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The Efficacy of Light Therapy in the Treatment of Seasonal Affective Disorder: A Meta-Analysis of Randomized Controlled Trials

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Seasonal affective disorder · Winter depression · Bright light therapy · Meta-analysis

Abstract
Background: Bright light therapy (BLT) has been used as a treatment for seasonal affective disorder (SAD) for over 30 years. This meta-analysis was aimed to assess the efficacy of BLT in the treatment of SAD in adults. ***Method:*** We performed a systematic literature search including randomized, single- or double-blind clinical trials investigating BLT (≥1,000 lx, light box or light visor) against dim light (≤400 lx) or sham/low-density negative ion generators as placebo. Only first-period data were used from crossover trials. The primary outcome was the post-treatment depression score measured by validated scales, and the secondary outcome was the rate of response to treatment. ***Results:*** A total of 19 studies finally met our predefined inclusion criteria. BLT was superior over placebo with a standardized mean difference of –0.37 (95% CI: –0.63 to –0.12) for depression ratings (18 studies, 610 patients) and a risk ratio of 1.42 (95% CI: 1.08–1.85) for response to active treatment (16 studies, 559 patients). We found no evidence for a publication bias, but moderate heterogeneity of the studies and a moderate-to-high risk of bias. ***Conclusions:*** BLT can be regarded as an effective treatment for SAD, but the available evidence stems from methodologically heterogeneous studies with small-to-medium sample sizes, necessitating larger high-quality clinical trials.

Introduction

Seasonal affective disorder (SAD) is a subtype of recurrent major depressive or bipolar disorder defined by a regular temporal relationship (over at least 2 years) between the onset and remission of affective episodes and a particular time of the year. Over the life-time of an individual, seasonal affective episodes should substantially outnumber nonseasonal episodes. The most frequent pattern is fall-winter depression with onset of depression during fall or winter with spontaneous remission or, optionally, hypomania/mania during the subsequent spring/

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summer period [1]. The disorder has first been described by the group of Rosenthal et al. [2]. Depressive symptoms and a disruption of the circadian rhythm in SAD patients have been hypothesized to be precipitated by a deficiency of environmental light in the darker seasons [3]. For this reason, treatment with bright full-spectrum visible light (bright light therapy [BLT]) was propagated early on for SAD patients [4]. Today, BLT is considered as the first line of treatment for SAD beside conventional antidepressant medication [5–7].

The exact mode of action of BLT remains still unclear, but stimulation of specialized light-sensitive melanopsin-containing retinal ganglion cells [8–10], which project to the anterior hypothalamus by way of the retinohypothalamic tract, releases glutamate in the suprachiasmatic nucleus [11], which is regarded as the circadian pacemaker of the brain [12]. Entrainment of phase-shifted circadian rhythms [13] and suppression of excessive melatonin production [14, 15] could also contribute to the mechanism of action of BLT. Furthermore, as indicated by challenge [16] and depletion studies [17], BLT seems to restore disrupted monoaminergic neurotransmitter systems [18], influences key molecules of neurotransmission like the serotonin transporter [19, 20] and monoamine oxidase A [21], and could also influence altered immune functions [22, 23].

In 2005, Golden et al. [24] conducted a meta-analysis on the efficacy of BLT in SAD and nonseasonal depression. This study included 8 trials with SAD patients and revealed a significant reduction in depressive symptoms for patients treated with BLT versus placebo with an effect size of 0.84 (95% CI: 0.60–1.08). Mårtensson et al. [25] published an updated meta-analysis on the topic of BLT in SAD and nonseasonal depression. However, the authors selected only studies with high or medium quality, which resulted in inclusion of 8 SAD trials and a standardized mean difference (SMD; using endpoint data) of –0.54 (95% CI: –0.95 to –0.13).

The aim of this study was to perform an updated systematic review of the available literature, to summarize the current evidence for the efficacy of BLT in adult SAD patients, and to assess the methodological quality of the available studies.

Method

Search Strategy

We systematically searched PubMed, EMBASE, PsycINFO, CINAHL, Cochrane Central, Google Scholar, OpenGrey, ClinicalTrials.gov, and the EU Clinical Trials Register. Language was restricted to literature published in English, German, and French between January 1980 and July 2019. The MeSH (medical subject heading) terms for this search included one term for BLT (phototherapy, light therapy, light treatment), a second term to specify the disorder (psychiatr*, depress*, affective), and/or one further term to focus on seasonality (season*, SAD, winter, pattern).

