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Review article

Bright light therapy for nonseasonal depression: Meta-analysis of clinical trials

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ABSTRACT

Background: Bright light therapy (BLT) is a well-established treatment for seasonal depression. In the last two decades, the interest in BLT has expanded to involve other nonseasonal types of depression. The role of BLT for nonseasonal depression remains unsettled. In view of the growing number of studies in this area, this review aimed to assess the efficacy of BLT in nonseasonal depression.
Methods: We searched Pubmed; Scopus; PsychINFO; Evidence Based Medicine Guidelines and Cochrane Library until December 2015. The Standardized mean difference was calculated to assess the efficacy of BLT in nonseasonal depression. Data were subgrouped according to different study characteristics. Heterogeneity was assessed by examining the I^2 index.
Results: Nine trials met the inclusion criteria. After employing the more conservative random-effects model, the overall model showed a significant reduction of depressive symptoms after BLT administration (SMD = −0.62, $P < 0.001$, $I^2 = 37\%$). In particular, BLT appears to be efficacious when administered for 2-5 weeks (SMD = −0.78, $P < 0.001$, $I^2 = 0\%$), and as monotherapy (SMD = −0.71, $P < 0.001$, $I^2 = 18\%$). Studies of BLT for perinatal depression have found statistically insignificant improvement (SMD = −0.17, $P > 0.05$, $I^2 = 44\%$).
Limitations: The overall heterogeneity of the included trials was moderate. The participants were not adequately blinded to the intervention. The sample size was small for certain subgroups. The long-term effect of BLT on depression was not explored.
Conclusions: BLT appears to be efficacious, particularly when administered for 2–5 weeks' duration and as monotherapy. There is an obvious need to optimize the duration and intensity of exposure, the timing and the duration of treatment sessions.

Contents

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1. Introduction

The description of light therapy as a treatment option was first mentioned in association with the syndrome of seasonal affective disorder/winter type (SAD) (Rosenthal et al., 1984). This syndrome is characterized by episodes of major depression which follow a seasonal pattern, mostly occurring in winter and fall with full remission during spring and summer seasons (Even et al., 2008). Since these seasonal changes in mood are mediated by alterations in melatonin, which is a central hormone secreted by the pineal gland in a circadian pattern and regulated by the light-dark cycle (day and night) and the seasonal cycle, the exposure to bright light was proposed as the treatment of choice (Lewy et al., 1980). Several mechanisms were suggested to explain how bright light therapy (BLT) may alleviate depressive symptoms. First, early animal studies showed that light is able to shift the circadian and seasonal rhythms (De Coursey, 1960; Pittendrigh, 1960), thus modulating the chronobiological cycle (Murray et al., 2005). Second, it is believed that extending the duration of daylight during the winter season will modulate these rhythms by regulating the master clock, the suprachiasmatic nucleus (SCN), resulting in an antidepressant effect (Rosenthal et al., 1984). Afterwards, these hypotheses were supplanted by the phase shift hypothesis which attributed depression in SAD patients to phase delay in circadian rhythms relative to the sleep/wake cycles, with a smaller subgroup of these patients becoming depressed due to a phase advance (Lewy et al., 1987). However, the exact mechanism of action of BLT in the treatment of depression remains unclear (Pail et al., 2011).

The interest in BLT has expanded beyond SAD; many clinical trials reported conflicting conclusions about whether BLT is effective as a treatment modality in nonseasonal depression (Even et al., 2008). Earlier meta-analyses of trials on the efficacy of BLT revealed that it is efficacious in the treatment of the seasonal type of depression (Golden et al., 2005; Martensson et al., 2015). However, its application in nonseasonal depression is less clear as recent reviews have refrained from meta-analytically pooling data, due to the heterogeneity of studies (Even et al., 2008; Martensson et al., 2015). Because new trials on the efficacy of BLT in nonseasonal depression have been recently published, we decided to conduct a meta-analysis in order to assess the clinical efficacy of such treatment in nonseasonal depression.

2. Methods

2.1. Literature search

This systematic review protocol was registered at Prospero International Prospective Register of Systematic Reviews (Registration ID= CRD42015032297). We have systematically searched the following online databases: Pubmed; Scopus; PsycINFO; Evidence Based Medicine (EBM) Guidelines; JAMA evidence and the Cochrane library. Several MeSH terms were used to identify relevant literature: bright light therapy OR phototherapy AND depression OR major depressive disorders OR nonseasonal depression AND clinical trials AND efficacy OR effect. The search was restricted to trials published in English language only. The references mentioned in the identified trials were also scanned for relevant publications. The guidelines as described in the *Preferred Reporting Items for Systematic Reviews and Meta-analysis*, the PRISMA statement, were followed during the identification and selection of relevant studies (Moher et al., 2009). The initially-identified studies were imported into the EndNote reference management software to screen for duplication. Initially, we screened the titles and abstracts against the inclusion criteria, then the full-text of the relevant articles was retrieved for further assessment and scrutiny.

