RESEARCH ARTICLE

Bright light therapy in the treatment of patients with bipolar disorder: A systematic review and meta-analysis

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Abstract

The treatment of depressive symptoms of bipolar disorder (BD) has received increasing attention. Recently, some studies have shown that bright light therapy (BLT) seems to be useful for BD depression. This meta-analysis is intended to further elucidate the role of BLT in depressive symptoms in patients with BD. Register of Systematic Reviews PROSPERO: CRD 42019133642. Randomized controlled trials and cohort studies were retrieved in PubMed, Cochrane Library, EMBase, Web of Science, CINHAL, CBM, CNKI, VIP, and Wanfang from their foundation to March 2020, and other sources as supplement was also retrieved. Data were extracted after strict evaluation of literature quality by two researchers, and Meta-analysis was conducted on literatures that met the inclusion criteria. Meta-analysis was performed using Revman 5.3 software. In total, 12 studies including 847 patients with BD depression were included in our meta-analysis. A meta-analysis found significant differences between BLT and placebo for the following outcomes: (1) depression severity before and after BLT [SMD = -0.43, 95% CI (-0.73, -0.13), P < 0.05] in RCT and [SMD = -2.12, 95% CI (-2.3, -1.94), P < 0.05] in cohort studies.; (2) the efficacy of duration/timing of light therapy for depressive symptoms in BD [I2 = 85%, SMD = -1.88, 95% CI (-2.04, -1.71), P < 0.05] and [I2 = 71%, SMD = -2.1, 95% CI (-2.24, -1.96), P < 0.05]; (3) the efficacy of different color/color temperatures for depressive symptoms in BD [I2 = 0%, SMD = -0.56, 95% CI (-0.92, -0.19), P < 0.05] and [I2 = 97%, SMD = -1.74, 95% CI (-1.99, -1.49), P < 0.05]. We performed a subgroup meta-analysis of studies that used different light intensities. The results showed that light intensity ≥5000 lux significantly reduced the severity of depression. And patients without psychotropic drugs revealed significantly decreased disease severity [I2 = 0%, SMD = -0.6, 95% CI (-1.06, -0.13), P < 0.05]. Limitations of the study include studies only assessed short-term effects, and insufficient duration may underestimate adverse reactions and efficacy. Our results highlight the significant efficiency of BLT in the treatment of bipolar depression. Prospective studies with more rigorous design and consistent follow-up.
Introduction

Bipolar Disorder (BD) is a complex, chronic, sporadic mood disorder [1,2]. It affects more than 1% of the world’s population, and studies have shown that the total lifetime prevalence rates of BD I and II are 0.6%, and 0.4% respectively [3–6]. Formerly known as manic depression, BD is a serious chronic mood disorder characterized by manic episodes, hypomania and alternating or intertwined depressive episodes. Among these manifestations, depressive episodes are the most common, accounting for more than 50% of patients with BD [7,8]. BD is complicated, and the rates of misdiagnosis and missed diagnosis are high. The most widely acknowledged diagnostic classifications are the 10th revision of the International Classification of Diseases (ICD-10) and the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [9–12]. Some studies have found that patients with BD make serious suicide attempts, and the annual mortality rate is higher than that of the general population [7,13–15]. Therefore the main purpose of treating depressive symptoms in BD is to quickly reduce disease severity and prevent suicide, which is considered the main challenge in long-term treatment [16–18]. Mood stabilizers and antipsychotics are the mainstays of acute treatment for mania and depression in BD [19], and lithium is considered to be one of the most effective treatments for preventing both types of symptoms [20]. However, given the high rate of recurrence of BD, these strategies can lead to complications such as nephrotoxicity or liver damage [21–23].

Bright light therapy (BLT), also called phototherapy, refers to the use of glare therapy to treat depressive symptoms [24], BLT was originally used to treat patients with seasonal affective disorder [25–29]. Numerous studies indicate direct and indirect effects of light on mood. One of the core symptoms of BD is difficulty sleeping [30–33], 20% of patients with BD also have sleep disorders, and circadian rhythm adjustment is a potential treatment. In circadian rhythm research, photoperiod was coded by the biological clock into the duration signal of nocturnal melatonin secretion, and melatonin secretion could be suppressed by bright light in humans. melatonin could be a mild soporific for many psychiatric sleep problems [34–36]. Wirz-Justice et al. [34] combines information about clock gene variants, correlations with symptoms, neurotransmission and brain imaging found that serotonin (5-HT) neurotransmission, noradrenaline (NA), dopamine (DA) are all affected by sleep deprivation (SD). Multiple neurobiological effects can lead to clinical mood improvement. The conversion of neurotransmitters could provide a core biological underpinning for circadian preference in diurnal and for the antidepressant effects of chronotherapeutics. Garbazza et al. [37] reported multiple genetic mutations in clock mechanism linked to depression. Including gene polymorphisms of the core clock machinery or the seasonal change of daylight duration affects biological clock [34]. Cortical excitability normalizes the time course of its daily homeostatic variation. The circadian timing system and sleep homeostasis influence connectivity among brain areas, while functional connections between cerebral cortex areas is widely disrupted and is considered to be the main biological basis for emotional disorders and cognitive impairment [38]. Phototherapy is effective in treating depressive symptoms [39], and the sustained antidepressant effect of BLT has been confirmed in clinical studies [40,41]. In recent years, some systematic review and meta-analysis have investigated the effectiveness of BLT for patients with BD. Some meta-analyses have suggested that BLT is effective [42–45], while others have shown that BLT does not have a significant antidepressant effect [46]. Lam et al. [42] reported that a small-to-moderate and significant effect of active light treatment in reducing depressive symptoms. But the evidence is positive but not conclusive. There are some limitations included different light treatment parameters, short treatment durations, small sample sizes and variable quality across trials. The International Society of Bipolar Disorders (ISBD) Task Force on Chronobiology
and Chronotherapy [43] recommended BLT had the strongest evidence among current chronotherapeutic options. Limitations of this evidence included the small number of RCTs and small sample sizes in each. Many different LT parameters were used and many of these patients were also taking mood stabilizing and other medications. Geoffroy et al. [44] shows a clear superiority of the combination of LT and AD. The main limitation is the small number of randomized trials which reduces statistical power and does neither allow further assessments of moderators nor to analyze all subgroups of patients. Tseng et al. [45] reported that treatment with BLT had statistically significant antidepressant effects. This study had some limitations included in the meta-analysis lacked a well-designed control group, the small number of RCTs and small sample sizes. However, another meta-analysis reported the opposite conclusion. Takeshima et al. [46] suggested BLT does not significantly improve depressive symptoms in BD. Importantly, no meta-analysis so far has examined the efficacy of duration / timing of light therapy and different color temperatures for depressive symptoms in BD.

