determine someone's chronotype. These cutoff scores are not available for the MCTQ and therefore the categorization of morning type and evening type might seem more arbitrarily. A disadvantage of the MEQ and CSM is that chronotype is based on preferred sleep times in ideal circumstances and statements. Therefore, we preferred to use the MCTQ as we aimed to describe actual sleeping patterns from cancer survivors with and without CRF.

Additionally, our results are based on self-reported data from a cross-sectional survey study. Self-reported sleep times are also influenced by work and social obligations. Therefore, the absence of an association between circadian rhythm disruptions and CRF needs to be confirmed with objective measurements of circadian rhythms, e.g. actigraphy assessments or the DLMO. The baseline actigraphy results of the light therapy study seem to confirm this conclusion but this was based on a comparison of published outcomes in the general population. To draw robust conclusions, it is necessary to perform statistical tests on this comparison.

Overall conclusions

- ❖ It is unlikely that circadian disruptions are associated with cancer-related fatigue in long-term cancer survivors.
  - There was no relationship between chronotype and cancer-related fatigue in long-term (non-)Hodgkin lymphoma survivors (**chapter 6**).
  - Two aspects of sleep quality, i.e. subjective sleep quality and daily dysfunctioning, were associated with cancer-related fatigue in long-term (non-)Hodgkin lymphoma survivors (**chapter 6**).
  - Baseline levels of actigraphy-derived sleep-wake cycles in participants of the SPARKLE study suggested the presence of sleep problems and the absence of circadian disruptions when compared to the general population (**chapter 3**).

Clinical implications

The aim of our survey study was to learn more about the association between sleep times and CRF. This information is valuable to determine the most optimal timing of light therapy. If the results would show that survivors with CRF showed an advanced sleep-wake rhythm compared to survivors without CRF, i.e. going to bed at 21:00 h and waking up at 5:00, than light therapy in the evening would be most effective because this will delay the sleep-wake cycle. On the other hand, if the results would show that survivors with CRF showed a delayed sleep-wake rhythm compared to survivors without CRF, i.e. going to bed at 1:00 h and waking up at 9:00 h, than light therapy in the morning would be most effective because this would advance the sleep-wake cycle.

However, the results described in this thesis showed no indications for a relationship between the timing of the circadian sleep-wake cycle and CRF in long-term HL and DLBCL survivors. There was an association between sleep quality and CRF, indicating that survivors with a lower sleep quality suffered from higher levels of fatigue. Therefore, survivors with CRF might benefit most from a closer inspection of sleep problems and interventions aiming to improve sleep quality, e.g. CBT.

Directions for future research

Disruptions in circadian rhythms have been associated with fatigue in patients with cancer. However, the number of studies on this association in cancer survivors are limited and mostly focus on patients with cancer while receiving treatment. We performed a survey study to investigate the association of chronotype, which correlates to endogenous circadian rhythms, and cancer-related fatigue. Although we found no association between chronotype and CRF in long-term HL and DLBCL survivors, a closer inspection of the bed times showed differences between survivors with and without fatigue. Survivors with severe fatigue tended to go to bed at an earlier time compared to non-fatigued survivors (22:48 h and 23:23 h, respectively) and needed more time to fall asleep (24 min and 11 min, respectively). Moreover, moderately to severely fatigued survivors tended to use more time to get up in the morning and spend less time outside during the day. Consequently, we cannot rule out that survivors with fatigue go to bed too early with respect to their circadian sleep drive. This hypothesis could not be investigated in this survey study but can be studied if future research includes objective assessments, for example, actigraphy assessments or determinations of the DLMO from saliva or with the BodyTime assay[85]. These studies are necessary to draw firm conclusions about the association between circadian disruptions and CRF in cancer survivors.