2.2. Inclusion criteria

For a trial to be considered in this meta-analysis, it had to meet the following criteria; *Criterion A:* has to be a controlled trial with intervention and control arms; *Criterion B:* must have enrolled only patients with nonseasonal depression who have been diagnosed by standardized depression scales; *Criterion C:* must have bright light therapy as primary independent intervention; *Criterion D:* must have a valid placebo as control (such as dim light or in case of negative air ions; the low-density type was assumed acceptable); *Criterion E:* must have quantified the improvement in depression as the key outcome variable by standardized depression scales; *Criterion F:* if the trial administered BLT as adjunctive to another intervention (such as antidepressant medication or sleep deprivation therapy), it must be equally administered in both intervention and control arms to be able to rule out the effect of the adjunct treatment; and *Criterion G:* must have at least "moderate" final global rating by a quality assessment tool. The literature search was independently conducted by the authors. The summary of the literature search process is depicted as PRISMA flow chart (Fig. 1).

2.3. Data abstraction and quality assessment

Two reviewers (DA and LJ) independently abstracted data from the identified trials by utilizing a pre-piloted data form. Relevant information about the age of participants, gender, the use of psychotropic medication, past medical history, the presence of other comorbidities, the study design and setting, sample size, the diagnostic criteria of depression and the assessment of seasonality, the type and the intensity of intervention, the duration of treatment, the type of study control, and the major findings reported were all retrieved. The extracted data were matched and discussed in a consensus meeting. Inconsistencies or disagreements were resolved by discussion and referring back to the original trials.

We employed the Quality Assessment Tool for Quantitative Studies to evaluate the quality of the included trials (Effective Public Health Practice Project, 2008). This tool offers a standardized method to appraise the quality of the evidence which is presented as an overall rating of strong, moderate or weak in eight areas: selection bias; study design; adjustment for confounders; blinding; data collection method; withdrawals and dropouts; intervention integrity; and the appropriateness of the analysis to the question. The final global rating for each study is quantified according to the number of "weak" ratings in each of the above-mentioned areas with a final score of "strong" rating (no weak rating), "moderate" rating (one weak rating) or "weak" rating (two or more weak ratings) (Effective Public Health Practice Project,

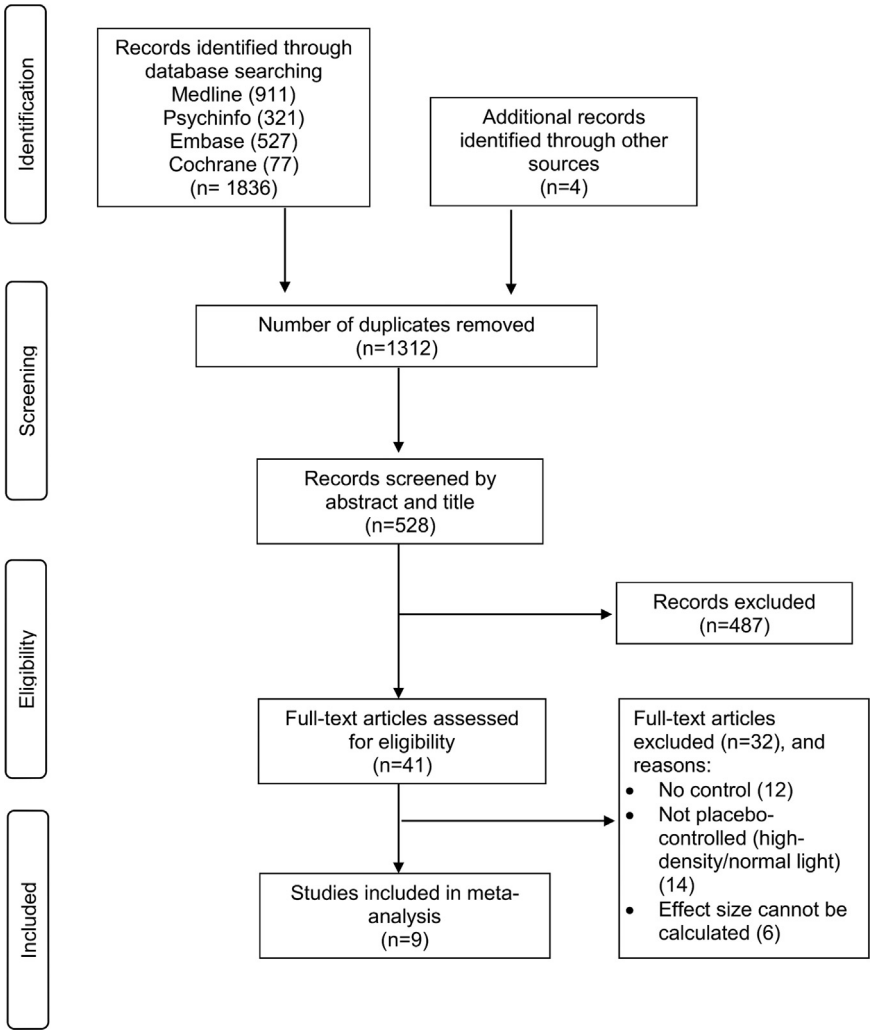

Fig. 1. Selection process of studies for meta-analysis of trials of bright light therapy for nonseasonal depression.

2008). The appraisal of the evidence was independently performed. The results were discussed and discrepancies were resolved by referring to the Quality Assessment Tool guidelines and dictionary.