In this systematic review and meta-analysis, we evaluated the efficacy of BLT for depressive symptoms in BD, and we determined the efficacy of duration / timing of light therapy and different color temperatures for depressive symptoms in BD, and we also evaluated subgroup analysis of auxiliary measures, effects of different light intensity / colors, and drugs on depressive symptoms. In addition, in order to expand the number of articles, we also searched 4 Chinese databases.

Materials and methods

This meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist and the Cochrane Handbook for Systematic Reviews (v5.1.0).

Inclusion and exclusion criteria

The inclusion criteria were: (1) randomized controlled trial (RCT) or cohort study on the effects of BLT on depressive symptoms in patients with BD; (2) clearly defined diagnosis of BD. The exclusion criteria were: (1) data were incomplete or could not be extracted,(2) study subjects included pregnant women.

Data sources and search strategies

A systematic literature search was performed within English (PubMed, Web of Science, Embase, Cochrane Library and CINHAL) and major Chinese(China National Knowledge Infrastructure, Wanfang, SinoMed and VIP) databases, from their inception dates to March,2020. The search was performed using the search terms “(bright light therapy OR light therapy OR light-therapy OR phototherapy OR light treatment OR Analytical, Diagnostic and Therapeutic Techniques and Equipment Category OR Therapeutics OR Color Therapy OR Heliotherapy OR Intense Pulsed Light Therapy OR Low-Level Light Therapy) AND (Psychiatry and Psychology Category OR Mental Disorders OR Bipolar and Related Disorders OR Bipolar Disorder OR Bipolar affective disorder)”. We used a combination of subject terms and free word retrieval and assessed related references. The search strategy are provided in S1 File. Two individuals simultaneously conducted independent searches according to the established inclusion and exclusion criteria, and EndNote X8 software was used for document management. In case of disagreement, a third person participated in the discussion until consensus was reached.
Study selection

Using a standardized electronic form, two researchers independently completed the data extraction and checked. When a difference occurred, a third person participated in the discussion until consensus was reached. The extracted data include author names, publication year, sample size, intervention measures, country, research design, whether to use allocation concealment, blinding status, and outcome. The primary outcome was depression severity, as assessed by the Hamilton Depression Rating Scale (HDRS), Inventory of Depressive Symptomatology, Clinician Rating (IDS-C), or the Structured Interview Guide for the HDRS.

Quality assessment

Two investigators independently evaluated the literature, Cohort studies and case-control studies were scored using the Newcastle Ottawa Scale (NOS) [47], and RCTs were evaluated using the Cochrane Handbook (5.1.0) bias risk assessment tool [48].

Statistical analysis

Meta analysis was performed with RevMan 5.3 software. A meta-analysis aggregates indexes of effectiveness of individual trials into one pooled estimate. When the result is a continuous variable, then the effect size is usually expressed as mean difference (MD) or normalized mean difference (SMD). The outcome measure was analyzed using standardized mean differences (SMD). The MD is the difference in the means of the treatment group and the control group, while the SMD is the MD divided by the standard deviation (SD) [49]. Meta-analysis of trials that have used different continuous or rating scales to record outcomes of a similar nature requires sophisticated data handling and data transformation to a uniform scale, the standardized mean difference (SMD) [50]. The measurement data adopt the standardized mean difference (SMD) as the effect index, and each effect quantity gives its point estimate and 95% confidence interval (CI). Heterogeneity among included studies was analyzed using χ² tests (a = 0.1), and the magnitude was quantified in conjunction with I². If there was no statistical heterogeneity between study results, a fixed effect model was used for meta-analysis; if there a random effect model was employed. Studies with obvious clinical heterogeneity were included in subgroup or sensitivity analysis, or only descriptive analysis [51]. In the first step, we conducted a separate meta-analysis of RCTs and cohort studies. To explore possible confounding effects of clinical variables, we also performed subgroup meta-analysis of studies based on different treatment parameters, including other auxiliary measures, light intensity and concomitant medication.

Results

Literature search results

A total of 3618 related publications were initially retrieved. According to the inclusion and exclusion criteria, 12 were selected after screening [52–63]. The study flow diagram is shown in Fig 1.

Study and patient characteristics

The include studies are described in Table 1. A total of 12 articles including 5 RCTs and 7 cohort studies were include with samples of 7220 patients for a total of 847 cases. The research publication period was from 1995 to 2018, and 7 articles were published after 2010. The DSM-IV criteria were used for BD diagnosis in all studies. With regard to literature quality, 4 RCTs were grades B and 1 was C. Among cohort studies, 1 study scored 8 points on the NOS, 4 had 7 points, 1 had 6 points, and 1 had 5 points.
Main meta-analysis results

The primary outcome measures included the following: (1) depression severity before and after BLT; (2) the efficacy of duration / timing of light therapy for depressive symptoms in BD; (3) the efficacy of different color/color temperatures for depressive symptoms in BD.

Flowchart of the study selection process

[Flowchart showing the study selection process]

Fig 1. Study flow diagram.

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Table 1. Characteristics and quality assessment result of the included studies.