Additionally, it is interesting to further investigate the longitudinal influence of cancer and cancer treatment on circadian disruptions and the association between circadian disruptions and CRF. As mentioned above, the association between circadian rhythm disruptions and CRF has been consistently shown for patients with cancer while receiving treatment but not for cancer survivors. The same discrepancy has been described above for studies on light therapy. Several studies suggest superiority of BWL compared to DRL in patients with cancer while receiving treatment but not for cancer survivors with CRF. Therefore, we hypothesize that biological changes during cancer treatment, i.e. circadian disruptions, might be responsible for negative health outcomes, including fatigue, sleep problems, depression, and diminished quality of life. In cancer survivors, these underlying biological causes might no longer be present. Instead, behavioral and mental adaptations might be responsible for maintaining these negative outcomes. One approach to study this is by using patient reported outcomes (PROMS) used in clinical practice and biobank blood samples. These blood samples could be used to determine changes in dim light melatonin onset, which can be determined with the BodyTime assay[85]. Within such a cohort, researchers could also investigate the course of CRF and determine whether maladaptive behavior and/or cognitions are responsible for the shift from acute fatigue to chronic fatigue.

For the methodology of future studies investigating the association between circadian disruptions and CRF, it is important to formulate guidelines describing the most optimal

procedure to identify individuals with clinically relevant circadian disruptions for scientific purposes. Currently, actigraphy and DLMO are used in clinical practice to determine whether someone's circadian activity rhythm or endogenous circadian rhythm are not entrained to environmental rhythm. However, for scientific purposes, there are no clear guidelines how clinically relevant circadian disruptions can be determined in large datasets. A first step in this process might be to publish norm data per gender and age group for actigraphy-derived variables. These are currently not available although large datasets, for example from the UK Biobank[76], exist.

CONCLUSIONS

In view of the high prevalence of CRF in long-term HL and DLBCL survivors, we evaluated the efficacy of light therapy to reduce this symptom. Although there was no superiority of exposure to BWL compared to DWL, both groups, irrespective of light intensity, showed clinically relevant improvements. Therefore, we recommend future studies to investigate which elements of the current study protocol were responsible for this positive effect before the implementation of light therapy in clinical practice. Moreover, the effect of light therapy on circadian rhythms was evaluated. The results showed no effect of light therapy on circadian activity rhythms or neuroendocrine correlates of the circadian system (melatonin and cortisol). This might be explained by the lack of an association between circadian rhythm disturbances and CRF in long-term cancer survivors. Future studies should investigate whether circadian rhythm disruptions are an initial cause of CRF that play no, or only a limited, role in the maintenance of this symptom. Furthermore, one-third of the long-term HL and DLBCL survivors with CRF suffers from cognitive dysfunctioning, specifically in verbal memory. Physicians should be aware of these symptoms and might refer their patients to specialized neuropsychologist for further screening and treatment of these complaints.

REFERENCES

1. 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.
2. 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.
3. 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.
4. Johnson J A, Garland S N, Carlson L E, Savard J, Simpson J S A, Ancoli-Israel S, et al. (2017). Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial. *J Cancer Surviv*, 12:1-10.
5. Garland S N, Johnson J A, Carlson L E, Rash J A, Savard J, Campbell T S (2020). Light therapy for insomnia symptoms in fatigued cancer survivors: a secondary analysis of a randomized controlled trial. *J. Psychosoc. Oncol.*, 2(3):e27.
6. Johnson J A, Subnis U, Carlson L E, Garland S N, Santos-Iglesias P, Piedalue K-A L, et al. (2020). Effects of a light therapy intervention on diurnal salivary cortisol in fatigued cancer survivors: A secondary analysis of a randomized controlled trial. *J Psychosom Res*, 139:110266.
7. Kronish I M, Cheung Y K, Julian J, Parsons F, Lee J, Yoon S, et al., editors. Clinical Usefulness of Bright White Light Therapy for Depressive Symptoms in Cancer Survivors: Results from a Series of Personalized (N-of-1) Trials. Healthcare; 2020: Multidisciplinary Digital Publishing Institute.
8. Fox R S, Baik S H, McGinty H, Garcia S F, Reid K J, Bovbjerg K, et al. (2020). Feasibility and Preliminary Efficacy of a Bright Light Intervention in Ovarian and Endometrial Cancer Survivors. *Int J Behav Med*:1-13.
9. Rogers V E, Mowbray C, Rahmaty Z, Hinds P S (2020). A Morning Bright Light Therapy Intervention to Improve Circadian Health in Adolescent Cancer Survivors: Methods and Preliminary Feasibility. *J Pediatr Oncol Nurs*:1043454220975457.
10. 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.
11. 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.
12. Valdimarsdottir H B, Figueiro M G, Holden W, Lutgendorf S, Wu L M, Ancoli-Israel S, et al. (2018). Programmed environmental illumination during autologous stem cell transplantation hospitalization for the treatment of multiple myeloma reduces severity of depression: A preliminary randomized controlled trial. *Cancer medicine*, 7(9):4345-53.
13. Crabtree V M, LaRosa K N, MacArthur E, Russell K, Wang F, Zhang H, et al. (2020). Feasibility and Acceptability of Light Therapy to Reduce Fatigue in Adolescents and Young Adults Receiving Cancer-Directed Therapy. *Behav Sleep Med*:1-13.
14. Stein K D, Jacobsen P B, Blanchard C M, Thors C (2004). Further validation of the multidimensional fatigue symptom inventory-short form. *J Pain Symptom Manage*, 27(1):14-23.
15. Norman G R, Sloan J A, Wyrwich K W (2003). Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*:582-92.
16. Gielissen M F, Verhagen S, Witjes F, Bleijenberg G (2006). Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *J Clin Oncol*, 24(30):4882-7.
17. Persoon S, Kersten M J, van der Weiden K, Buffart L M, Nollet F, Brug J, et al. (2013). Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: a systematic review and meta-analysis. *Cancer Treat Rev*, 39(6):682-90.
18. McCarney R, Warner J, Iliffe S, Van Haselen R, Griffin M, Fisher P (2007). The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol*, 7(1):30.
19. Abrahams H J, Gielissen M F, Donders R R, Goedendorp M M, van der Wouw A J, Verhagen C A, et al. (2017). The efficacy of internet-based cognitive behavioral therapy for severely fatigued survivors of breast cancer compared with care as usual: a randomized controlled trial. *Cancer*, 123(19):3825-34.

