Psychological and behavioural interventions in bipolar disorder that target sleep and circadian rhythms: a systematic review of randomised controlled trials

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Abstract

Sleep and circadian disruptions are prominent symptoms of bipolar disorder (BD) and potential targets for adjunctive interventions. The aim of this review was to appraise the effectiveness of psychological and behavioural interventions in BD that target sleep and circadian rhythms, as reported by randomised controlled trials. Nineteen studies met the inclusion/exclusion criteria. They were summarised via narrative synthesis and meta-analysis wherever appropriate. Six studies delivered bright light therapy, five interpersonal and social rhythm therapy, two blue-light blocking glasses, one cognitive behavioural therapy for insomnia, one total sleep deprivation, and four combination treatments. More than half of the studies (N=10, 52%) did not measure sleep or circadian rhythms despite being the principal target of the intervention. Overall, the evidence base for the effectiveness of these interventions was limited. There was a small number of studies for each intervention, and a lack of consistency in protocols and outcomes. Meta-analysis was possible for the effect of bright light therapy on depression, revealing a medium-to-large post-treatment effect (Nc=6; g=-0.74 [95% CI=-1.05 to -0.42], $p<0.001$). For data, source, and supplementary materials see: https://osf.io/gv3pe/

Keywords: bipolar disorder, mania, depression, sleep, circadian rhythms, insomnia, bright light therapy, sleep deprivation, cognitive behavioural therapy, interpersonal and social rhythm therapy

Introduction

Bipolar disorder (BD) is a chronic mood disorder characterised by recurrent episodes of (hypo)mania and depression, with interim periods of more stable mood, termed euthymia. It is a condition associated with cognitive impairment, poorer quality of life, increased rates of suicide, and substantial costs for the individual and society at large (1). Current treatment guidelines recommend pharmacological approaches as the first-line treatment (2, 3). However, these approaches are only partially effective (4-6) and have varied acceptability rates (7, 8). Efforts to improve persistent symptoms with medication often lead to polypharmacy (9), thus amplifying calls for novel targets and multidisciplinary treatment approaches, including behavioural interventions (10).

A promising target for adjunctive behavioural interventions in BD is sleep and circadian rhythms (11). Sleep disruption is a hallmark of bipolar symptomatology (12) and particularly salient to both patients and clinicians (13, 14). The nature of sleep disturbance in BD depends on episode polarity. Decreased need for sleep is a core symptom of mania, and insomnia or hypersomnia are core features of depression (15, 16). Such problems are ubiquitous in acute illness episodes (17), while approximately 70% of BD patients in euthymia report insomnia symptoms too. Individuals with BD further exhibit a delayed circadian phase, favouring a late bed and rise-time (18), along with hypersensitivity to evening light (19). Sleep and circadian disruptions in BD are associated with increased suicidality (20) and a range of psychosocial (10, 21) and cognitive impairments (22, 23), as well as episode relapse (24, 25). Beyond their role as symptoms, sleep and circadian rhythms might also be causal factors in BD. For example, circadian genes have been implicated in the genetic diathesis of BD (19), sleep loss has been directly linked to the causation of mania (26, 27), and sleep and circadian disruptions are the most well-replicated risk factors for later development of BD in people at high risk of BD (28, 29).

At present, treatment guidelines for BD do not directly address sleep and circadian disruptions, besides the short-term use of GABA modulators for sedative purposes (2, 3). Psychotherapy is mainly recommended as maintenance treatment (2, 3) or for the management of subthreshold symptoms (2). However, psychological and behavioural interventions that target sleep and circadian rhythms, have been explored in other transient and chronic psychiatric conditions, with improvements observed in sleep, circadian rhythms, and mood (30, 31), setting the precedent for these effects being observed in BD patients too.

Recent reviews have produced mostly positive findings regarding the effectiveness of psychological and behavioural interventions in BD that target sleep and circadian rhythms. Such interventions typically rely on the therapeutic effects of light (e.g., bright light therapy or blue-light blocking glasses), the stabilisation of daily rhythms (e.g., interpersonal and social rhythm therapy), the modification of dysfunctional beliefs and behaviours around sleep (e.g., cognitive behavioural therapy for insomnia), or changes in mood following acute sleep loss (e.g., total sleep deprivation). Bright light therapy (BLT) and total sleep deprivation (TSD) were found to be effective both as monotherapies and in combination (11, 32-37). Antidepressant treatment standard effect sizes for BLT or BLT in combination with TSD ranged from -1.48 to -0.25 (33, 35, 37), and response rates to TSD ranged from 27.4% to 59.4% (11, 32). However, conclusions from these reviews should be interpreted cautiously, as they relied predominantly on uncontrolled non-randomised trials or studies that largely recruited participants with unipolar depression. Review findings may be different if only RCTs are included. For example, a commentary recently highlighted that the antidepressant effect of BLT in unipolar depression decreases substantially when only controlled trials are meta-analysed (38, 39). Additionally, due to the unique symptom profile of BD, and concerns over the effect of sleep loss on mania, it is necessary to evaluate data about the effects of these interventions in BD independently from other psychiatric disorders.