| Study         | Country | Numbers | Diagnostic criteria | Subjects | Mean age (year) | Intervention duration (h) | Color Temperature (k) | Timing | Light intensity (lux) | Light color | Drug free | Study type | Quality |
|---------------|---------|---------|---------------------|----------|-----------------|--------------------------|---------------------|--------|----------------------|-------------|-----------|------------|---------|
| Zhou2018 China | 37/37   | DSM-IV  | BD, depress         | 35.1 ±14.2 | 14              | 4000                      | morning             | 5000   | White                | Yes         | RCT       | B          | 4       |
| Sit D2018 USA  | 23/23   | DSM-IV  | BD, depress         | 45.7 ±14.3 | 31.5            | 10000                    | midday              | 7000   | White                | No          | RCT       | B          | 5       |
| D.Sikkens2018 Holland | 10/10 | DSM-IV  | BD, depress         | 47.6 ±16.9 | 5               | N/A                      | morning + night     | 10000  | White                | No          | Cohort study | 5          | 4       |
| Suzuki2018 Italy | 220/220 | DSM-IV  | BD-I, depress       | 46.8 ±11.2 | 5               | 4600                      | morning + night     | 10000  | White                | No          | Cohort study | 7          | 5       |
| Suzuki2016 Italy | 147/147 | DSM-IV  | BD-I, depress       | 47.4 ±10.8 | 8.5             | 4600                      | morning + night     | 10000  | White                | No          | Cohort study | 7          | 5       |
| Benedetti2014 Italy | 143/143 | DSM-IV  | BD-I, depress       | 47.2 ±11.6 | 8.5             | 4000                      | morning + night     | 10000  | White                | Yes         | Cohort study | 8          | 5       |
| Dauphinas2012 USA | 18/20   | DSM-IV  | BD, depress         | 42.4 ±12.4 | 36.3            | N/A                      | morning             | 7000   | N/A                  | No          | RCT       | B          | 4       |
| Wu2009 USA | 32/17   | DSM-IV  | BD, depress         | 39.4 ±13.6 | 6               | N/A                      | morning             | 5000   | N/A                  | Yes         | RCT       | C          | 5       |
| Benedetti 2009 Italy | 44/44   | DSM-IV  | BD-I, depress       | 46.6 ±9.5  | 3               | N/A                      | morning + night     | 400    | Green                | Yes         | Cohort study | 7          | 5       |
| Benedetti 2007 Italy | 39/39  | DSM-IV  | BD-I, depress       | 45.5 ±13.2 | 3               | N/A                      | morning + night     | 400    | Green                | Yes         | Cohort study | 7          | 5       |
| Benedetti 2003 Italy | 18/12   | DSM-IV  | BD, depress         | 54.3 ±11.3 | 7               | N/A                      | morning             | 400    | Green                | No          | RCT       | B          | 5       |
| Papatheodorou 1995 Canada | 7/7     | DSM-IV  | BD, depress         | 19.4 ±2.0  | 10.5            | N/A                      | morning + night     | 10000  | White                | No          | Cohort study | 6          | 5       |

Abbreviation: BD-I: Bipolar I disorder; BD: Bipolar disorder; N/A: not available; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; Data presentation: mean ±SD

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We first analyzed studies comparing depressive severity before and after BLT. A total of 12 articles [44–55] were included. Because of the different research designs, the cohort studies and RCTs were analyzed separately. There was less heterogeneity between RCTs [44,45,50,51,54] \((I^2 = 20\%, P = 0.29)\), so a random effects model was employed. The results showed that BLT significantly reduce depression severity \([SMD = -0.43, 95\% CI (-0.73, -0.13), P < 0.05]\). A total of 7 cohort studies were included \([46–49,52,53,55]\), and a sensitivity analysis was conducted because of the high heterogeneity. This decreased after omitting Sikkens et al. \((I^2 = 26\%, P = 0.24)\). The findings revealed that BLT significantly decrease the severity of depression \([SMD = -2.12, 95\% CI (-2.3, -1.94), P < 0.05]\) (Fig 2). Disease severity was significantly lower in the patients with BD-D episodes after light therapy, either in the form of monotherapy or in combination with other treatment (sleep deprivation or lithium therapy).

Fig 3 shows the efficacy of duration of light therapy for depressive symptoms in BD. There were 4 studies with phototherapy greater than 10 hours, including 3 RCTs [50,51,56] and 1 cohort study [61] \((I^2 = 45\%, SMD = -0.41, 95\% CI (-0.72, -0.11), P < 0.05)\); less than 10h included 2 RCTs [57,60] and 6 cohort studies [52–55,58,59] \((I^2 = 85\%, SMD = -1.88, 95\% CI (-2.04, -1.71), P < 0.05)\) (Fig 4). Light conditions were superior to light control conditions in clinician-rated depressive symptoms. Fig 5 shows the efficacy of timing of light therapy for depressive symptoms in BD. We analyzed the effects of different phototherapy timings on depression. 4 articles [50,52,56,57] used morning light therapy \((I^2 = 42\%, SMD = -0.41, 95\% CI (-0.71, -0.11), P < 0.05)\) and 7 articles [53–55,58–61] used morning plus evening light therapy.
I = 71%, SMD = -2.1, 95% CI (-2.24, -1.96), P < 0.05 (Fig 6), the analysis showed significant difference between conditions.

Different light color were used in the included study, and the effect of different light color on the treatment of patients is inconclusive. Therefore, we performed a meta-analysis of studies that used different light color. 7 articles were included: 2 RCTs [50,51] and 5 cohort studies [53–56,61], that were discussed separately according to the study design. We found that white
light therapy resulted in significantly decreased disease severity in BD patients, including RCT \([I^2 = 0\%, SMD = -0.56, 95\% CI (-0.92, -0.19), P < 0.05]\) (Fig 7), cohort studies \([I^2 = 29\%, SMD = -2.17, 95\% CI (-2.37, -1.98), P < 0.05]\). Because of the high heterogeneity, we conducted a sensitivity analysis. Three studies used green light. We found that in one RCT study [60], \(P\) was greater than 0.05, which was not statistically significant \([SMD = -0.7, 95\% CI (-1.45, 0.06), P > 0.05]\), while the other two cohort studies [58, 59] showed green light therapy resulted in significantly decreased disease severity in BD patients \([I^2 = 0\%, SMD = -1.92, 95\% CI (-2.29, -1.56)]\) (Fig 4).
Data for color temperatures were available for five trials. There were three studies with color temperatures greater than 4500K, and two studies with less than 4500K. The studies of color temperatures greater than 4500K showed light superior to control conditions for improvement in depressive symptoms \[ I^2 = 93\%, \ SMD = -2.06, \ 95\% \ CI(-2.23, -1.88), \ P<0.05 \] (Fig 9). Similarly, the studies of color temperatures less than 4500K showed differences between light and control conditions in improvement in depressive symptoms \[ I^2 = 97\%, \ SMD = -1.74, \ 95\% \ CI(-1.99, -1.49), P<0.05 \] (Fig 10).

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**Fig 6. Forest plots for morning plus night phototherapy.**

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**Fig 7. Forest plots for white light therapy.**

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Subgroup meta-analysis results of studies with or without auxiliary measures

To exclude a possible confounding effect of auxiliary measures, we performed a subgroup meta-analysis. Auxiliary measures mean that in some studies, researchers used sleep deprivation or lithium therapy to treat BD. A total of 7 articles used auxiliary measures: 6 cohort studies [46–49,52–53] and 1 RCT [51]. Since the number of RCTs was too small, we only assessed the 6 cohort studies. A sensitivity analysis showed significantly decreased depression severity in BD patients after BLT with auxiliary measures \( I^2 = 0\%, \text{ SMD} = -2.16, 95\% \text{ CI} (-2.31,-2.12, P<0.05) \) (Fig 11). Five articles did not use auxiliary measures, 4 RCTs and 1 cohort study. Analysis of the RCTs revealed significantly decreased depression severity in BD patients after BLT with auxiliary measures \( I^2 = 39\%, \text{ SMD} = -0.42, 95\% \text{ CI} (-0.71,-0.12, P<0.05) \) (Fig 12).