Eligibility Criteria

We included published and unpublished randomized, placebo-controlled clinical trials. Currently, there are no generally accepted definitions of adequate brightness and minimum treatment durations for BLT. Average indoor light has approximately 100–300 lx. In line with the previous review by Golden et al. [24], we defined a minimum illuminance of 1,000 lx for BLT. As the placebo condition, we accepted a nonphotic control (i.e., a low-density or sham negative ion generator) or dim-light therapy of ≤500 lx, which is in line with the previous meta-analysis by Mårtensson et al. [25] and thought not to suppress plasma melatonin levels [26]. If a selected study implemented a crossover design, we only included first-period data, in order to avoid possible carryover effects. Trials without information on the crossover sequence were excluded from this analysis.

Adult patients suffering from SAD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R [27], DSM-IV [28], or DSM-5 [1]) and/or the Kasper-Rosenthal criteria [2, 29] were included. Studies investigating nonseasonal major depressive disorder or subsyndromal SAD [29] were excluded. We allowed the inclusion of trials with patients suffering from bipolar seasonal depression in the meta-analysis, as a bipolar course of illness (especially bipolar II) in SAD is quite prevalent [30, 31] and the response to BLT does not seem to differ between bipolar and unipolar SAD [32, 33].

Study Selection

A PICO chart [34] was used to assess studies' appropriateness for this review. All steps of study selection and data extraction were carried out by two independent reviewers. In case of discrepancies, a third reviewer was involved to reach a consensus. Duplicate search results from different sources were initially removed. After title screening, a subset of 151 studies was subjected to abstract analysis. A consecutive full-text analysis was carried out on 49 studies (online suppl. Fig. 1 [96]; for all online suppl. material, see www.karger.com/doi/10.1159/000502891). Data extraction was performed using a predesigned form.

Outcomes

The primary outcome for this meta-analysis were post-treatment data on depressive symptom levels measured by validated psychiatric symptom scales. The secondary outcome were treatment response rates. If outcome data were only incompletely described in the publication, we contacted the corresponding authors of the study or attempted a calculation from statistical measures or from single patient data where available.

Data Analysis

The meta-analysis was performed using R (version 3.5.2; R Project for Statistical Computing) [35] together with the packages "meta" [36] and "metafor" [37]. We employed a random-effects model [38] for the analysis of primary and secondary outcome measures. This approach allows more robust inferences

when there is significant study heterogeneity [39]. We calculated the SMD (Hedges' *g*) [40] for the primary outcome (continuous outcome measure, depression scores). Values <0.0 indicate a larger reduction of depression scores in the BLT group than in the placebo group. Mantel-Haenszel risk ratios (RRs) [41] were calculated for the secondary outcome (dichotomous data, response rates). A RR >1.0 indicates a higher response rate for BLT than for placebo. Forest plots were used to display pooled estimates. The $p \leq 0.05$ level of significance (two-tailed) was assumed.

The Cochrane Collaboration's "Risk of Bias 2.0" tool [42] was used independently by two reviewers to evaluate the methodological quality of every single study included in the analysis. This test contains information about the randomization process, the adherence to the intervention, missing outcome data, the measurement of the outcome, and selective outcome reporting. In case of an incomplete description of the study methodology, we tried to contact the corresponding authors of the studies.

Heterogeneity between the included studies was assessed using the I^2 statistics and the *Q* test. I^2 values of <30, 30–59, 60–75, and >75% were classified as low, moderate, substantial, and considerable heterogeneity, respectively [43]. Funnel plots and statistical tests for small-study effects (Begg and Mazumdar test [44] and Egger's test [45]) were employed to test for publication bias. Sensitivity analyses were carried out first by employing a leave-one-out approach, second by excluding the outliers from the respective funnel plots, third by also calculating a fixed-effects model according to the recommendations by Bown and Sutton [46], and forth by recalculating the meta-analysis without the trials with a high risk of bias.

Subgroup analysis was performed to calculate differential effects of studies using BLT as monotherapy and studies investigating BLT as an add-on to (stable) antidepressant medication. Meta-regressions were calculated to examine the effect of publication year, treatment illuminance, treatment duration, and light dosage on the effect sizes.

Results

Study Characteristics

Nineteen studies met our inclusion criteria; 6 crossover trials were excluded [47–52] because they did not provide details on the sequence of treatment. The characteristics of the included studies are presented in online supplementary Table 1. All studies used light boxes for BLT except one, where light visors were employed [53]. Treatment illuminance varied between 1,350 and 10,000 lx. Thirteen studies had a dim-light condition (light box or light visor), 5 studies utilized a sham negative ion generator [54–58], and 1 study employed either dim light or a low-density negative ion generator [59]. Placebo illuminance was 500 lx in 1 study [60], 400 lx in 2 studies [21, 61], and ≤300 lx in all other trials.