2.4. Statistical analysis

Because the included trials quantified the improvement in depression by using different psychometric scales, a decision was made to utilize the standardized mean difference (SMD) to unify the units of measurement before these studies were combined. The SMD represents the size of the intervention effect relative to the variability observed in that study (standard deviation) (Higgins JPT, 2011). However, this method accounts for the differences in the measurement scale but not the real differences between studies. For this reason, the random-effects model and generic inverse variance were used to pool the data. This model assumes that these variations are the result of both inter-study differences and random variations (DerSimonian and Laird, 1986). The SMD and its corresponding 95% confidence interval (CI) was calculated for individual studies and the combined effect was also calculated. We pooled the standard deviation (SD) by following this formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$. Since the included trials did not report the correlation coefficient (R), we assumed that it is equal to 0.5. A subsequent sensitivity analysis was performed to ascertain that the results of this meta-analysis were not affected by this assumption. Therefore, the analysis was repeated with different R values ranging from 0.1 to 0.9. In addition, the robustness of the results was also examined by the leave-one-out method (Higgins, 2008). This was done by excluding one study each time and assessing its effect on the overall effect size.

Since the included studies were inconsistent in terms of the characteristics of the patients, the duration of the intervention, the intensity of exposure to BLT, whether BLT was administered as monotherapy or adjunctive to antidepressants, and the quality of the evidence, data were subgrouped and the effect sizes were recalculated. Such comparisons were thought to be helpful to identify any confounding factors that may potentially influence the outcome of the treatment. In addition, heterogeneity assessment was performed by examining the I^2 index and chi-squared analysis. Because the number of included trials is small and the latter analysis may have a low power, a P value of 0.1 was considered to determine statistical significance of heterogeneity (Higgins JPT, 2011). The publication bias was assessed by the visual inspection of the funnel plot which reflects the inverse standard error versus the effect size. This was also statistically assessed by Egger's linear regression method (Egger et al., 1997). Review Manager Software (version 5.3.0) from Cochrane Collaboration was used to perform this meta-analysis.

3. Results

3.1. Description of the included studies

Of the 1840 studies identified during the initial stage of the literature search, 41 full-text articles were retrieved and evaluated based on the selection criteria. Nine trials met the inclusion criteria. Fig. 1 depicts the selection process of the included trials. Data were extracted and pooled from 9 clinical trials (Corral et al., 2007; Dauphinais et al., 2012; Goel et al., 2005; Kripke et al., 1992; Lam et al., 2015; Lieverse et al., 2011; Mackert et al., 1991; Martiny et al., 2005; Wirz-Justice et al., 2011). In total, 419 patients were enrolled in these trials, with 211 patients receiving BLT intervention and 208 patients receiving placebo control. All these patients were diagnosed with unipolar major depression or bipolar disorder (depression phase) by utilizing standardized screening tools. Most of the patients enrolled in the included trials received bright light as monotherapy except in two trials (Dauphinais et al., 2012; Martiny et al., 2005), which had bright light as adjunctive to antidepressants. All the included trials quantified the improvement in depression as the primary end point of the study by employing standardized scales as described earlier. The included trials in this meta-analysis were published between 1991 and 2015. Table 1 describes the characteristics of the included studies.

3.2. Risk of bias assessment

The Quality Assessment Tool for Quantitative Studies Guidelines (Effective Public Health Practice Project, 2008) was utilized to appraise the included trials (supplementary data). Of the total, seven trials scored a “strong” global final rating, while two trials scored a “moderate” final rating (Dauphinais et al., 2012; Goel et al., 2005). The latter trials had “weak” scoring in the selection bias criteria as the participants were volunteers (self-referred) and were unlikely to be representative of the target population. In addition, Goel et al. (2005) also scored “moderate” in the confounding adjustment criteria as the authors did not report on the baseline balance between trial arms in key confounding variables such as the demographic characteristics of the participants (Goel et al., 2005). The same trial also scored “moderate” in the blinding criteria as it was single-blinded (Goel et al., 2005). Subgroup analysis was also conducted to assess the difference between “strong” and “moderate” rating trials, and the effect size of bright BLT on depression was recalculated.

3.3. The clinical efficacy of bright light therapy in patients with nonseasonal depression and subgroup analyses

The meta-analysis of the pooled data from the 9 clinical trials showed that BLT significantly improved depression (SMD = −0.62, 95% CI = −0.88, −0.35, P < 0.001, I^2 = 37%) (Fig. 2). This effect size was robust and insensitive to any single trial as assessed by the leave-one-out sensitivity analysis. Data were also subgrouped based on study characteristics (Table 2). Data were stratified by the duration of exposure to BLT. The medium-term exposure to BLT yielded the highest reduction in depression score with pooled effect size of −0.78 (95% CI = −1.05, −0.51, P < 0.001, I^2 = 0%) as compared to short-term exposure (SMD = −0.46, 95% CI = −0.96, −0.03, P = 0.05, I^2 = 0%) and long-term exposure to BLT which had no significant effect on depression (SMD = −0.20, 95% CI = −0.91, 0.52, P > 0.05, I^2 = 65%).On the other hand, subgrouping data by the intensity of BLT showed that exposure to high intensity BLT (SMD = −0.59, 95% CI = −0.93, −0.25, P < 0.001, I^2 = 50%) was not significantly different compared to exposure to low intensity BLT (SMD = −0.66, 95% CI = −1.12, −0.09, P = 0.005, I^2 = 0%).

