

Light Therapy Reduces Fatigue in Patients With Cancer: Protocol for a Systematic Review and Meta-analysis

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Protocol

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Abstract

Background

Fatigue is a common symptom in cancer patients that can occur throughout the course of cancer, with a prevalence ranging from 75% to 100%. Nonpharmacological intervention is currently mainly used to address cancer-related fatigue (CRF). Light therapy has been gradually used to treat CRF and has been found to be effective. However, to date, there is no systematic review on light therapies for reducing CRF to verify its effectiveness. This is a protocol for a systematic review that aims to evaluate the effectiveness of light therapies for treating fatigue in cancer survivors. This systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database.

Methods

This protocol was designed in accordance with the PRISMA-P guidelines. We will search the PubMed, Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library), Embase (OVID), and CINAHL databases as well as relevant sources of gray literature. Randomized controlled trials (RCTs) and quasi-experimental trials that have evaluated the use of light therapy among cancer patients at any survival phase, with fatigue as an outcome measure, will be included. Two members of the review team will independently extract data from the selected studies and assess their methodological quality using the Cochrane Collaboration Risk of Bias Tool.

Discussion

This systematic review and meta-analysis will build upon previous evaluations of light therapies in patients during and after cancer treatment. Due to the multifactorial nature of CRF and the growing demand for etiological-based intervention research, this review seeks to highlight a gap in current practice and to strengthen the evidence base of randomized controlled trials in the area.

Systematic review registration

CRD42020215446

Background

Description of the condition

Cancer, the leading cause of death worldwide, has been an important focus of public health in China due to its rapid population growth and socioeconomic development [1]. According to International Agency for Research on Cancer reported, there would be approximately 4.51 million cancer cases by 2020 in China, which would undoubtedly put a huge burden on individuals, families, and society [2]. The physical symptoms induced by cancer itself or its treatment impact the functional status and daily life of patients and induce symptom-related distress, thus having an adverse impact on prognosis [3,4]. Cancer-related

fatigue (CRF), the most prevalent symptom reported by patients [5,6], is one of the most consistent and distressing symptoms experienced by patients of all ages during and after cancer treatment; its prevalence ranges from 75% to 100% depending on cancer types, treatments, and methods of assessment [7]. Compared to general fatigue, CRF is more severe, more persisting, more debilitating, not relieved by rest, and not proportional to exerted energy [8]. Moderate to severe fatigue may lead to treatment noncompliance or discontinuation, and approximately one-quarter to one-third of cancer patients experience persistent fatigue throughout the whole survival phase after the cancer diagnosis, which significantly diminishes patients' quality of life and shortens survival rates [8].

However, the pathogenesis of CRF has not been definitively concluded, and there is no standard treatment for CRF. Underlying mechanisms implicated in the development of CRF include circadian rhythm disruption, cancer itself and its treatment, skeletal muscle and mitochondrial dysfunction, cytokine dysregulation and inflammatory response, and altered neuroendocrine pathways [9]. These etiological hypotheses provide research directions for reducing CRF.

Description of the intervention

An increasing number of studies have used nonpharmacological interventions as the first choice for the treatment of CRF, including physical activity (PA), psychological intervention (e.g., CBT, psychoeducation), and other complementary and alternative medicine therapies (e.g., music intervention, yoga, acupuncture, qigong, massage) [10]. Although these treatments have their own sets of advantages for addressing CRF and show a large or small effect size, there are limitations in clinical practice. For instance, patients with CRF do not have enough motivation to complete exercise [11]. Additionally, CBT is labor intensive since it requires professional guidance for several weeks [12]. Light therapy [13], which is another nonpharmacological intervention, has been developed in recent years to treat CRF. It consists of daily exposure to bright, fluorescent light delivered via a lightbox or other device for a certain amount of time upon awaking. The parameters of light include wavelength, intensity, timing of exposure during the day, and total daily exposure time, which varies by population, disease type, and treatment target. Currently, light therapy is recommended as a first- or second-line treatment for seasonal and nonseasonal major depressive disorder (MDD) in clinical guidelines [14] and has shown a simple operation and a low possibility of side effects in many clinical studies and meta-analyses [15-17].

How the intervention might work

According to the potential mechanisms of CRF and some empirical studies about light therapy, there are several hypotheses regarding the effect of light therapy on CRF.

First, light therapy may normalize sleep-wake cycles to reduce CRF. Studies have found that cancer patients usually spend more time in bed and exercise less during the day, thus interfering with the body's steady-state sleep drive and circadian rhythm, resulting in sleep-wake cycle disruptions, which were proven to be related to increased CRF [18]. Moreover, a study of breast cancer patients during chemotherapy showed that bright light during their first 4 cycles of chemotherapy can return sleep-wake

cycles to baseline levels [19], and secondary analysis showed that it improved sleep efficiency to normal ranges, while this improvement was not seen in the control group receiving dim red light [20].