![Forest plots for green light therapy.](https://doi.org/10.1371/journal.pone.0232798.g008)

![Forest plots with a color temperature greater than 4500k.](https://doi.org/10.1371/journal.pone.0232798.g009)
Subgroup meta-analysis result of studies with different light intensities

We performed a subgroup meta-analysis of studies that used different light intensities. Nine articles were included: 4 RCTs [44–45, 50–51] and 5 cohort studies [46–49, 55], that were discussed separately according to the study design. The meta-analysis of the RCTs showed that:

- Light intensity \( \geq 5000 \) lux significantly reduced the severity of depression \( I^2 = 33\% \), SMD = -0.38, 95% CI (-0.73, -0.04), \( P < 0.05 \).

Because of the high heterogeneity among the cohort studies \( I^2 = 67\% \), \( P = 0.02 \), we conducted a sensitivity analysis. Heterogeneity decreased after omitting Sikkens et al. \( I^2 = 29\% \), \( P = 0.24 \), and the subgroup meta-analysis of cohort studies revealed that light intensity \( \geq 5000 \) lux significantly reduced depression severity \( I^2 = 29\% \), SMD = -2.17, 95% CI (-2.37, -1.98), \( P < 0.05 \) (Fig 13). There were 3 studies with light intensities \( \geq 5000 \) lux, 2 cohort studies [52,53], and 1 RCT [54]. Only the cohort study results were assessed. We found that even low light intensities could reduce the severity of depression \( I^2 = 0\% \), SMD = -1.92, 95% CI (-2.29, -1.55), \( P < 0.05 \) (Fig 14).
To rule out possible confounding effects of drug treatment, we performed a subgroup meta-
analysis focusing on BLT in the absence of any psychotropic drug prescriptions. Seven articles
[45–48, 50, 54–55] were included. Because of the different research designs, the cohort studies
[46–48, 55] and RCTs [45, 50, 54] were analyzed separately. Sensitivity analysis, revealed signifi-
cantly decreased disease severity in BD patients after BLT without psychotropic drugs in RCTs
[$I^2 = 0\%, SMD = -0.6, 95\% CI (-1.06, -0.13), P<0.05$] (Fig 15) and cohort studies [$I^2 = 75\%,$
$SMD = -1.99, 95\% CI (-2.43, -1.55), P<0.05$] (Fig 15). Given the small number of studies and
high heterogeneity, this finding requires confirmation.

### Subgroup meta-analysis results of studies without psychotropic drugs

To rule out possible confounding effects of drug treatment, we performed a subgroup meta-
analysis focusing on BLT in the absence of any psychotropic drug prescriptions. Seven articles
[45–48, 50, 54–55] were included. Because of the different research designs, the cohort studies
[46–48, 55] and RCTs [45, 50, 54] were analyzed separately. Sensitivity analysis, revealed signifi-
cantly decreased disease severity in BD patients after BLT without psychotropic drugs in RCTs
[$I^2 = 0\%, SMD = -0.6, 95\% CI (-1.06, -0.13), P<0.05$] (Fig 15) and cohort studies [$I^2 = 75\%,$
$SMD = -1.99, 95\% CI (-2.43, -1.55), P<0.05$] (Fig 15). Given the small number of studies and
high heterogeneity, this finding requires confirmation.

#### Table 1. Subgroup meta-analysis results of studies without psychotropic drugs

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference | IV, Fixed, 95% CI |
|------------------|------------------|----|-------|-------------|----|-------|--------|---------------------|------------------|
| 1.3.1 RCT        |                  |    |       |             |    |       |        |                     |                  |
| Benedetti 2003   | 7.39             | 7.72| 18    | 13.08       | 8.3| 12    | 15.0%  | -0.70 [-1.45, 0.06] |                  |
| Daephinais2012   | 18.1             | 9.6 | 18    | 15.8        | 10.8| 20    | 20.9%  | 0.22 [-0.42, 0.86]  |                  |
| Sit D2018        | 6.82             | 6.04| 23    | 10.17       | 6.29| 23    | 24.6%  | -0.53 [-1.12, 0.06] |                  |
| Zhou2018         | 8.61             | 3.41| 37    | 10.53       | 3.22| 37    | 39.4%  | -0.57 [-1.04, -0.11] |                  |
| Subtotal (95% CI)| 96               |    |       | 92          |    | 100.0%|       | -0.42 [-0.71, -0.12] |                  |

Heterogeneity: $Chi^2 = 4.92, df = 3 (P = 0.18); I^2 = 39%$
Test for overall effect: $Z = 2.79 (P = 0.005)$

#### Table 2. Subgroup meta-analysis results of studies without psychotropic drugs

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference | IV, Random, 95% CI |
|------------------|------------------|----|-------|-------------|----|-------|--------|---------------------|------------------|
| 1.4.1 RCT        |                  |    |       |             |    |       |        |                     |                  |
| Daephinais2012   | 18.1             | 9.6 | 18    | 15.8        | 10.8| 20    | 21.1%  | 0.22 [-0.42, 0.86]  |                  |
| Wu2009           | 10.1             | 9.6 | 32    | 15.2        | 10.2| 23    | 23.7%  | -0.53 [-1.12, 0.06] |                  |
| Zhou2018         | 8.61             | 3.41| 37    | 10.53       | 3.22| 37    | 31.9%  | -0.57 [-1.04, -0.11] |                  |
| Subtotal (95% CI)| 110              |    |       | 97          |    | 100.0%|       | -0.38 [-0.73, -0.04] |                  |

Heterogeneity: $Tau^2 = 0.04; Chi^2 = 4.48, df = 3 (P = 0.21); I^2 = 33%$
Test for overall effect: $Z = 2.16 (P = 0.03)$

#### Table 3. Subgroup meta-analysis results of studies without psychotropic drugs

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference | IV, Random, 95% CI |
|------------------|------------------|----|-------|-------------|----|-------|--------|---------------------|------------------|
| 1.4.2 Cohort studies |                |    |       |             |    |       |        |                     |                  |
| Benedetti 2014   | 7.8             | 6.5 | 143   | 20.1       | 4.4 | 143   | 29.2%  | -2.21 [-2.51, -1.92] |                  |
| D.Sikkens2018    | 28.8            | 10  | 10    | 42.6       | 11.7| 10    | Not estimable |                  |                  |
| Papatheodorou 1995 | 11.1          | 8.9 | 7     | 21.3       | 10  | 7     | 2.9%   | -1.01 [-2.15, 0.13] |                  |
| Suzuki2016       | 8.3             | 6.8 | 147   | 20.6       | 4.1 | 147   | 29.9%  | -2.19 [-2.47, -1.90] |                  |
| Suzuki2018       | 8.3             | 6.7 | 220   | 20.4       | 3.8 | 220   | 38.0%  | -2.22 [-2.46, -1.98] |                  |
| Subtotal (95% CI)| 517             |    |       | 517        |    | 100.0%|       | -2.17 [-2.37, -1.98] |                  |

Heterogeneity: $Tau^2 = 0.01; Chi^2 = 4.22, df = 3 (P = 0.24); I^2 = 29%$
Test for overall effect: $Z = 21.79 (P < 0.00001)$

Fig 12. Forest plots without auxiliary measures.