20. Bruggeman-Everts F Z, Wolvers M D, Van de Schoot R, Vollenbroek-Hutten M M, Van der Lee M L (2017). Effectiveness of two web-based interventions for chronic cancer-related fatigue compared to an active control condition: results of the "Fitter na kanker" randomized controlled trial. *J Med Internet Res*, 19(10):e336.
21. Bruggeman-Everts F, Van der Lee M, Wolvers M, Van de Schoot R (2019). Understanding change in online mindfulness-based cognitive therapy for chronic cancer-related fatigue. *Evaluation of two different Web-based interventions for chronic cancer-related fatigue*:159.
22. Stockler M R, O'Connell R, Nowak A K, Goldstein D, Turner J, Wilcken N R, et al. (2007). Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-blind randomised trial. *The lancet oncology*, 8(7):603-12.
23. Spathis A, Fife K, Blackhall F, Dutton S, Bahadori R, Wharton R, et al. (2014). Modafinil for the treatment of fatigue in lung cancer: results of a placebo-controlled, double-blind, randomized trial. *J Clin Oncol*, 32(18):1882-8.
24. Junior P N A, Barreto C M N, Cubero D d I G, Del Giglio A (2020). The efficacy of placebo for the treatment of cancer-related fatigue: a systematic review and meta-analysis. *Support Care Cancer*, 28(4):1755-64.
25. Hoenemeyer T W, Kaptchuk T J, Mehta T S, Fontaine K R (2018). Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. *Sci Rep*, 8(1):1-8.
26. Yeung V, Sharpe L, Glozier N, Hackett M L, Colagiuri B (2018). A systematic review and meta-analysis of placebo versus no treatment for insomnia symptoms. *Sleep Med Rev*, 38:17-27.
27. Schmidt T M, Chen S-K, Hattar S (2011). Intrinsically photosensitive retinal ganglion cells: many subtypes, diverse functions. *Trends Neurosci*, 34(11):572-80.
28. Wams E J, Woelders T, Marring I, van Rosmalen L, Beersma D G, Gordijn M C, et al. (2017). Linking light exposure and subsequent sleep: A field polysomnography study in humans. *Sleep*, 40(12):zsx165.
29. Abrahams H, Gielissen M, Schmits I, Verhagen C, Rovers M, Knoop H (2016). Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors. *Ann Oncol*, 27(6):965-74.
30. Servaes P, Verhagen S, Schreuder H B, Veth R P, Bleijenberg G (2003). Fatigue after treatment for malignant and benign bone and soft tissue tumors. *J Pain Symptom Manage*, 26(6):1113-22.
31. Hjermstad M J, Fosså S D, Oldervoll L, Holte H, Jacobsen A B, Loge J H (2005). Fatigue in long-term Hodgkin's Disease survivors: a follow-up study. *J Clin Oncol*, 23(27):6587-95.
32. 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.
33. 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. *World J. Biol. Psychiatry*, 8(2):67-104.
34. Lucas R J, Peirson S N, Berson D, Brown T, Cooper H, Czeisler C A, et al. Irradiance toolbox. Oxford; 2013.
35. CIE S (2018). 026/E: 2018 CIE System for Metrology of Optical Radiation for ipRGC-Influenced Responses to Light. CIE, Vienna.
36. Spitschan M, Stefani O, Blattner P, Gronfier C, Lockley S W, Lucas R J (2019). How to report light exposure in human chronobiology and sleep research experiments. *Clocks & sleep*, 1(3):280-9.
37. Aoki H, Yamada N, Ozeki Y, Yamane H, Kato N (1998). Minimum light intensity required to suppress nocturnal melatonin concentration in human saliva. *Neurosci Lett*, 252(2):91-4.
38. Figueiro M, Nagare R, Price L (2018). Non-visual effects of light: How to use light to promote circadian entrainment and elicit alertness. *Light. Res. Technol.*, 50(1):38-62.
39. Shechter A, Julian J, Davidson K W, Cheung K, Lee J, Kronish I M (2019). A within-subject comparison of the effect of two putative sham light therapies on mood and fatigue in cancer survivors: Results from a series of N-of-1 trials. *Psychiatry Res*, 279:385-6.
40. Cella D (2013). The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale: Summary of development and validation.
41. 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.
42. Schwarz R, Krauss O, Hinz A (2003). Fatigue in the general population. *Oncology Research and Treatment*, 26(2):140-4.