Most studies had morning treatment sessions, 1 study had treatments after 11:00 a.m. [62], 1 study employed evening treatments [63], and 2 studies had both morning and evening BLT [2, 64]. The daily treatment duration varied between 30 and 360 min and seemed to be longer in earlier studies (often in trials with lower treatment illuminance). The study duration varied between 7 and 42 days; 1 study investigated the acute effect of a single session [62].

Seven studies used different versions of the Hamilton Depression Rating Scale (HDRS) [65], 8 studies used the Structured Interview Guide for the HDRS, SAD version (SIGH-SAD) [66], 2 studies employed the Beck Depression Inventory (BDI) [67] or the BDI-II [68], and 2 studies had the SIGH-SAD self-rating (SIGH-SAD-SR) [69] as the primary outcome measure. Five studies allowed stable psychopharmacological medication [53, 59, 60, 64, 70], 1 study investigated combined treatment with hypericin at 900 mg and BLT or dim light [71], the other trials did not allow any psychoactive medication. Response to treatment was defined as a ≥50% decrease in depressive symptoms measured on the primary outcome measure in almost all studies. Two trials used the response criterion of a ≥50% decrease in symptoms in combination with a depression score ≤8 [70, 72], and 1 study defined response as a ≥50% symptom reduction together with a depression score <16 [55].

Meta-Analysis

Regarding our primary outcome (post-treatment depression scores), BLT was superior over placebo with an SMD of –0.37 (95% CI: –0.63 to –0.12) based on a random-effects model with 18 studies and 610 patients ($z = -2.89$, $p = 0.004$; online suppl. Fig. 2). We observed moderate heterogeneity between studies for this analysis ($I^2 = 52.3\%$ [95% CI: 18.3–72.1]; $Q = 35.61$, df = 17, $p = 0.005$). There was no indication of significant publication bias, either by inspection of the funnel plots (online suppl. Fig. 3 [97]) or from the small-study tests (Begg's test: $z = -0.19$, $p = 0.850$; Egger's test: $t = -0.17$, df = 16, $p = 0.864$).

The RR of response to BLT versus placebo was 1.42 (95% CI: 1.08–1.85) based on data from 16 studies and 559 patients ($z = 2.54$, $p = 0.011$; online suppl. Fig. 3). The absolute risk reduction of nonresponse with BLT was 20.6%, which corresponds to a number needed to treat of 4.86. A moderate degree of heterogeneity was present between studies ($I^2 = 44.3\%$ [95% CI: 0.0–69.0]; $Q = 26.91$, df = 15, $p = 0.029$). We did not observe significant publication bias from the funnel plot (online suppl. Fig. 4 [97]) or Begg's ($z = 1.71$, $p = 0.087$) and Egger's tests ($t = 2.13$, df = 14, $p = 0.051$).

Risk of Bias

Based on the Cochrane Risk of Bias 2.0 assessment criteria [42], 2 studies obtained a low risk of bias, 6 studies a moderate risk of bias, and 11 studies a high risk of bias (online suppl. Table 2). Randomization bias (mostly due to insufficient reporting of generation and concealment of the allocation sequence) and bias due to deviations from the intended interventions (mostly due to insufficient reporting or implementing of measures of ensuring subjects' adherence to the intervention) were the most common sources of bias.

Sensitivity Analysis

The leave-one-out analysis (random-effects model) showed no significant change of pooled estimates, neither for the primary (SMD –0.31 to –0.42, all p values <0.05; I^2 38.8–55.1%; online suppl. Fig. 5) nor for the secondary outcome measure (RR 1.32–1.51, all p values <0.05; I^2 36.4–48.7%; online suppl. Fig. 6).

We also excluded the outliers of the funnel plots in a further sensitivity analysis. When removing Michalon et al. [72], Terman et al. [58], and Spies et al. [21] for the primary outcome, the resulting meta-analysis was still in line with the results of the original analysis (SMD = –0.27, 95% CI: –0.45 to –0.08; z = –2.83, p = 0.005) but with greatly reduced heterogeneity (I^2 = 2.7%; Q = 14.39, df = 14, p = 0.421). For the secondary outcome, we removed the studies by Levitt et al. [53] and Avery et al. [73], which did not yield different results (RR = 1.61, 95% CI: 1.20–2.17; z = 3.17, p = 0.002) except for a reduction of heterogeneity (I^2 = 27.6%; Q = 17.96, df = 13, p = 0.159).