Therefore, the aim of this review was to critically appraise the efficacy of psychological and behavioural interventions in BD that target sleep and circadian rhythms, as observed in the context of the gold standard design for intervention evaluation, RCTs. A narrative synthesis approach was generally adopted. Consistent with pre-registered plans, quantitative meta-analytic models were applied when at least five studies evaluated the same intervention and measured the same outcome.

Methods

This systematic review was conducted in accordance with the PRISMA guidelines (40) and was preregistered in PROSPERO (ID: CRD42019156782) .

Literature search

EMBASE, PsycINFO, MEDLINE and AMED were searched through Ovid, and CINAHL was searched through SOLO (the Bodleian Libraries online search platform). Databases were searched from inception to the 3rd of January 2021. Two previous iterations were conducted, one on the 13th of November 2019 and one on the 28th of March 2020. The terms used in the search were: "sleep" or "sleep disorder" or "sleep disturb*" or "insomnia" or "circadian" or "parasomnia" or "hypersomnia" AND "bipolar" or "bipolar disorder" or "mania" or "bipolar depression" or "euthymia" AND "cognitive behav* therapy" or "therapy" or "intervention" or "treatment*" or "chronotherapy" or "sleep deprivation" or "bright light therapy" or "darkness therapy". Bibliographies from other relevant reviews were also hand-searched (11, 32-37). Grey literature was not included. All records were screened by the first author together with HJF or CKL. In the case of uncertainty, an inclusion decision was reached after consulting KEAS and SDK.

Study selection

Studies were included in the review if they: a) were a peer-reviewed parallel or crossover randomised controlled trial, b) delivered an intervention specifically focused on sleep or circadian rhythms with no restrictions on the type of control arm, c) participants were adults (≥ 18 years old), and d) diagnosed with BD.

Records were excluded if: a) the primary focus of the study was on BD comorbid with any psychiatric or medical condition, apart from sleep disorders, b) sleep and/or circadian rhythms were not the principal treatment targets but simply additive elements to another proposed intervention, c) the sleep or circadian intervention was administered to both groups and the randomisation was based on other elements of the study, such as a pharmacological agent, d) the study compared pre-to-post outcomes in a single group, and e) the study investigated the effect of the same intervention in two different patient groups. There was no exclusion based on the nature of the control group.

Quality assessment

The credibility of the conclusions drawn by the included studies was assessed based on the justification of their aims, the rigour of their methodological design, and the transparency of their reporting. Thus, all studies were independently appraised by LB, HJF, and CKL using a modified version of the AXIS tool for risk of bias assessment (41). This tool was selected due to its principal focus on the rationale, methods and reporting of the study. It includes 18 questions, each one of which is given a high, low or unclear risk of bias. Discrepancies between the two assessors were resolved based on consensus and after consulting with KEAS and SDK. Data on safety of the interventions were extracted by LB alone.

Data handling and analysis plan

Following the Cochrane Collaboration recommendations, all findings were summarised via narrative synthesis (42). This review only considered differences between the treatment and control arms at post-treatment and follow-up. As such, only data relevant to between-group comparisons were extracted and analysed. The outcomes of interest for this review were related to sleep and circadian rhythms, depression, mania, functioning, and quality of life. Other reported outcomes were also extracted and are presented in the Supplementary Materials.

Hedge's g effect sizes and the corresponding 95% confidence intervals for all extracted outcomes at post-treatment and follow-up were calculated whenever possible. In crossover trials, outcome scores were extracted prior to exposure to the second arm. Hedge's g was the preferred measure of standardised mean difference over Cohen's d, as the latter can be positively biased in studies with small sample sizes. Similar to Cohen's d, Hedge's g effects of 0.00-0.20 were interpreted as small, 0.21-0.80 as moderate and 0.81- onwards as large. The effect sizes were calculated using the published means and standard deviations. In cases where other measures of central tendency or dispersion were reported, means and standard deviations were estimated (see Supplementary Materials). In instances where there was not enough information to estimate the appropriate effect sizes, the lead or senior author was contacted and asked to provide the necessary statistics from the published papers. When an answer was not received, the missing statistics were estimated using previously validated methods (see Supplementary Materials).