43. 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.
44. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V (2003). Assessment and management of cancer-related fatigue in adults. *The lancet*, 362(9384):640-50.
45. 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.
46. 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.
47. Johnson J. Light Therapy for Post-Treatment Cancer-Related Fatigue: An Investigation of Impact on Psychological Outcomes and Biological Mechanisms 2016.
48. Bentler P M, Chou C-P (1987). Practical issues in structural modeling. *Sociological methods & research*, 16(1):78-117.
49. Kaptchuk T J, Miller F G (2015). Placebo effects in medicine. *N Engl J Med*, 373(1):8-9.
50. Evers A W, Colloca L, Blease C, Annoni M, Atlas L Y, Benedetti F, et al. (2018). Implications of placebo and nocebo effects for clinical practice: expert consensus. *Psychother Psychosom*, 87(4):204-10.
51. Kaptchuk T J, Friedlander E, Kelley J M, Sanchez M N, Kokkotou E, Singer J P, et al. (2010). Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One*, 5(12):e15591.
52. Carvalho C, Caetano J M, Cunha L, Rebouta P, Kaptchuk T J, Kirsch I (2016). Open-label placebo treatment in chronic low back pain: a randomized controlled trial. *Pain*, 157(12):2766.
53. Locher C, Nascimento A F, Kirsch I, Kossowsky J, Meyer A, Gaab J (2017). Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. *Pain*, 158(12):2320-8.
54. Kam-Hansen S, Jakubowski M, Kelley J M, Kirsch I, Hoaglin D C, Kaptchuk T J, et al. (2014). Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Sci Transl Med*, 6(218):218ra5-ra5.
55. Gielissen M, Verhagen C, Bleijenberg G (2007). Cognitive behaviour therapy for fatigued cancer survivors: long-term follow-up. *Br J Cancer*, 97(5):612-8.
56. Feenstra H E, Murre J M, Vermeulen I E, Kieffer J M, Schagen S B (2018). Reliability and validity of a self-administered tool for online neuropsychological testing: The Amsterdam Cognition Scan. *J Clin Exp Neuropsychol*, 40(3):253-73.
57. Klaver K, Duijts S, Geusgens C, Aarts M, Ponds R, van der Beek A, et al. (2020). Internet-based cognitive rehabilitation for WORking Cancer survivors (i-WORC): study protocol of a randomized controlled trial. *Trials*, 21(1): 1-12
58. 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.
59. Dekker K, Benjamins J S, Maksimovic T, Filardi M, Hofman W F, Van Straten A, et al. (2020). Combined internet-based cognitive-behavioral and chronobiological intervention for insomnia: a randomized controlled trial. *Psychother Psychosom*, 89(2):117-8.
60. Bean H R, Stafford L, Little R, Diggens J, Ftanou M, Alexander M, et al. (2020). Light-enhanced cognitive behavioural therapy for sleep and fatigue: study protocol for a randomised controlled trial during chemotherapy for breast cancer. *Trials*, 21:1-14.
61. Michielsen H J, De Vries J, Van Heck G L, Van de Vijver F J, Sijtsma K (2004). Examination of the dimensionality of fatigue. *Eur J Psychol Assess*, 20(1):39-48.
62. Lai J-S, Crane P K, Cella D (2006). Factor analysis techniques for assessing sufficient unidimensionality of cancer related fatigue. *Qual Life Res*, 15(7):1179-90.
63. Barsevick A M, Cleeland C S, Manning D C, O'Mara A M, Reeve B B, Scott J A, et al. (2010). ASCPRO recommendations for the assessment of fatigue as an outcome in clinical trials. *J Pain Symptom Manage*, 39(6):1086-99.
64. 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.
65. Payne J K (2011). Altered circadian rhythms and cancer-related fatigue outcomes. *Integr Cancer Ther*, 10(3):221-33.
66. 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.
67. 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.