Second, light therapy may normalize the HPA axis and then affect inflammatory cytokine activity to reduce CRF. There is growing evidence that serum levels of proinflammatory cytokine markers (e.g., interleukin 6, C reactive protein) are significantly higher in fatigued cancer patients than in non-fatigued cancer patients or healthy controls [21-23]. There are well-characterized feedback inhibition pathways between HPA and inflammation [24]. Moreover, bright light treatment has been found to normalize HPA axis function in elderly patients with nonseasonal major depressive disorder [25]. Therefore, light therapy may affect inflammatory cytokine activity either directly or indirectly to reduce CRF.

Third, light therapy may normalize the circadian rhythms of cortisol and melatonin to reduce CRF. The plasma concentrations of cortisol and melatonin showed obvious rhythmicity, which was controlled by the main center of human circadian rhythm, that is, the suprachiasmatic nucleus (SCN) [26]. The dysregulation of this rhythmicity has been shown to be strongly associated with greater CRF and mood disorders [27,28]. Light therapy has been proven to be effective in regaining the circadian rhythms of melatonin and cortisol in clinical depressive patients [29]. Moreover, improvements in CRF over time have been shown to be associated with normalization of the circadian cortisol rhythm; however, one study showed that light therapy for reducing CRF did not mediate the secretion of cortisol rhythms [30]. Hence, these potential effects and mechanisms need to be further clarified based on the present evidence.

Above all, light therapy as a nonpharmacological intervention may be a good alternative method for the management of CRF, and empirical studies have shown that it has a smaller side effect than medication [31,32]. Several trials have investigated the effectiveness of light therapy for the management of CRF and showed different results [33-37], and some protocols or pilot trials of light therapy have been designed to reduce CRF [38-40]. However, no systematic review has examined the effect size of light therapy on CRF.

Objectives

The main objective is to systematically assess the effects of light therapy on CRF. The secondary objective is to evaluate the effects of light therapy on sleep difficulties, depression, cortisol rhythms and quality of life in cancer patients.

Methods/design

Criteria for considering studies for this review

This systematic review and meta-analysis will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [41] and detailed in Table 1. This systematic review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42020215446).

The PRISMA checklist [41] encourages authors to describe eligibility criteria using the PICO reporting system (which describes the participants, interventions, comparisons, outcome(s), and study design of the included studies).

Types of studies

This review will include randomized controlled trials (RCTs) and quasi-experimental studies that compare light therapies with treatment as a control condition. Studies will be included regardless of light treatment intensity, duration, time of lighting exposure (e.g., morning, midday), or follow-up time.

Types of participants

Studies involving cancer patients, regardless of age, sex, tumor type, and type of treatment, will be included. Pregnant and lactating women will be excluded. Patients who had severe psychiatric disorder (e.g., severe major depressive disorder), suicidal ideations with a risk of attempting suicide, diseases contraindicating light therapies (e.g., severe cataracts, diabetes), and patients who had been taking photosensitive medication (e.g., imipramine) were excluded.

Types of interventions

Studies reporting the effects of a light intervention (e.g., bright light therapy) on multiple outcomes will be included if fatigue is one of the outcomes of interest. Studies of light therapy combined with another treatment, such as cognitive behavior therapy and the control condition, that did not include the other treatment will be considered for exclusion.

Types of comparators

The control group will be a waiting list, dim red light, usual care, psychotherapy (e.g., cognitive behavior therapy), exercise or medications.

Types of outcome measures

Primary outcomes

The included studies must have fatigue as an outcome of interest. This will incorporate fatigue measured as the main outcome or within a cluster measurement of physical symptoms or quality of life.

Studies will be included if fatigue was measured by a questionnaire specifically designed to evaluate fatigue. Fatigue subscales as sections of a broader quality-of-life measure will also be included if specific fatigue-related data are available. Fatigue may be measured in terms of characteristics such as intensity, distress, duration, or frequency or as dimensions such as physical fatigue, mental fatigue, or general fatigue.

Secondary outcomes

- Mood disturbances (e.g., depression and/or anxiety or distress) were measured by any reliable and valid instrument.
- Sleep difficulties and subjective data are obtained from any reliable and valid self-reported scale, and objective data are obtained from Actiwatch and/or Actigraphy.
- Cortisol rhythms measured by saliva and/or blood samples.
- Quality of life was measured by any reliable and valid instrument.
- Adherence.
- Adverse events.

Search methods for identification of studies

No date restriction will be imposed on the studies. Studies will be included if a full-text paper in English is available either through databases or through contact with the study authors. Whenever available, protocol methods will be compared with the methods and results reported in the included study.