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Fig 13. Forest plots with light intensities greater than 5000 lux.

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Discussion

According to the published 2010 Global Burden of Disease Study, BD is the 18th most disabling health condition in the world and the treatment of depression in this population is a major challenge, with few effective approaches [64–67]. We also found that the efficacy of antidepressants for BD requires more evidence [68–70]. Besides pharmacologic treatment, studies have assessed the use of cognitive-behavioral therapy, social rhythm therapy, and family-centered treatment [32,64,71,72]. BLT is recognized as an alternative to psychotherapy and psychopharmacology for treating adults with depression [73], and there is ample evidence that morning BLT is effective and safe for depression in BD [74–77]. A study of phototherapy for bipolar disorder also showed that phototherapy has a treatment for bipolar disorder [45]. However, due to the different types of research design and the quality of the literature, Tseng’s has different quality and limitations. Therefore, our study will discuss the randomized control group and the cohort study group separately, taking into account the confounding factors such as color, intensity and drug impact.

To our knowledge, this is the first systematic review and meta-analysis that has evaluated the effectiveness of BLT in different colors, color temperatures, and duration / time for depressive symptoms in BD. The main results were that depressive severity decreased after BLT, and that treatment effect were observed, with different light color / color temperatures, with different duration / time, with or without auxiliary measures, with different light intensities, and

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Table 1: Forest plots with light intensities less than 5000lux.

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Fig 14. Forest plots with light intensities less than 5000lux.

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Table 2: Forest plots with without psychotropic drugs.

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Fig 15. Forest plots with without psychotropic drugs.

https://doi.org/10.1371/journal.pone.0232798.g015
without psychotropic drugs. The first result confirms that both RCTs and cohort studies showed that BLT can reduce depressive severity, indicating that it is feasible and effective in patients with BD. The mechanism by which BLT ameliorates depressive symptoms is likely accomplished by adjusting sleep-wake rhythms, inhibiting melatonin secretion, and increasing serotonin and norepinephrine levels [78,79].

Subgroup analyses were performed to eliminate the effects of auxiliary measures, light intensity, and psychotropic drug. In a subgroup analysis of adjuvant therapy, we found that phototherapy was effective in improving the degree of depression with or without adjuvant therapy. In the subgroup analysis of light intensity, the result was statistically significant, but only 2 studies used a light intensity ≤ 5000 lux, so confirmatory results are required. In a subgroup analysis for drug interventions, significant effects for BLT were found regardless of pharmacologic treatment. In addition, our subgroup analysis revealed that the study by Sikkens et al. (2018) introduced significant, heterogeneity that almost disappeared after its omission. This may be the study did not report the basic subject characteristics in detail, and the document quality score was only 5 points. In addition, the IDS-C scale was used as the outcome, which is different from the other studies and may have introduced bias. In this meta-analysis, only 2 studies [44,45] applied BLT as the sole intervention, underscoring the need for more large-sample RCTs.

Limitation
This major limitation of this meta-analysis is that the included studies only assessed short-term effects, and insufficient duration may underestimate adverse reactions and efficacy. Rigorously designed RCTs are needed to clarify the benefits and adverse effects of BLT for depression in BD.

Conclusion
In summary, Our results highlight the significant efficiency of BLT in the treatment of bipolar depression, and we determined the efficacy of duration / timing of light therapy and different color temperatures for depressive symptoms in BD, and we also evaluated subgroup analysis of auxiliary measures, effects of different light intensity / colors. However, the existing evidence is not sufficient, and there are no uniform standards for light box use or light intensity standards. Prospective studies with more rigorous design and consistent follow-up periods are needed to confirm the effects of BLT on depressive symptoms in patients with BD.

Supporting information
S1 File. PubMed search strategy.
(DOCX)

S2 File. PRISMA 2009 checklist.
(DOC)