As higher placebo light intensities might have affected the outcome, we analyzed differences between studies with placebo illuminance <300 lx and those with placebo illuminance ≥300 lx, as well as between studies with placebo illuminance <400 lx and those with placebo illuminance ≥400 lx. We also calculated a meta-regression with placebo illuminance as the covariate, but none of these tests showed a statistically significant influence of the moderator variable.

A sensitivity analysis was also performed by changing the statistical model of the meta-analysis, i.e., by applying a fixed-effects model. However, the results for the primary outcome (SMD = –0.37, 95% CI: –0.53 to –0.20; z = –4.34, p < 0.001) and the secondary outcome (RR = 1.48, 95% CI: 1.24–1.77; z = 4.27, p < 0.001) were virtually the same.

In a final run of sensitivity analyses, we excluded studies which were judged to have a high risk of bias. For the primary outcome (8 studies), the resulting SMD was –0.70 (95% CI: –1.14 to –0.26; z = –3.11, p = 0.002) with an I^2 of 67.5% (Q = 21.55, df = 7, p = 0.003). The corresponding meta-analysis for the secondary outcome (7 studies) yielded an RR of 2.30 (95% CI: 1.35–3.90; z = 3.08, p = 0.002) with an I^2 of 37.5% (Q = 9.60, df = 6, p = 0.142).

Subgroup Analysis and Meta-Regression

We compared studies using BLT as monotherapy with studies also including patients on psychopharmacological medication (stable in all but 1 study) beside BLT. For the primary outcome, the 6 studies with comedication obtained a numerically lower effect size (SMD = –0.19, 95% CI: –0.50 to 0.13; I^2 = 16.9%) than the 12 studies without comedication (SMD = –0.48, 95% CI: –0.82 to –0.13; I^2 = 59.7%), but the effect of this subgroup variable was not significant (Q = 1.45, df = 1, p = 0.228). The same was observed for the secondary outcome when comparing 5 studies with comedication (RR = 1.13, 95% CI: 0.88–1.46; I^2 = 0.0%) and 11 studies without comedication (RR = 1.69, 95% CI: 1.11–2.57; I^2 = 53.4%) – again without any significant group difference (Q = 2.52, df = 1, p = 0.113). A retrospective power analysis of the medication subgroup analysis of the primary outcome parameter [74] yielded a minimum detectable SMD between groups of 0.49 with 80% power at the $p \leq 0.05$ level.

Meta-regression by year of study publication did not yield a significant effect of this covariate on the primary (p = 0.947) or secondary outcome (p = 0.891). We attempted to find a relationship between the primary or secondary outcome and BLT illuminance, duration of daily treatment, length of treatment in days, and daily light dosage (illuminance × daily treatment duration, or, alternatively, illuminance × treatment duration × days of treatment), but none of these calculations were statistically significant (with a very low amount of heterogeneity of <1% accounted by the model for all tests).

Discussion

As BLT is among the treatments of choice for patients suffering from SAD [75, 76], this update of the existing evidence is clinically relevant. Our study differs in several methodological aspects from the prior meta-analysis by Golden et al. [24]. First, we found more studies (19 vs. 8) by broadening our search and not only using the term "phototherapy," which was popular in some of the first trials, but also using the term "light therapy." Second, Golden et al. [24] also included data from crossover trials

irrespective of the sequence of treatment, which might have introduced bias due to carryover effects. Mårtensson et al. [25] only included 8 studies, since they decided to analyze trials with a low or medium risk of bias only. However, we preferred to include the complete evidence and exclude studies with a high risk of bias within the sensitivity analyses. Moreover, Mårtensson et al. [25] only included BLT studies with treatment in the morning. While morning BLT might indeed be superior to evening BLT [56, 58], there is no indication that evening BLT is ineffective at all, which is why we also included these trials.

While the superiority of BLT over placebo was questioned by several authors in the past [55, 60], the results of our meta-analysis indicate significant benefits for SAD patients from BLT. Our primary outcome shows a lower SMD (–0.37) than those reported by Golden et al. [24] (SMD = 0.84) or Mårtensson et al. [25] (SMD = –0.50), but still favors active treatment. Cohen [77] defined an effect size of 0.2 as small and 0.5 as medium; hence, the effect of BLT as seen here lies between small and medium. A number needed to treat of 4.86, which was derived from the secondary outcome, leads us to conclude that BLT in SAD has response rates similar to those shown for conventional antidepressants in nonseasonal major depressive disorder [78, 79].