Electronic searches

We will search the following electronic databases: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase (OVID), and CINAHL (EBSCO). All databases will be evaluated from the date of creation. The same search strategies will be used with alterations as appropriate for each database interface. Details of the search strategy for PubMed are shown in Table 1. A combination of MeSH terms and keywords will be applied. We also searched grey literature in the ProQuest Dissertations & Theses databases and <http://clinicaltrials.gov>.

Finally, the reference lists of all relevant studies and review articles will be searched for additional studies not identified by electronic searches.

Table 1

Details of the search strategy for PubMed

Search term
1. (neoplasms [MeSH] OR neoplasm* [tiab] OR cancer*[tiab] OR carcino*[tiab] OR tumo*[tiab] OR malignanc*[tiab] OR oncolog*[tiab])
2. (phototherapy [MeSH] OR phototherap*[tiab] OR heliotherap*[tiab] OR "light treatment*" [tiab] OR "light therap*" [tiab] OR "light exposur*" [tiab] OR "artificial light" [tiab] OR "bright light" [tiab] OR sunlight [tiab])
3. (fatigue [MeSH] OR fatig*[tiab] OR tire*[tiab] OR lassitude[tiab] OR letharg*[tiab] OR astheni*[tiab])

Data collection and analysis

Selection of studies

All studies retrieved were sent into EndNote 8. We will use EndNote8 to eliminate duplicate studies. One member (XP) will initially screen study titles and abstracts and eliminate those that are unrelated to this review. Two members of the review team (DS and XJ) will then independently screen the remaining titles and abstracts for their eligibility for inclusion in accordance with the abovementioned criteria. Ineligible studies will be excluded at this stage. When the title and abstract do not provide all the information concerning the criteria, the full texts of the papers will be retrieved and screened. We will retrieve full texts of all studies if either the members who review the studies determine that the study possibly or definitely meets the inclusion criteria and need to record the reason for rejection after reading the full text. Any disagreements between the two reviewers will be resolved by discussion, with the involvement of a third member where agreement cannot be reached (ZY, LX, or DY). Multiple reports of the same study will be counted as a single study. The PRISMA template will be used to produce a flow chart (Figure 1) showing details of studies included and excluded at each stage of the study selection process.

Data extraction and management

Two members of the review team (XP and XJ) will independently extract data from the studies using a specifically designed data extraction form. The form will be piloted on a sample of three studies and then revised if required before full data extraction begins. Discrepancies will be resolved by discussion, with the involvement of a third member where necessary. Authors will be contacted to obtain any missing data. Findings will be reported regardless of their direction. Positive and negative findings must be clearly defined in the included studies. The following information will be extracted from the studies:

- Bibliometric (author and year of publication).
- Study characteristics (sample size, sample description, country, study design, study settings, the form of recruitment, recruitment time, and funding).
- Participant characteristics (age, sex, treatment type, cancer stage, main physical symptoms that light therapy targets).
- Intervention information for each arm of the study (light parameters, duration, the timing of the day of treatment, comparison/s).
- Outcome (measurement methods used in the study; when the total score of the outcomes is different, the values will be converted to a scale of 0 to 100 points).
- Timing of assessment for each outcome.
- Results of the studies (mean and standard deviation or median and interquartile range and confidence interval).

Assessment of risk of bias in included studies

Criteria for features of the RCT design are based on those set out by the Cochrane Collaboration Risk of Bias Tool and will be considered for each of the included studies to assess the risk of bias. These criteria include the following: (1) random sequence generation, (2) allocation concealment, (3) performance bias, (4) detection bias, (5) attrition bias (bias due to the amount, nature, or handling of incomplete outcome

data), (6) selective reporting bias (bias due to selective outcome reporting by comparing in-publication reporting of the outcomes of interest reported in the methods section to those reported in the results section), and (7) other sources of bias (e.g., bias due to baseline differences, the inappropriate influence of the study sponsor, and early stopping for the benefit) [42]. Each domain will be judged independently by two authors as having a high, low, or unclear risk of bias. Inconsistence will be resolved by discussion, with the involvement of a third reviewer where necessary.

Measures of treatment effect

We will use Review Manager (RevMan) 5.3 software for all analyses. For continuous data, we will report the mean differences between groups and the 95% confidence interval (95% CI). Where no standard deviations are reported, we will calculate the standard deviation using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions [43]. Where the same outcome is measured using different measurement methods, we will calculate the standardized mean difference and the 95% CI for continuous data. For categorical data, we will report the odds ratios (ORs) between groups and the 95% CI. For arms with zero events, we impute a 0.5 event score.

Assessment of heterogeneity

Statistical heterogeneity will be tested using the standard chi-square tests (significance level: 0.1) and I^2 statistics (0 to 40%: might not be important; 30 to 60%: may represent moderate heterogeneity; 50 to 90%: may represent substantial heterogeneity; 75 to 100%: considerable heterogeneity). Statistical heterogeneity will be regarded as substantial when the χ^2 p-value is <0.1 or I^2 is >50%. Meta-analyses will be conducted by using RevMan 5.3.