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References
1. Chandrasekaran V, Brennan-Olsen SL, Stuart AL, Pasco JA, Berk M, Hodge JM, et al. Bipolar disorder and bone health: A systematic review. Journal of Affective Disorders. 2019; 249:262–9. https://doi.org/10.1016/j.jad.2019.02.013 PMID: 30784723
2. Phillips ML, Kuperf DJ. Bipolar disorder diagnosis: challenges and future directions. Lancet (London, England). 2013; 381(9878):1663–71. https://doi.org/10.1016/s0140-6736(13)60989-7 PMID: 23663952
3. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet (London, England). 2016; 387(10027):1561–72. https://doi.org/10.1016/s0140-6736(15)00241-x
4. Sherazi R, McKeon P, McDonough M, Daly I, Kennedy N. What's new? The clinical epidemiology of bipolar disorder. Harvard review of psychiatry. 2006; 14(6):273–84. https://doi.org/10.1080/1067320601070047 PMID: 17162652
5. Bauer M, Pfennig A. Epidemiology of bipolar disorders. Epilepsia. 2005; 46 Suppl 4:8–13.
6. Walaich P, Goldner EM, Somers JM, Hsu L. Prevalence and incidence studies of mood disorders: a systematic review of the literature. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2004; 49(2):124–38. https://doi.org/10.1177/070674370404900208 PMID: 15065747
7. Wang XH, Zhao N, Shi JJ, Wu YH, Liu J, Xiao Q, et al. Discussion on Patients with Bipolar Disorder and Depressive Episode by Ratio Low Frequency Amplitude Combined with Grey Matter Volume Analysis. Journal of Medical Systems. 2019; 43(5). https://doi.org/10.1007/s10916-019-1212-x PMID: 30905048
8. Okasha T, Fikry M, Kowailed A, El-Guwiely T, Sadek H. Screening for bipolar disorder among patients undergoing a major depressive episode: Report from the BRIDGE study in Egypt. Journal of Affective Disorders. 2013; 147(1–3):217–24. https://doi.org/10.1016/j.jad.2012.11.007 PMID: 23196197
9. Kessler RC, Abelson J, Demler O, Escobar JI, Gibbon M, Guyer ME, et al. Clinical calibration of DSM-IV diagnoses in the World Mental Health (WMH) version of the World Health Organization (WHO) Composite International Diagnostic Interview (WMH/CIDI). International journal of methods in psychiatric research. 2004; 13(2):122–39. https://doi.org/10.1002/mpr.169 PMID: 15297907
10. Price AL, Marzani-Nissen GR. Bipolar disorders: a review. American family physician. 2012; 85(5):483–93. PMID: 22534227
11. Vieta E, Phillips ML. Deconstructing bipolar disorder: a critical review of its diagnostic validity and a proposal for DSM-V and ICD-11. Schizophrenia bulletin. 2007; 33(4):886–92. https://doi.org/10.1093/schbul/sbm057 PMID: 17562693
12. Vieta E, Valenti M. Mixed states in DSM-5: Implications for clinical care, education, and research. Journal of Affective Disorders. 2013; 148(1):28–36. https://doi.org/10.1016/j.jad.2013.03.007 PMID: 23561484
13. Vieta E, Suppes T. Bipolar II disorder: arguments for and against a distinct diagnostic entity. Bipolar disorders. 2008; 10(1 Pt 2):163–78. https://doi.org/10.1111/j.1399-5618.2007.00561.x PMID: 18199235
14. Wulsin LR, Vaillant GE, Wells VE. A systematic review of the mortality of depression. Psychosomatic Medicine. 1999; 61(1):6–17. https://doi.org/10.1097/00006842-199901000-00003 PMID: 10024062
15. Leverich GS, Altshuler LL, Frye MA, Suppes T, Keck PE, McElroy SL, et al. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. Journal of Clinical Psychiatry. 2003; 64(5):506–15. https://doi.org/10.4088/jcp.v64n0503 PMID: 12759632
16. Calabrese J. One-year outcome with antidepressant treatment of bipolar depression—is the glass half empty or half full? Acta psychiatraca Scandinavica. 2005; 112(2):85–7. https://doi.org/10.1111/j.1600-0447.2005.00534.x PMID: 15992388
17. Jick H. Antidepressants and the risk of suicidal behaviors—Reply. Jama-Journal of the American Medical Association. 2004; 292(23):2833–. https://doi.org/10.1001/jama.292.23.2833-c
18. Machado-Vieira R, Salvador G, Luckenbaugh DA, Manji HK, Zarate CA. Rapid onset of antidepressant action: A new paradigm in the research and treatment of major depressive disorder. Journal of Clinical Psychiatry. 2008; 69(6):946–58. https://doi.org/10.4088/jcp.v69n0610 PMID: 18435963
19. Grande I, Vieta E. Pharmacotherapy of Acute Mania: Monotherapy or Combination Therapy with Mood Stabilizers and Antipsychotics? Cns Drugs. 2015; 29(3):221–7. https://doi.org/10.1007/s40263-015-0235-1 PMID: 25711483

20. Miura T, Noma H, Furukawa TA, Mitsuaysu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014; 1(5):351–9. https://doi.org/10.1016/S2215-0366(14)70314-1 PMID: 26360999

21. Kendall T, Morriss R, Mayo-Wilson E, Marcus E, Guideline Dev G. Assessment and management of bipolar disorder: summary of updated NICE guidance. Brit-J-British Medical Journal. 2014; 349. https://doi.org/10.1136/bmj.g5673 PMID: 25258392

22. Castellani A, Girlanda F, Barbui C. Rigour of development of clinical practice guidelines for the pharmacological treatment of bipolar disorder: Systematic review. Journal of Affective Disorders. 2015; 174:45–50. https://doi.org/10.1016/j.jad.2014.11.032 PMID: 25484176

23. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moeller H-J, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar disorder. World Journal of Biological Psychiatry. 2010; 11(2):81–109. https://doi.org/10.3109/15622970903555881 PMID: 20148751

24. Maruani J, Geoffroy PA. Bright Light as a Personalized Precision Treatment of Mood Disorders. Frontiers in psychiatry. 2019; 10:85. https://doi.org/10.3389/fpsyt.2019.00085 PMID: 30881318

25. Desan PH, Weinstein AJ, Michalak EE, Tam EM, Meesters Y, Ruiter MJ, et al. A controlled trial of the Livebook light-emitting diode (LED) light device for treatment of Seasonal Affective Disorder (SAD). Bmc Psychiatry. 2007; 7. https://doi.org/10.1186/1471-244x-7-38 PMID: 17683643

26. Evans M, Rohan KJ, Sitnikov L, Mahon JN, Nillni YI, Tierney Lindsey K, et al. Cognitive Change Across Outcome in Seasonal Affective Disorder. Journal of Affective Disorders. 2014; 166:343–6. https://doi.org/10.1016/j.jad.2014.05.034 PMID: 25012451

27. Knappen SE, Van De Werken M, Gordijn MCM, Meesters Y. The duration of light treatment and therapy outcome in seasonal affective disorder. Journal of Affective Disorders. 2014; 166:343–6. https://doi.org/10.1016/j.jad.2014.05.034 PMID: 25012451

28. Levitan RD. What is the optimal implementation of bright light therapy for seasonal affective disorder (SAD)? Journal of Psychiatry & Neuroscienc. 2005; 30(1):72–2.

29. Thompson C. Light therapy in the treatment of seasonal and non-seasonal affective disorders: A meta-analysis of randomised controlled trials. Journal of Affective Disorders. 2002; 68(1):89–.