Subgroup analysis of BLT for peripartum depression revealed moderate heterogeneity across studies and failed to find evidence of efficacy (SMD = −0.17, 95% CI = −1.05, 0.71, P > 0.05, I^2 = 44%). Similarly, when administered as adjunctive to antidepressants, BLT did not show any significant reduction of depressive symptoms with considerable heterogeneity across studies (SMD = −0.35, 95% CI = −1.09, 0.40, P > 0.05, I^2 = 75%). In contrast, the exposure to BLT as monotherapy without concomitant administration of psychotropic medications had the highest effect on depression (SMD = −0.71, 95% CI = −1.00, −0.43, P < 0.001, I^2 = 18%). Data were also subgrouped by the quality of the evidence. High quality trials demonstrated that BLT had a statistically significant effect in reducing depressive symptoms (SMD = −0.63, 95% CI = −0.84, −0.43, P < 0.001, I^2 = 11%). While also significant, the pooled moderate quality trials revealed substantial heterogeneity across the studies (SMD = −0.66, 95% CI = −1.20, −0.01, P = 0.05, I^2 = 65%).

In addition, the I^2 index and chi-squared value were used to assess the inter-study heterogeneity. The results showed an overall moderate heterogeneity with a non-significant heterogeneity index when all included trials were pooled (I^2 = 37%, X^2 = 12.73, df = 8, P > 0.1). In addition, between-subgroups differences were also assessed and showed minimal heterogeneity, with subgroup differences between short-term, medium-term and long-term exposure to treatment (I^2 = 12.3%, p > 0.1); high versus low intensity of intervention (I^2 = 0%, p > 0.1); pregnancy related major depression versus other types of nonseasonal depression (I^2 = 16.1%, p > 0.1); BLT monotherapy versus BLT as adjunctive to antidepressant (I^2 = 0%, p > 0.1); high quality versus moderate quality trials (I^2 = 5%, p > 0.1).

3.4. Publication bias

Visual inspection of the funnel plot showed minimal evidence of bias as demonstrated in Fig. 3. Moreover, we found no evidence of publication bias by Egger's linear regression method (intercept = 0.78, standard error = 1.13, 95% CI = −2.04, 3.11, t = 0.90, p > 0.05) (Egger et al., 1997).

4. Discussion

4.1. Main findings and implications

In this meta-analysis, we included 9 clinical trials with a total of 419 patients enrolled in the intervention and control arms. The result of the analysis revealed that BLT significantly improved depressive symptoms in patients with nonseasonal depression. The leave-one-out sensitivity analysis showed that the efficacy of BLT on depression is robust and consistent, irrespective of the individual effect of any trial. Our results are consistent with previous reviews; Tuunainen et al. (2004) reported that BLT had a significant effect in nonseasonal depression, especially during the first week when administered in the early morning (Tuunainen et al., 2004). Similarly, Golden et al. (2005) reported that BLT was efficacious in nonseasonal depression (Golden et al., 2005). However, the latter meta-analysis pooled data from two trials (Baumgartner et al., 1996; Mackert et al., 1991) which were based on the same study. In addition, Kripke (1998) compared the efficacy of light treatment in seasonal and nonseasonal depression and concluded that BLT is comparably efficacious and may synergistically enhance standard antidepressant therapy (Kripke, 1998). As previously explained, several mechanisms were proposed to explain the efficacy of BLT in nonseasonal depression (Pail et al., 2011). However, the involvement of serotonergic mechanisms seems to be more compelling in explaining the antidepressant effect of BLT. This was further confirmed by aan het Rot et al. (2008) by employing the tryptophan

Table 1
The characteristics of the included trials.

Trial	Participants (No. I/C)	Medication	Diagnosis of depression	Intervention	Treatment duration (weeks)	Control	Major findings
Corral et al. (2007)	Women with postpartum depression (10/5)	No antidepressants	DSM-IV with postpartum onset, SIGH-SAD$_{29} \geq 15$	BL (10,000lx)	6 weeks	DL (600lx)	Both group significantly improved with no significant difference between groups
Dauphinais et al. (2012)	Patients with bipolar disorder, depressed phase (18/20)	Psychotropic medications which were stable during the trial	DSM-IV for Bipolar I or II, depressed phase for at least one month before screening with no manic episode, SIGH-ADS ≥ 20, HAM-D ≥ 10, CGI-S ≥ 4	BL (7000lx)	In the morning exposure, 8 weeks	Low-density negative ion ($1.7*10^{11}$ ions/s)	No significant difference in the reduction of depression scores between groups.
Goel et al. (2005)	Patients with chronic major depression (10/10)	Psychotropic medication (except pre-established SSRI for two patients) were not allowed	DSM-IV, chronic (episode duration ≥ 2 years)	BL (10,000lx)	In the morning for 1 h, 5 weeks	Low-density negative ion ($1.7*10^{11}$ ions/s)	Depression significantly improved in BL group as compared to patients receiving low-density negative ion treatment. Similar remission rate to SAD but without seasonal dependency
Kripke et al. (1992)	Patients with MDD or depressed phase of bipolar disorder (25/26)	No psychotropic medication for at least 10 days prior to the study	DSM-III,HDS$_{24} \geq 15$	BL (2000–3000lx)	In the morning or evening time, 2–3 h per day, 1 week	DL ($\leq$ 50lx)	Significant improvement of depression among BL treated patients.
Lam et al. (2015)	Patients with moderate to severe MDD (28/24)	No psychotropic medication for at least two weeks prior to the trial	DSM-IV-TR, HAM-D ≥ 20	BL (10,000lx)	30 min/day at early morning, 8 weeks	Inactive negative ions	Significant improvement in depression scores as a result of BLT. When combined with fluoxetine, BLT had the highest effect on depression.
Lieverse et al. (2011)	Patients older than 60 years, with MDD (42/47)	No medication except sporadic use of Aspirin	GDS$_{15} \geq 5$ DSM-IV Axis I disorder, HAM-D,	BL (7500lx)	One hour early morning, 3 weeks	DL (50lx)	BLT improved depression, enhanced mood and sleep efficiency, and this effect was sustained even after the discontinuation of treatment
Mackert et al. (1991)	36 patients with MDD, 6 with bipolar disorder (22/20)	Anti-depressants were discontinued for 8.7 days (mean) before trial	RDC for major depression, DSM-III-R	BL (2500lx)	Two hours/day in the morning, 1 week	DL (50lx)	BLT was not effective in improving depression
Martiny et al. (2005)	Patients with major depression (48/54)	Sertraline, 50 mg/day	DSM-IV for major depression,	BL (10,000lx)	One hour/day for BL and 30 min/day for DL, 5 weeks	DL (50lx)	Significant reduction of depression scores with BLT in comparison to DL
Wirz-Justice et al. (2011)	Pregnant women with MDD (16/11)	No anti-depressant medication	DSM-IV criteria for major depression	BL (7000lx)	One hour/day in the morning, 5 weeks	DL (70lx)	Significant improvement of depression in patients receiving BLT with significantly higher remission rate.