Consistent with pre-registered plans, random-effects models were implemented when at least five studies delivered the same intervention and measured the same outcome. Random-effects models estimate the weighted pooled effect sizes, and were preferred over fixed-effects models due to expected heterogeneity in the included studies. Heterogeneity was inspected based on the I^2 values and the associated 95% confidence intervals using the Q-profile method

(43). All analyses were performed in the software R, version 3.6.0 (44) using the *tidyverse* (45) and *metafor* (46) packages.

Registered clinical trials

Complementary to the initial search, registered trials in ClinicalTrials.gov, International Standard Randomised Controlled Trial Number, and EU Clinical Trials Register were searched from inception to the 30th of March 2020. The search terms were "sleep" AND "bipolar", with studies in humans and written in English as the only restrictions. The resultant records were assessed against the original screening parameters. The aim of this process was to collate information about prospective studies, and therefore describe in more factual terms the future of this emergent research area.

Results

After removing duplicate entries (n=1,545), 9,858 title and abstract records were screened. This resulted in the exclusion of 8,174 references, and the retrieval of 138 full-text records. A total of 19 studies reporting on 16 RCTs met the inclusion and exclusion criteria and were subsequently included in this review (see Figure 1). Details of the results, including datasets and analysis scripts, are publicly accessible on the following Open Science Framework page: https://osf.io/gv3pe/

[INSERT FIGURE 1 HERE]

Figure 1. PRISMA flowchart of the included studies

Study characteristics

Key characteristics of all included studies are displayed in Table 1. The earliest study was conducted in 1984 and the most recent in 2020, with almost half of all studies (n=9; 47%) published in the last five years. The included studies recruited a total of 1,094 participants, ranging from 9 to 192. Overall, of the 1,094 recruited participants, 852 completed the study protocols and provided post-treatment data (78%). A total of 62% of the sample was female. Four studies recruited inpatients (21%), nine recruited outpatients (47%), four recruited volunteers (21%) and two studies recruited both in- and outpatients (10%). 13 studies (68%) reported on the safety of the administered intervention. None of these studies reported any serious adverse event and side-effects were rare (see Supplementary Table 1).

Six studies reported on the administration of BLT as a treatment (47-52), four on IPSRT (7, 53-55), two on blue-light blocking glasses (56-58), one on CBT-I (5), one on TSD (59), and four on combination treatments (60-63). Most studies included both BD-I and II (n=9; 47%), followed by BD-I alone (n=6; 32%), and one study looked specifically at BD-II (5%). Three studies did not specify the BD subtype of their participants (16%). Ten studies recruited people in a depressive phase (53%), three recruited patients in a euthymic phase (16%), two recruited patients in a manic phase (10%), and two in either a manic, depressed or mixed phase (10%). Two studies did not specify the mood phase of their participants (10%). Following this, 15 studies reported outcomes for depression (79%), ten for mania (53%), nine for sleep and/or circadian rhythms (47%), and four for functioning and/or quality of life (21%). Only three trials specifically recruited patients with sleep or circadian rhythm disruption at baseline, all of which recruited BD patients with a comorbid diagnosis of insomnia (16%).

[INSERT TABLE 1 HERE]

Table 1. Characteristics of the included trials

Quality assessment

Supplementary Tables 3 and 4 present the quality assessment of the included studies. The mean interrater reliability score for the quality assessment was 92%. Although the appraisal produced mixed results, there is a distinct trend of improvement. Studies published in the last five years were more comprehensive and transparent in their reporting than previous work in the area. Of the four studies (21%) judged to have a low risk of bias in all domains, three explored the treatment effects of blue light-blocking glasses (56-58), and the fourth investigated the effects of BLT (49).