30. Colom F, Vieta E, Sanchez-Moreno J, Palomino-Otiniano R, Reinares M, Goikolea JM, et al. Group psychoeducation for stabilised bipolar disorders: 5-year outcome of a randomised controlled trial. The British journal of psychiatry: the journal of mental science. 2009; 194(3):260–5. https://doi.org/10.1192/bjp.bp.107.040485 PMID: 19252157

31. Krane-Gartiser K, Steinain MK, Langsrud K, Vestvik V, Sand T, Falmer OB, et al. Mood and motor activity in euthymic bipolar disorder with sleep disturbance. J Affect Disord. 2016; 202:23–31. https://doi.org/10.1016/j.jad.2016.05.012 PMID: 27253213

32. Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagioli ni AM, et al. Two-year outcomes for interpersonnal and social rhythm therapy in individuals with bipolar I disorder. Archives of general psychiatry. 2005; 62(9):996–1004. https://doi.org/10.1001/archpsyc.62.9.996 PMID: 16143731

33. Kaplan KA, Harvey AG. Behavioral Treatment of Insomnia in Bipolar Disorder. American Journal of Psychiatry. 2013; 170(7):716–20. https://doi.org/10.1176/appi.ajp.2013.12050708 PMID: 23820830

34. Wirz-Justice A, Benedetti F. Perspectives in affective disorders: Clocks and sleep. The European journal of neuroscience. 2020; 51(1):346–65. https://doi.org/10.1111/ejn.14362 PMID: 30702783

35. Kreutzmann JC, Hovekes R, Avel T, Meerol P. Sleep deprivation and hippocampal vulnerability: changes in neuronal plasticity, neurogenesis and cognitive function. Neuroscience. 2015; 309:173–90. https://doi.org/10.1016/j.neuroscience.2015.04.053 PMID: 25937398

36. Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in humans. Science (New York, NY). 1980; 210(4475):1267–9. https://doi.org/10.1126/science.7434030 PMID: 7434030

37. Garbazza C, Benedetti F. Genetic Factors Affecting Seasonality, Mood, and the Circadian Clock. Frontiers in endocrinology. 2018; 9:481. https://doi.org/10.3389/fendo.2018.00481 PMID: 30190706

38. Vai B, Bolletini I, Benedetti F. Corticolimbic connectivity as a possible biomarker for bipolar disorder. Expert review of neurotherapeutics. 2014; 14(6):631–50. https://doi.org/10.1586/14737175.2014. 915744 PMID: 24852228
Bright light therapy for bipolar disorder: A systematic review and meta-analysis

39. Geoffroy PA, Schroder CM, Bourgin P. Light treatment in depression: An antique treatment with new insights. Sleep medicine reviews. 2018; 40:218–9. https://doi.org/10.1016/j.smrv.2018.03.002 PMID: 29678399

40. Benedetti F, Barbini B, Fulgosi MC, Colombo C, Dallapiccola S, Pontiggia A, et al. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. The Journal of clinical psychiatry. 2005; 66(12):1535–40. https://doi.org/10.4088/jcp.v66n1207 PMID: 16401154

41. Martiny K, Lunde M, Unden M, Dam H, Bach P. Adjunctive bright light in non-seasonal major depression: results from patient-reported symptom and well-being scales. Acta psychiatria Scandinavica. 2005; 111(6):453–9. https://doi.org/10.1111/j.1600-0447.2005.00532.x PMID: 15877712

42. Lam RW, Teng MY, Jung YE, Evans VC, Gottlieb JF, Chakrabarty T, et al. Light Therapy for Patients With Bipolar Depression: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2019; 706743719892471. https://doi.org/10.1177/0706743719892471 PMID: 31826657

43. Gottlieb JF, Benedetti F, Geoffroy PA, Henriksen TEG, Lam RW, Murray G, et al. The chronotherapeutic treatment of bipolar disorders: A systematic review and practice recommendations from the ISBD task force on chronotherapy and chronobiology. Bipolar disorders. 2019; 21(8):741–73. https://doi.org/10.1111/bdi.12847 PMID: 31609530

44. Geoffroy PA, Schroder CM, Reynaud E, Bourgin P. Efficacy of light therapy versus antidepressant drugs, and of the combination versus monotherapy, in major depressive episodes: A systematic review and meta-analysis. Sleep medicine reviews. 2019; 48:101213. https://doi.org/10.1016/j.smrv.2019.101213 PMID: 31600678

45. Tseng PT, Chen YW, Tu KY, Chung W, Wang HY, Wu CK, et al. Light therapy in the treatment of patients with bipolar depression: A meta-analytic study. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology. 2016; 26(6):1057–47. https://doi.org/10.1016/j.euroneuro.2016.03.001 PMID: 26993616

46. Takeshima M, Utsumi T, Aoki Y, Wang Z, Suzuki M, Okajima I, et al. Efficacy and safety of bright light therapy for manic and depressive symptoms in patients with bipolar disorder: A systematic review and meta-analysis. Psychiatry and clinical neurosciences. 2020. https://doi.org/10.1111/pcn.12976 PMID: 31917880

47. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European journal of epidemiology. 2010; 25(9):603–5. https://doi.org/10.1007/s10654-010-9491-z PMID: 20652370

48. Shuster JJ. Review: Cochrane handbook for systematic reviews for interventions, Version 5.1.0, published 3/2011. Julian P.T. Higgins and Sally Green, Editors. Research Synthesis Methods. 2011; 2 (2):126–30.

49. Takeshima N, Sozu T, Tajika A, Ogawa Y, Hayasaka Y, Furukawa TA. Which is more generalizable, powerful and interpretable in meta-analyses, mean difference or standardized mean difference? BMC medical research methodology. 2014; 14:30. https://doi.org/10.1186/1471-2288-14-30 PMID: 24559167

50. Getzsche PC, Hróbjartsson A, Maric K, Tendal B. Data extraction errors in meta-analyses that use standardized mean differences. Jama. 2007; 298(4):430–7. https://doi.org/10.1001/jama.298.4.430 PMID: 17652297

51. Deeks JJ, Higgins JP, Altman DG. Analysing Data and Undertaking Meta-Analyses2008.

52. Zhou TH, Dang WM, Ma YT, Hu CQ, Wang N, Zhang GY, et al. Clinical efficacy, onset time and safety of bright light therapy in acute bipolar depression as an adjunctive therapy: A randomized controlled trial. Journal of Affective Disorders. 2018; 227:90–6. https://doi.org/10.1016/j.jad.2017.09.038 PMID: 29053981

53. Sit DK, McGowan J, Willtrout C, Diller RS, Dills JJ, Luther J, et al. Adjuventive Bright Light Therapy for Bipolar Depression: A Randomized Double-Blind Placebo-Controlled Trial. The American journal of psychiatry. 2018; 175(2):131–9. https://doi.org/10.1176/appi.ajp.2017.16101200 PMID: 28969438

54. Sikkens D, Lek FRFR-vd, Meesters Y, Schoevers RA, Haarman BCM. Combined sleep deprivation and light therapy: clinical treatment outcomes in patients with complex unipolar and bipolar depression. Journal of Affective Disorders. 2018.