Furthermore, the findings of this meta-analysis are robust in the light of the sensitivity analyses that were performed (leave-one-out analysis and reanalysis after outlier removal). For our set of sensitivity analyses that were performed without the high-bias-risk trials, the SMD and RR were even higher than for all studies in these calculations, which emphasizes that the low-quality studies were not responsible for influencing the results towards a higher difference between BLT and placebo. However, our selection of analyses of higher-quality studies was not identical to that used by Mårtensson et al. [25]. In their meta-analysis, 4 studies were included that were judged as having a high risk of bias in the present meta-analysis [55, 56, 60, 73], while 4 additional studies were included here [21, 54, 61, 62]. These differences are most likely due to methodological differences regarding the risk-of-bias assessment. While Mårtensson et al. [25] employed a checklist developed by the Swedish Council on Technology Assessment in Health Care, we used the Cochrane Collaboration's tool for assessing risk of bias (Risk of Bias 2.0) [43].

Our subgroup analysis of the studies using BLT as monotherapy versus those trials which allowed psychotropic medication showed numerically lower effect sizes for those studies that used BLT as add-on treatment. The differences between the groups were not statistically significant, but it has to be taken into account that this subgroup analysis was not powered for a significant difference of $g \leq 0.49$. Lower effect sizes for BLT in combination with antidepressants have also been observed in two meta-analyses on nonseasonal depression [24, 80], which only resulted in significant findings for BLT as monotherapy, whereas BLT in combination with antidepressants did not result in superiority over placebo. However, it has to be taken into account that another systematic review [81] found evidence for the efficacy of BLT as an adjuvant to antidepressants, whereas trials that evaluated BLT as monotherapy for nonseasonal depression showed inconsistent results. Concerning this matter, we just have marginal knowledge about BLT adjunctive to antidepressant therapy and its possible interactions.

Meta-regression by publication year of the included studies was not significant, leading us to conclude that over a period of nearly 35 years there was no consistent trend for better or worse treatment effects of BLT. In an effort to analyze our source studies for possible methodological differences that could explain differences in outcomes [82], especially regarding the illuminance used for BLT, the daily treatment duration, and the number of days of treatment from baseline to endpoint, we tried to ascertain whether the effect size of BLT was dependent on these factors. Specifically, we tried to combine these factors into two definitions of light dosage (either daily or cumulatively over the study period). However, none of these meta-regressions resulted in a significant effect of the covariate. The most plausible explanation for these results is that the illuminance used for BLT and the treatment duration were sufficient for a reliable effect in the included clinical trials.

Due to a lack of systematic data collection and insufficient reporting in these source studies, we were not able to meta-analytically assess the tolerability of BLT. However, we tried a descriptive approach and extracted side effects from 7 of 19 included studies [2, 53, 54, 64, 70, 73, 83], creating the following list: headache, (hypomanic) irritability, hyperactivity, nausea, eyestrain, insomnia, and nervousness. However, this enumeration is in line with systematic studies on the tolerability of BLT [84–87], whereby these adverse events seem to be mostly mild to moderate. Long-term studies have also ascertained the safety of BLT, especially regarding ophthalmological problems [88, 89].

Several limitations of our meta-analysis should be noted. We did not focus on side effects or preventative prop-

erties of BLT, and we limited our results to its efficacy for adults, excluding children and adolescents. Furthermore, our study only included trials investigating short-term effects; hence, our meta-analysis cannot serve to draw any conclusions on the long-term efficiency of BLT. Some of these studies were of limited methodological quality (mainly problems with randomization and insufficient control of adherence to the treatment) and/or had fairly small sample sizes (mean sample size 35.3 ± 21.7), which might be the reason for a nonsignificant study outcome in about 80% of the single studies (14 of 18 studies on the primary and 13 of 16 studies on the secondary outcome).

The problem of how to establish a credible placebo control, as discussed by Rosenthal et al. [90] and Eastman [91], impacts our source studies to a varying degree. In this regard, it is important to recognize that the treatment and placebo responses in all the included studies were influenced by the interactive combination of multiple factors, such as demographic variables, illness characteristics, the social environment, therapeutic experiences, and the treatment setting itself [92]. There was a moderate degree of heterogeneity; the included studies showed differences regarding the parameters of BLT (duration, time of the day, and illuminance), the type of placebo used (dim light or sham/low-density negative ion generator), and the presence of psychopharmacological comedication. However, our conclusions are strengthened by the lack of publication bias.

Although the present meta-analysis ascertained the short-term efficacy of BLT for patients with SAD, further larger placebo-controlled trials using state-of-the-art methodology are necessary. Particularly, evidence for the long-term efficacy of BLT [93] and its potential in the prevention of further SAD episodes is limited, and recommendations on treatments are therefore lacking [94, 95].

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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