Assessment of publication biases

We will examine funnel plots corresponding to a meta-analysis of the primary outcomes to assess the potential for small-study effects such as publication bias if a sufficient number of studies (i.e., more than 10) are identified [44].

Data synthesis

Data will only be pooled if selected studies are sufficiently homogeneous in design and comparators. Otherwise, a narrative synthesis of the data will be conducted.

Continuous data will be combined only where (i) means and standard deviations are available or calculable and (ii) there is no clear evidence of skew in the distribution (using methods described in the Cochrane Handbook for Systematic Reviews of Interventions (2011)).

If it is possible to combine mean differences of scales measuring the same clinical outcomes in different ways, they will be standardized to combine results across scales (otherwise, weighted mean differences will be used).

We anticipate that there will be clinical heterogeneity driven by differences in light treatment parameters, study duration, and so on. Therefore, we will use a random effects meta-analysis model to produce an overall summary of the average treatment effect across the included trials.

Subgroup analysis and investigation of heterogeneity

We hypothesize that each of the factors below has the potential to have a clinically meaningful effect on the response to light therapy among fatigued cancer survivors. Therefore, if sufficient data are available, we will undertake a subgroup analysis based on the following:

- High-intensity light ($\geq 2,000$ lux) versus low-intensity light ($< 2,000$ lux).

Most studies have shown that white light above 2,000 lux has therapeutic effects and few effects below 500 lux [45]. Therefore, this review will compare light therapies with high intensity and those with low intensity.

- Light treatment duration (≥ 4 weeks versus <4 weeks).
- Low-light versus nonlight control conditions.
- Intervention for specific cancer type only versus intervention for any cancer type.
- Cancer population (pediatric or adolescent and young adult versus adult).
- Fatigue as the inclusion standard of the study versus other physical symptoms as the inclusion standard of the study.

Sensitivity analysis

Trial quality

To evaluate the reliability and stability of the meta-analysis outcomes, we will conduct a sensitivity analysis based on trial quality, whereby studies of high or unclear risk of bias across different domains (see the section on “Assessment of risk of bias in included studies”) will be excluded to assess for any substantive difference to the overall effect estimates. If no substantive difference exists, the studies will be left in for the main analysis. This sensitivity analysis will be conducted for the fatigue outcomes only.

Outcome validity

Given that there is no accepted definition of CRF and no agreement on how it should be measured [46], a sensitivity analysis will be conducted based on outcome measurement. Scales may vary in the quality of psychometric properties. Studies that confirm that the scales are validated measures of fatigue will be compared to those that do not meet the following a priori criteria based on criteria outlined by Minton and Stone [46].

The paper that used the scale should have referred to at least three of the following: internal consistency, test-retest reliability, known group validity (discriminant validity), responsiveness to change, or convergent

validity (against other scales). The original scale reference will be accessed if this information is not provided. The original paper will also be cross-referenced for citing articles to evaluate the frequency of scale use and the type of populations studied.

Additionally, single-parameter fatigue subscales as part of a broader quality-of-life measure will be compared to multiple-parameter scales that were specifically designed to assess fatigue.

Discussion

CRF is a significant health concern among cancer patients. To the best of our knowledge, our review will be the first to evaluate the evidence for the effects of light therapies on fatigue among cancer patients. Light therapy has many advantages for managing CRF in clinical practice, such as low cost, few side effects, and reduced concurrent symptoms (e.g., depression). pain), and so on [13]. As a result, it is important to determine the effectiveness and acceptability of light therapies for cancer patients. Our proposed systematic review and meta-analysis will synthesize the available evidence using rigorous methods, which will shed light on the effects of light treatment on fatigue and explore potential mechanisms, including chronobiological and psychosocial pathways and permit the identification of evidence gaps, thereby informing clinical decision-making and guiding future research initiatives for cancer-related fatigue management.

List Of Abbreviations

CRF Cancer-related fatigue

MeSH Medical Subject Headings

PICO Participants, Interventions, Comparisons, Outcome(s)

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QoL Quality of life

RCT Randomized controlled trial

VAS Visual analogue scale

RevMan Review Manager

CI Confidence interval

OR Odds ratios

Declarations

Ethics approval and consent to participate

The data used in this systematic review will be collected from published studies. Based on this, the study does not require ethical approval.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

XP, DS and XJ carried out the initial background research and conceived the study. XP and DY also drafted the manuscript. LL, ZY, XF and DS helped in drafting the manuscript or revising it critically for important intellectual content. LL, ZY, LX and Andy SK made substantial contributions to the conception and design of the project, including revising the manuscript. All authors gave final approval of the version to be published.

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Not applicable.

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Figure

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