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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

Letter to the Editor

Bright light exposure (phototherapy) can improve depressive symptoms in some psychiatric conditions, and is gaining popularity among cancer survivors to improve fatigue (Johnson et al., 2018). Bright light is thought to achieve its therapeutic effects on mood and function via a realignment of biological rhythms with the environment and/or the sleep-wake cycle (Boivin and Shechter, 2014). Melanopsins, a class of non-image forming photopigments in the retina, aid in the transmission of light information to the hypothalamus, and mediate the effects of light on mood (Boivin and Shechter, 2014). The melanopsin system shows highest sensitivity to light of ~450–480 nm, such that shorter wavelength light (i.e., within the blue portion of the visible light spectrum range, as compared to more reddish-hued longer wavelength light) is more effective in influencing the outputs of the biological clock.

There may be other mechanisms whereby phototherapy achieves its effects, including relaxation or expectation bias. Dim red light (DR) or dim white light (DW) are traditionally used as a sham to control for these other possible mechanisms in controlled trials of bright full-spectrum white light (high in blue-wavelength light), since DR and DW are expected to have minimal effects on the melanopsin system and therefore be physiologically inert (Lucas et al., 2014). Progress in the field has been hindered by uncertainty over which condition constitutes an ideal sham against which to judge the efficacy of bright light therapy.

To address this, we conducted a multiple crossover within-subject trial (N-of-1 trials) to compare the effect of two putative sham treatments, DR vs. DW, on depressive and fatigue symptoms in cancer survivors. Participants were five English-speaking cancer survivors who completed primary cancer therapies, with at least mild depressive symptoms (8-item Patient Health Questionnaire (PHQ-8) score ≥5). Participants all had an iOS smartphone for data collection purposes. Exclusion criteria were suicidal ideation, severe mental illness (psychotic disorder or bipolar disorder), and planned chemotherapy, radiation, or surgery within 12 weeks of enrollment.

Using an N-of-1 trial design, participants were randomized to a balanced treatment sequence with one repetition (DR-DW/DW-DR or DW-DR/DR-DW). Patients were instructed to use one of two identical appearing portable lightboxes (Litebook Advantage, Litebook, Ltd. Medicine Hat, Canada) emitting DR or DW (labeled A or B), each morning at home for 30 min per day, for 3 weeks at a time. DR consisted of narrow band light emitting diodes (LEDs) emitting dim red light of ~633 nm at 50 lx. DW consisted of narrow band LEDs emitting dim white light (peak spectral power ~460), with brightness reduced to 50 lx. The full experimental period was 12 weeks. Participants were instructed to keep the lightbox within their field of vision and within an arm's length during use. Patients were informed that the goal of the study was to learn which lightbox was best for them, and were not told that the lightboxes were expected to be shams.

A customized smartphone application guided patients through the protocol by sending push notifications to use lightbox A or B each morning and complete end-of-day assessments. Patients reported their depressive symptoms and fatigue daily by answering the following questions: “On a scale of 0–10, how depressed were you today?” and “On a scale of 0–10, how fatigued were you today?” The IRB of Columbia University Medical Center approved study procedures and participants provided informed consent.

Treatment effects were assessed using an autoregressive model that included type of light therapy as the main exposure, adjusted for time (days since enrollment) linearly as a covariate, and accounted for autocorrelations of the order 1.

All patients ($n = 5$) were female breast cancer survivors. None had metastatic cancer. Mean age (± SD) was 60.0 ± 17.6 y. Three patients had mild depressive symptoms (PHQ-8: 5–7), one had moderately severe symptoms (PHQ-8: 17), and one had severe depressive symptoms (PHQ-8: 21). Mean baseline PHQ-8 score was 11.2 ± 7.3.

Symptom assessments were completed on 78.4% of possible days (69.2 ± 15.6 days out of a possible 87.8 ± 2.2 days). In adjusted analyses, 2 patients had significantly ($p \leq 0.04$) lower depressive symptoms (−0.40 and −0.63 points) with DR vs. DW. The same two patients had significantly ($p \leq 0.01$) lower fatigue symptoms (−0.59 and −1.03 points) with DR vs. DW. The remaining 3 patients showed no significant difference in depressive or fatigue symptoms between treatments. This suggests heterogeneity in patient response to dim light treatments. The two patients showing benefit of DR vs. DW had mild depressive symptoms at baseline (PHQ-8 scores: 5 and 6), although another patient showing no difference in symptoms between treatments also had a relatively low PHQ-8 score at baseline (score: 7). Interestingly, the two patients who showed benefit were taking medications for sleep, whereas the other patients were not.

Despite the demonstrated efficacy of bright light for improving symptoms of affective disorders, there is not yet a sham standardized for wavelength. Expectancy is thought to play a role in the emergence of therapeutic effects in response to an inert treatment (placebo effect), including phototherapy. Indeed, sham procedures or devices appear to produce greater placebo effect responses than pharmacological placebos (Brim and Miller, 2013). Although the possibility exists that DR becomes “active” only when used in comparison to DW (i.e. under these circumstances the expectancy shifts), DR may not necessarily be truly inert, and therefore not adequate for use as a sham.

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To our knowledge, no study has compared the effects of DR vs. DW on depressive and fatigue symptoms. Although both are expected to be physiologically inert in terms of melanopsin-mediated effects (Lucas et al., 2014), we did not assess circadian physiology and cannot conclude whether effects are driven by biological or psychological mechanisms. Future work should include circadian measures (e.g., melatonin), and also measures of sleep, to determine how DR may affect outcomes. Abnormal diurnal cortisol secretion patterns have also been related to cancer-related fatigue (Schmidt et al., 2016), which suggests that this hormone should also be measured to determine pathways by which DR may potentially impact outcomes. Our inclusion of only female breast cancer survivors may limit generalizability. Sample size was small, although this is mitigated by the number of assessments (daily throughout each of four separate 3-week intervention periods) and the within-subject multiple crossover nature of the study (2 repetitions of each intervention phase). Nevertheless, these findings should be replicated in a larger sample to determine what percentage of patients display a preferential treatment effect of DR.

An innovative approach for testing assumptions about sham light therapy treatments was used—the N-of-1 design. Current findings indicate that DR, contrary to long-held expectations, may improve depressive and fatigue symptoms, in some, just as bright light therapy appears to be effective for only some persons. These findings should be considered when designing light therapy trials for mood outcomes.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.04.018.

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