BLT: Bright Light Therapy; CGI-S: Clinical Global Impression Severity Scale; DL: Dim Light; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, Revised; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision; GDS$_{15}$: The Geriatric Depression Scale, 15-item version; HDS: Hamilton Depression Scale; HAM-D: Hamilton Depression Rating Scale; I/C: Intervention/Control; MDD: Major Depressive Disorders; RDC: Research Diagnostic Criteria for Major Depressive Disorders; SIGH-SAD$_{29}$: Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders, 29-item version; SIGH-ADS: Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement.

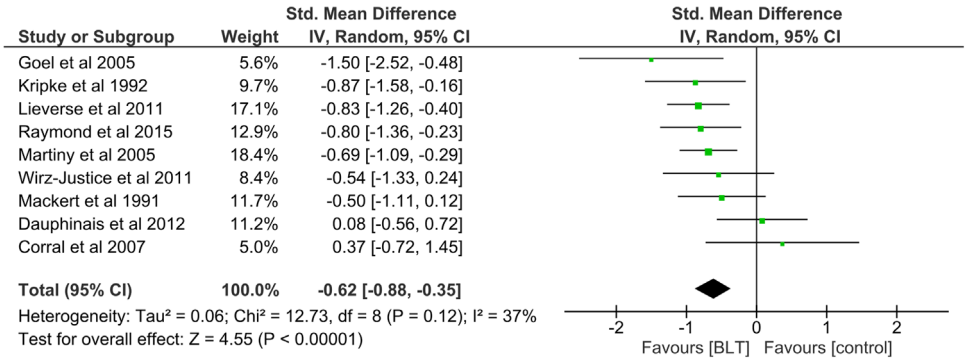

Fig. 2. Effect sizes in trials of treatment of nonseasonal depression with bright light.

Table 2
Subgroup analysis of the efficacy of Bright Light therapy on depressive symptoms.

Subgroups	No	I^2	Standardized Mean difference (95% CI)	P
Duration of intervention				
Short-term exposure (one week or less)	2	0%	−0.46 [−0.96, −0.03]	0.05
Medium-term exposure (one to five weeks)	4	0%	−0.78 [−1.05, −0.51]	< 0.001
Long-term exposure (more than five weeks)	3	65%	−0.20 [−0.91, 0.52]	NS
Intensity of bright light				
Low intensity (≤ 3000 lux)	2	0%	−0.66 [−1.12, −0.09]	0.005
High intensity (> 3000 lux)	7	50%	−0.59 [−0.93, −0.25]	< 0.001
Patients characteristics				
Pregnancy-related major depression	2	44%	−0.17 [−1.05, 0.71]	NS
Other types of nonseasonal depression	7	35%	−0.68 [−0.95, −0.41]	< 0.001
Intervention administered as adjunctive to antidepressant				
Light therapy with antidepressants	2	75%	−0.35 [−1.09, 0.40]	NS
Light therapy with no antidepressants	7	18%	−0.71 [−1.00, −0.43]	< 0.001
Quality of evidence				
High quality	7	11%	−0.63 [−0.84, −0.43]	< 0.001
Moderate quality	2	65%	−0.66 [−1.20, −0.01]	0.05

CI: Confidence Interval; NS: Not Significant.