68. 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.
69. Schmidt M E, Semik J, Habermann N, Wiskemann J, Ulrich C M, Steindorf K (2016). Cancer-related fatigue shows a stable association with diurnal cortisol dysregulation in breast cancer patients. *Brain Behav Immun*, 52:98-105.
70. 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.
71. 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.
72. Habers G E A, van der Helm-van A H M, Veldhuijzen D S, Allaart C F, Vreugdenhil E, Starreveld D E J, et al. (2021). Earlier chronotype in patients with rheumatoid arthritis. *Clin Rheumatol*, 40:2185-92.
73. Palesh O, Packer M M, George H, Koopman C, Innominato P F. Associations between morning–evening chronotype, fatigue, and QOL in breast cancer survivors. *J. Clin. Oncol*; 2016.
74. 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.
75. 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.
76. Jones S E, van Hees V T, Mazzotti D R, Marques-Vidal P, Sabia S, van der Spek A, et al. (2019). Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. *Nat. Commun.*, 10(1):1-12.
77. Häusler N, Marques-Vidal P, Haba-Rubio J, Heinzer R (2020). Association between actigraphy-based sleep duration variability and cardiovascular risk factors–Results of a population-based study. *Sleep Med*, 66:286-90.
78. Luik A I, Zuurbier L A, Direk N, Hofman A, Van Someren E J, Tiemeier H (2015). 24-hour activity rhythm and sleep disturbances in depression and anxiety: A population-based study of middle-aged and older persons. *Depress Anxiety*, 32(9):684-92.
79. Roveda E, Bruno E, Galasso L, Mulè A, Castelli L, Villarini A, et al. (2019). Rest-activity circadian rhythm in breast cancer survivors at 5 years after the primary diagnosis. *Chronobiol Int*, 36(8):1156-65.
80. Galasso L, Montaruli A, Mulè A, Castelli L, Bruno E, Pasanisi P, et al. (2020). Rest-activity rhythm in breast cancer survivors: an update based on non-parametric indices. *Chronobiol Int*, 37(6):946-51.
81. Rogers V E, Mowbray C, Zhu S, Liu L, Ancoli-Israel S, Barr E A, et al. (2020). Circadian activity rhythms and fatigue of adolescent cancer survivors and healthy controls: a pilot study. *J Clin Sleep Med*, 16(7):1141-7.
82. Roenneberg T, Wirz-Justice A, Merrow M (2003). Life between clocks: daily temporal patterns of human chronotypes. *J Biol Rhythms*, 18(1):80-90.
83. 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.
84. 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.
85. Wittenbrink N, Ananthasubramaniam B, Münch M, Koller B, Maier B, Weschke C, et al. (2018). High-accuracy determination of internal circadian time from a single blood sample. *J. Clin. Investig.*, 128(9):3826-39.