55. Suzuki M, Dallapiccola S, Locatelli C, Uchiyama M, Colombo C, Benedetti F. Does early response predict subsequent remission in bipolar depression treated with repeated sleep deprivation combined with light therapy and lithium? Journal of Affective Disorders. 2018; 229:371–6. https://doi.org/10.1016/j.jad.2017.12.066 PMID: 29331696

56. Suzuki M, Dallapiccola S, Locatelli C, Uchiyama M, Colombo C, Benedetti F. Discrepancy between subjective and objective severity as a predictor of response to chronotherapeutics in bipolar depression.
57. Benedetti F, Riccaboni R, Locatelli C, Poletti S, Dallaspezia S, Colombo C. Rapid Treatment Response of Suicidal Symptoms to Lithium, Sleep Deprivation, and Light Therapy (Chronotherapeutics) in Drug-Resistant Bipolar Depression. Journal of Clinical Psychiatry. 2014; 75(2):133–40. https://doi.org/10.1097/JCP.0000000000000455 PMID: 24345382

58. Dauphinais DR, Rosenthal JR, Terman M, DiFebo HM, Tuggle C, Rosenthal NE. Controlled trial of safety and efficacy of bright light therapy vs. negative air ions in patients with bipolar depression. Psychiatry Research. 2012; 196(1):57–61. https://doi.org/10.1016/j.psychres.2012.01.015 PMID: 22424890

59. Wu JC, Kelsoe JR, Schachat CS, Bunney BG, Demodena A, Golshan S, et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. Sleep and Biological Rhythms. 2011; 9(4):205–11. https://doi.org/10.1111/j.1479-8425.2011.00521.x

60. Benedetti F, Calabrese G, Bernasconi A, Cadioli M, Colombo C, Dallaspezia S, et al. Spectroscopic correlates of antidepressant response to sleep deprivation and light therapy: A 3.0 Tesla study of bipolar depression. Psychiatry Research: Neuroimaging. 2009; 173(3):238–42. https://doi.org/10.1016/j.psychresns.2008.08.004 PMID: 19682864

61. Benedetti F, Dallaspezia S, Fulgosi MC, Barbini B, Colombo C, Smeraldi E. Phase advance is a acti-metric correlate of antidepressant response to sleep deprivation and light therapy in bipolar depression. Chronobiology International. 2007; 24(5):921–37. https://doi.org/10.1080/07420520701649455 PMID: 17994346

62. Benedetti F, Calabrese G, Bernasconi A, Cadioli M, Colombo C, Dallaspezia S, et al. Spectroscopic correlates of antidepressant response to sleep deprivation and light therapy: A 3.0 Tesla study of bipolar depression. Psychiatry Research: Neuroimaging. 2009; 173(3):238–42. https://doi.org/10.1016/j.psychresns.2008.08.004 PMID: 19682864

63. Benedetti F, Dallaspezia S, Fulgosi MC, Barbini B, Colombo C, Smeraldi E. Phase advance is a acti-metric correlate of antidepressant response to sleep deprivation and light therapy in bipolar depression. Chronobiology International. 2007; 24(5):921–37. https://doi.org/10.1080/07420520701649455 PMID: 17994346

64. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. The Lancet. 2013; 381(9878):1672–82. https://doi.org/10.1016/S0140-6736(13)60857-0

65. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England). 2012; 380(9859):2163–96. https://doi.org/10.1016/S0140-6736(12)60161-2

66. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Aila M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disorders. 2013; 15(1):1–44. https://doi.org/10.1111/bdi.12025 PMID: 23237061

67. Frye MA, Ha K, Kanba S, Kato T, McElroy SL, Ozerdem A, et al. International consensus group on depression prevention in bipolar disorder. The Journal of clinical psychiatry. 2011; 72(10):1295–310. https://doi.org/10.1088/JCP.10123co1c PMID: 22075097

68. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. Lancet (London, England). 2013; 381(9878):1672–82. https://doi.org/10.1016/S0140-6736(13)60857-0 PMID: 23663953

69. Sidor MM, MacQueen GM. An update on antidepressant use in bipolar depression. Current Psychiatry reports. 2012; 14(6):696–704. https://doi.org/10.1007/s11920-012-0323-6 PMID: 23065437

70. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet (London, England). 2009; 373(9665):746–58. https://doi.org/10.1016/s0140-6736(09)60046-5

71. Lam DH, Hayward P, Watkins ER, Wright K, Sham P. Relapse prevention in patients with bipolar disorder: cognitive therapy outcome after 2 years. The American journal of psychiatry. 2005; 162(2):324–9. https://doi.org/10.1176/appi.ajp.162.2.324 PMID: 15677598

72. Hooley JM. Expressed emotion and relapse of psychopathology. Annual review of clinical psychology. 2007; 3:329–52. https://doi.org/10.1146/annurev.clinpsy.2002.022305.095236 PMID: 17716059

73. Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. Cochrane Database of Systematic Reviews. 2004(2):CD004050. https://doi.org/10.1002/14651858.CD004050.pub2 PMID: 15106233

74. Benedetti F, Avery DH, Bauer M, Bunney WE, Calihr O, Camardese G, et al. Evidence for the Efficacy of Bright Light Therapy for Bipolar Depression. The American journal of psychiatry. 2018; 175(9):905–6. https://doi.org/10.1176/appi.ajp.2018.18020231 PMID: 30173556
75. Yorguner Kupeli N, Bulut NS, Carkaxhiu Bulut G, Kurt E, Kora K. Efficacy of bright light therapy in bipolar depression. Psychiatry research. 2018; 260:432–8. https://doi.org/10.1016/j.psychres.2017.12.020 PMID: 29268206

76. Nasr SJ, Elmaadawi AZ, Patel R. Bright light therapy for bipolar depression. Current Psychiatry. 2018; 17(11):28–32.

77. Sit D, McGowan J, Willtrout C, Weingarden J, Diler RS, Dills JL, et al. A randomized, placebo-controlled trial of light therapy for bipolar depression: Antidepressant efficacy, side effects, changes in suicidality and sleep. Biological psychiatry. 2015; 77(9):66S.

78. Martiny K. Chronotherapeutics for affective disorders. A clinician’s manual for light and wake therapy, 2nd revised edition. By Wirz-Justice A., Benedetti F., Terman M. Published by Karger, Basel, Switzerland, 2013, 124 pp., Paperback EUR 34.00/USD 48.00/ISBN: 978–3. Acta psychiatrica Scandinavica. 2014; 129(2):160–.

79. Stephenson KM, Schroder CM, Bertschy G, Bourgin P. Complex interaction of circadian and non-circadian effects of light on mood: shedding new light on an old story. Sleep medicine reviews. 2012; 16 (5):445–54. https://doi.org/10.1016/j.smrv.2011.09.002 PMID: 22244990