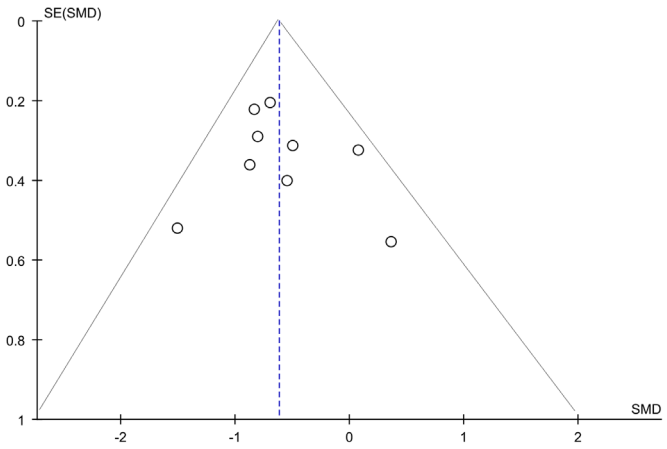

Fig. 3. Publication bias assessment plot.

depletion paradigm which reduces the bioavailability of serotonin in the brain as tryptophan is a precursor for serotonin synthesis. This evidence showed that administering BLT could prevent tryptophan depletion-mediated depression by directly interacting with serotonin function (aan het Rot et al., 2008).

While combining the retrieved data in this meta-analysis, we observed a certain pattern regarding the duration of treatment. Trials which administered BLT for either short duration (one week or less) or long duration (more than five weeks) had modest to non-significant effect on depression. Pooling studies of 2–5 weeks' duration yielded the highest antidepressant effect size of BLT based on study duration. Given that the included trials utilized different study protocols in terms of the duration and intensity of exposure, the number and duration of treatment sessions per day, a conclusion cannot be drawn regarding the optimal treatment duration. In addition, the included trials did not compare the efficacy of BLT when administrated for shorter or longer duration; therefore, it may be possible that shorter or longer duration exposure would have yielded the same results in these studies. This also casts doubt on whether the observed improvement in depression is sustainable beyond this timeframe and questions the long-term effectiveness of BLT in clinical settings. Surprisingly, Martensson et al. (2015) reported similar findings in a meta-analysis on the efficacy of BLT in the treatment of SAD. The latter review reported that BLT had significant effects only at two to three weeks of treatment (Martensson et al., 2015). This also raises a question of whether BLT exerts antidepressant effect through similar mechanisms in both seasonal and nonseasonal depression.

In addition, stratifying data revealed that there was no significant difference in the antidepressant effect of BLT based on the intensity of exposure. Given that no trial reported data on the intensity-response assessment, the optimal intensity of BLT to achieve the best outcome remains unknown. As previously explained, it is noteworthy that both the duration of treatment sessions and the intensity of exposure are equally important as a determinant of the outcome of the treatment. For instance, the daily exposure to 2500 lx of BLT for 2–3 h per session (Kripke et al., 1992) was almost as efficacious as the exposure to 10,000 lx of BLT for 30 min per session (Lam et al., 2015) in reducing depressive symptoms. Our results do not agree with the previous systematic review which reported an optimal response when the intensity of BLT is above 5000 lx (Even et al., 2008). In addition to the intensity of exposure, the outcome of BLT is influenced by several other determinants which collectively define the result of the treatment. All these variables should be simultaneously adjusted in order to benefit from BLT.

Data were also subgrouped based on patients' characteristics. Data are inconclusive as to whether BLT is efficacious in peripartum depression. One explanation credits that to the difference in the pathogenesis of perinatal depression which is induced by

fluctuations in estrogen which peaks during pregnancy and abruptly decreases after parturition (Meltzer-Brody, 2011). Although the evidence is limited, one study hypothesized that BLT may augment the secretion of luteinizing hormone (LH), a gonadotropin involved in the synthesis of estrogen (Kripke et al., 2010). However, the number of participants enrolled in these trials may not be large enough to demonstrate the effect of BLT on perinatal depression. In addition, some trials enrolled patients diagnosed with bipolar disorder (depression phase) (Dauphinais et al., 2012), or patients with either unipolar major depression or bipolar disorders (depressed phase) (Kripke et al., 1992; Mackert et al., 1991). As the latter trials did not report the effect based on whether the patient is diagnosed with unipolar or bipolar depression, we were not able to subgroup the effect according to the clinical type of depression. However, Dauphinais et al. (2012) demonstrated that BLT was not efficacious in the treatment of depression in patients with bipolar disorders. This is perhaps controversial as Kripke et al. (1992) revealed that patients with bipolar disorders tended to have greater, although non-significant, reduction of depressive symptoms. This was also confirmed by Deltito et al. (1991) who compared the efficacy of BLT between these clinical types of depression and reported that the trend was toward greater benefit among bipolar patients (Deltito et al., 1991).

Subgroup analysis found a statistically significant effect of BLT as monotherapy, but the effect size for BLT among studies of BLT as an adjunct to antidepressant medications was statistically insignificant.. Golden et al. (2005) reached a similar conclusion that BLT is not efficacious when administered as adjunctive to antidepressants (Golden et al., 2005). It is noteworthy that the latter review pooled data from five trials that we excluded because they did not meet the eligibility criteria in our meta-analysis for several reasons: used 2500 lx light as study control (Beauchemin and Hays, 1997); included patients diagnosed with SAD (Fritzsche et al., 2001); lack of dim light placebo control (Holsboer-Trachsler et al., 1994; Muller et al., 1997); and concomitantly administered BLT with partial sleep deprivation (Neumeister et al., 1996).

The heterogeneity of trials assessing the efficacy of BLT in nonseasonal depression was previously reported as a challenge to performing meta-analysis (Even et al., 2008; Martensson et al., 2015). However, the analysis of our data showed that there was moderate heterogeneity which was not statistically significant. In fact, we assumed that the included trials were different in terms of study characteristics and setting; therefore, we utilized the more conservative random-effects model which adjusts for inter-study variations as well. As heterogeneity seems to be inevitable in performing meta-analysis, we assumed that the included trials were sufficiently homogenous to draw conclusions. In addition, subgrouping data based on the quality of the evidence showed that high quality trials had minimal heterogeneity ($I^2 = 11\%$) with significant effect size ($P < 0.001$). This further confirms the efficacy of BLT in reducing depressive symptoms among patients with nonseasonal depression.

4.2. Limitations

There are several limitations that should be considered while interpreting the results of this meta-analysis. First, we agree with Golden et al. (2005) that it is quite challenging to design an efficient placebo control and thus blinding the participants to the intervention may not be efficient. The use of dim light may not be as effective since the objective of the trial regarding testing the efficacy of BLT may have been conveyed to the participants; thus the placebo effect cannot be ruled out (Martensson et al., 2015). Second, our results should be interpreted with caution owing to the reported moderate heterogeneity of the included trials. More importantly, the within-subgroup heterogeneity seemed high for the "long-term exposure to BLT", "BLT with antidepressants" and "moderate quality trials" subgroups, which limits the interpretation of the efficacy of BLT on nonseasonal depression. It was not possible to subgroup the effect size based on the clinical type, whether major depression or bipolar disorder, which may also explain the heterogeneity of the findings. Another limitation is acknowledged regarding the small sample size especially in trials regarding the efficacy of BLT on perinatal depression (Corral et al., 2007; Wirz-Justice et al., 2011), which also highlights the need for proper assessment of BLT in this group. In addition, the improvement in depression was quantified utilizing psychometrically standardized scales. However, the content validity and retest reliability of these scales have been previously criticized (Bagby et al., 2004). In addition, all included trials did not compare the efficacy of BLT when administered for shorter or longer period of time. Hence, we cannot tell if the duration of exposure was optimal or longer than necessary. Lastly, since we only estimated the improvement of depression based on the mean changes in depression scores during the treatment period, the long-term effect of BLT was not explored. At this stage, it is not clear whether such effect will be sustained.

4.3. Conclusions

The findings of our meta-analysis showed that BLT is efficacious in treating patients with nonseasonal depression. The highest antidepressant effect size of BLT was obtained when trials of 2-5 weeks' duration were pooled. Unlike administering BLT as monotherapy, studies that administered BLT as adjunct to antidepressant medications have failed to find evidence of efficacy. At this stage, the optimal duration of treatment, intensity and timing of exposure, and duration of treatment sessions remain unclear. Given the reported heterogeneity of the trials, larger clinical trials to investigate more homogenous subgroups should be conducted to further investigate the effect of BLT in nonseasonal depression. This is particularly the case with trials addressing the efficacy of BLT in perinatal depression. Moreover, the approach to investigating the efficacy of BLT needs to be standardized in terms of defining an acceptable placebo control, the optimal intensity of exposure and the duration of treatment. However, given the data on its efficacy in nonseasonal depression, the BLT is an excellent candidate as a new avenue in the treatment of nonseasonal depression.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2016.03.016.

References

Effective Public Health Practice Project, 2008. Quality Assessment Tool for Quantitative Studies. National Collaborating Centre for Methods and Tools, McMaster University, Hamilton, ON.

aan het Rot, M., Benkelfat, C., Boivin, D.B., Young, S.N., 2008. Bright light exposure during acute tryptophan depletion prevents a lowering of mood in mildly seasonal women. Eur. Neuropsychopharmacol.: J. Eur. Coll. Neuropsychopharmacol. 18, 14–23.

Bagby, R.M., Ryder, A.G., Schuller, D.R., Marshall, M.B., 2004. The Hamilton Depression Rating Scale: has the gold standard become a lead weight? Am. J. Psychiatry 161, 2163–2177.

Baumgartner, A., Volz, H.P., Campos-Barros, A., Stieglitz, R.D., Mansmann, U., Mackert, A., 1996. Serum concentrations of thyroid hormones in patients with nonseasonal affective disorders during treatment with bright and dim light. Biol. Psychiatry 40, 899–907.

Beauchemin, K.M., Hays, P., 1997. Phototherapy is a useful adjunct in the treatment of depressed in-patients. Acta Psychiatr. Scand. 95, 424–427.

Corral, M., Wardrop, A.A., Zhang, H., Grewal, A.K., Patton, S., 2007. Morning light therapy for postpartum depression. Arch. Women's Ment. Health 10, 221–224.
Dauphinais, D.R., Rosenthal, J.Z., Terman, M., DiFebo, H.M., Tuggle, C., Rosenthal, N. E., 2012. Controlled trial of safety and efficacy of bright light therapy vs. negative air ions in patients with bipolar depression. Psychiatry Res. 196, 57–61.
De Coursey, P.J., 1960. Daily light sensitivity rhythm in a rodent. Science 131, 33–35.
Deltito, J.A., Moline, M., Pollak, C., Martin, L.Y., Maremmani, I., 1991. Effects of phototherapy on non-seasonal unipolar and bipolar depressive spectrum disorders. J. Affect. Disord. 23, 231–237.
DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7, 177–188.
Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ Br. Med. J. 315, 629–634.
Even, C., Schroder, C.M., Friedman, S., Rouillon, F., 2008. Efficacy of light therapy in nonseasonal depression: a systematic review. J. Affect. Disord. 108, 11–23.
Fritzsche, M., Heller, R., Hill, H., Kick, H., 2001. Sleep deprivation as a predictor of response to light therapy in major depression. J. Affect. Disord. 62, 207–215.
Goel, N., Terman, M., Terman, J.S., Macchi, M.M., Stewart, J.W., 2005. Controlled trial of bright light and negative air ions for chronic depression. Psychol. Med. 35, 945–955.
Golden, R.N., Gaynes, B.N., Ekstrom, R.D., Hamer, R.M., Jacobsen, F.M., Suppes, T., Wisner, K.L., Nemeroff, C.B., 2005. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am. J. Psychiatry 162, 656–662.
Higgins, J.P.T., 2008. Commentary: heterogeneity in meta-analysis should be expected and appropriately quantified. Int. J. Epidemiol. 37, 1158–1160.
Holsboer-Trachsler, E., Hemmeter, U., Hatzinger, M., Seifritz, E., Gerhard, U., Hobi, V., 1994. Sleep deprivation and bright light as potential augmenters of antidepressant drug treatment – neurobiological and psychometric assessment of course. J. Psychiatr. Res. 28, 381–399.
JPT Higgins, G.S., 2011. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration.
Kripke, D.F., 1998. Light treatment for nonseasonal depression: speed, efficacy, and combined treatment. J. Affect. Disord. 49, 109–117.
Kripke, D.F., Mullaney, D.J., Klauber, M.R., Risch, S.C., Gillin, J.C., 1992. Controlled trial of bright light for nonseasonal major depressive disorders. Biol. Psychiatry 31, 119–134.
Kripke, D.F., Elliott, J.A., Youngstedt, S.D., Parry, B.L., Hauger, R.L., Rex, K.M., 2010. Weak evidence of bright light effects on human LH and FSH. J. Circadian Rhythm. 8, 5.
Lam, R.W., Levitt, A.J., Levitan, R.D., Michalak, E.E., Morehouse, R., Ramasubbu, R., Yatham, L.N., Tam, E.M., 2015. Efficacy of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder: a randomized clinical trial. JAMA Psychiatry, 1–9.
Lewy, A.J., Sack, R.L., Singer, C.M., White, D.M., 1987. The phase shift hypothesis for bright light's therapeutic mechanism of action: theoretical considerations and experimental evidence. Psychopharmacol. Bull. 23, 349–353.
Lewy, A.J., Wehr, T.A., Goodwin, F.K., Newsome, D.A., Markey, S.P., 1980. Light suppresses melatonin secretion in humans. Science 210, 1267–1269.
Lieverse, R., Van Someren, E.J., Nielen, M.M., Uitdehaag, B.M., Smit, J.H., Hoogendijk, W.J., 2011. Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. Arch. Gen. Psychiatry 68, 61–70.
Mackert, A., Volz, H.P., Stieglitz, R.D., Muller-Oerlinghausen, B., 1991. Phototherapy in nonseasonal depression. Biol. Psychiatry 30, 257–268.
Martensson, 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.
Martiny, K., Lunde, M., Unden, M., Dam, H., Bech, P., 2005. Adjunctive bright light in non-seasonal major depression: results from clinician-rated depression scales. Acta Psychiatr. Scand. 112, 117–125.
Meltzer-Brody, S., 2011. New insights into perinatal depression: pathogenesis and treatment during pregnancy and postpartum. Dialogues Clin. Neurosci. 13, 89–100.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann. Intern. Med. 151 (264–269), w264.
Muller, M.J., Seifritz, E., Hatzinger, M., Hemmeter, U., Holsboer-Trachsler, E., 1997. Side effects of adjunct light therapy in patients with major depression. Eur. Arch. Psychiatry Clin. Neurosci. 247, 252–258.
Murray, G., Michalak, E.E., Levitt, A.J., Levitan, R.D., Enns, M.W., Morehouse, R., Lam, R.W., 2005. Therapeutic mechanism in seasonal affective disorder: do fluoxetine and light operate through advancing circadian phase? Chronobiol. Int. 22, 937–943.
Neumeister, A., Goessler, R., Lucht, M., Kapitany, T., Bamas, C., Kasper, S., 1996. Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. Biol. Psychiatry 39, 16–21.
Pail, G., Huf, W., Pjrek, E., Winkler, D., Willeit, M., Praschak-Rieder, N., Kasper, S., 2011. Bright-light therapy in the treatment of mood disorders. Neuropsychobiology 64, 152–162.
Pittendrigh, C.S., 1960. Circadian rhythms and the circadian organization of living systems. Cold Spring Harb. Symp. Quant. Biol. 25, 159–184.
Rosenthal, N.E., Sack, D.A., Gillin, J.C., Lewy, A.J., Goodwin, F.K., Davenport, Y., Mueller, P.S., Newsome, D.A., Wehr, T.A., 1984. Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. Arch. Gen. psychiatry 41, 72–80.
Tuunainen, A., Kripke, D.F., Endo, T., 2004. Light therapy for non-seasonal depression. Cochrane Database Syst. Rev., Cd004050.
Wirz-Justice, A., Bader, A., Frisch, U., Stieglitz, R.D., Alder, J., Bitzer, J., Hosli, I., Jazbec, S., Benedetti, F., Terman, M., Wisner, K.L., Riecher-Rossler, A., 2011. A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. J. Clin. Psychiatry 72, 986–993.