Almost all studies (n= 17; 90%) reported clear aims and objectives. Most studies compared treatment to a non-active control (n=15; 79%), three studies (16%) used an active control arm, and one study (5%) included both an active a non-active control arm. Thirteen out of the 19 studies did not report a sample size justification (68%), with the six studies (32%) that reported a sample size justification being published in the last five years. 15 studies (79%) defined their population clearly using well-established diagnostic tools, whereas four studies (21%) did not provide sufficient information regarding the episode polarity of BD. One study (5%) did not provide enough details about the population their sample was selected from, and in another study (5%) there were concerns about the participant selection process. In this last study, there was a notable imbalance of inpatients and outpatients in the two study groups, with 66% inpatients and 34% outpatients in the treatment group, and 20% inpatients and 80% outpatients in the control group (52). Two studies (10%) did not address their drop-out rate at all, and two more studies did not address it sufficiently (10%). In these last two studies, the patients who switched polarity following TSD were defined as drop-outs (48, 60), while such instances could be additionally handled and interpreted as adverse events potentially related to the treatment (61). The scope of the measured outcomes was limited, with nine studies (47%) not assessing sleep or circadian rhythms in any capacity and one study providing unclear

information (5%). However, for the outcomes they did measure, almost all studies (n=18; 95%) used well-validated measures and statistical significance was clearly reported. Methodological reporting was more transparent than analytical reporting, with most studies (n=17; 90%) reporting sufficient information in the methods to allow a replication, but with one third of the included studies (n=6; 32%) not reporting aggregated scores or measures of dispersion for the raw data. In most cases, the results were internally consistent (n=16; 85%), and there were no omissions in the Results section of measures mentioned in the Methods section (n=16; 85%). In all studies (n=19; 100%), the interpretations were justified by the findings, and only one study did not mention any limitations (5%). In 14 studies (74%) there were no perceived conflicts of interest. In two papers there was a potentially strong conflict of interest (10%), and in three studies (16%) there was an unclear conflict of interest. Finally, all studies (n=19; 100%) had ethical approval for their protocol and informed consent from the participants.

Data synthesis

Details of the observed effects of the included studies are provided in Table 2.

[INSERT TABLE 2 HERE]

Table 2. Effect sizes classified by symptom outcome and ordered from improvement to worsening

Bright Light Therapy

Six studies reporting on six RCTs were included. All studies looked at BD-I and BD-II during depressive states. A random-effects model estimated a medium-to-large effect for reduced depression scores in the BLT group versus control at post-treatment (N_c=6; g=-0.74 [95% CI = -1.05 to -0.42], p<0.001; I^2=0.00 [95% CI = 0.00 to 82.85]) (see Figure 2). No

evidence of publication bias was detected after visual inspection of the associated funnel plot (See Supplementary Figure 1) or after conducting an Egger's test (z=-0.075; p=0.941). In one study there was a significant improvement in sleep quality at post-treatment (g=-0.81, p=0.027) (49), while in another study the difference in sleep quality was not significant (g=-.012, p=0.720) (51). Finally, in one study there was a large and significant improvement effect in functioning (g=0.71, p=0.031; Sit et al., 2018). Further details on anxiety and psychosis are presented in Supplementary Table 2.

[INSERT FIGURE 2 HERE]

Figure 2. Forest plot showing individual study and global effect size estimates for post-treatment comparisons between bright light therapy and control in depression outcomes

Interpersonal and Social Rhythm Therapy

Four studies reporting on four RCTs were included. One of the those studies did not provide adequate data for independent effect size calculation (53). No significant differences in depression (g=-0.15, p=0.435 for Miklowitz et al. 2007; g=0.74, p=0.105 for Swartz et al. 2012) or mania symptoms (g=0.19, p=0.312 for Miklowitz et al. 2007; g=-0.50, p=0.269 for Swartz et al. 2012) were detected in two studies. In one study there was significant improvement in both depression (g=0.94, p=0.003) and mania scores (g=-0.62, p=0.044) (7).

Blue light-blocking glasses

Three studies reporting two RCTs were included. In Esaki and colleagues (2020) there was a large reduction in depression symptoms (g=1.00, p=0.001), and a large shift towards morning preference for the treatment arm (g=1.03, p=0.003) but no significant difference in mania scores (g=0.04, p=0.911). In Henriksen and colleagues (2016; 2020) there was a large

and significant improvement in manic symptoms (g=1.81, p<0.001). Both studies found improvements in sleep efficiency using actigraphy. Further details on actigraphy findings from both studies are presented in Supplementary Table 2.

Cognitive Behavioural Therapy

One study reporting one RCT was included. The trial recruited patients who were euthymic. In Harvey and colleagues (2015) between-group differences in mania (g=-0.62, p=0.051) and depression (g=-0.38, p=0.232) following treatment did not reach statistical significance. Differences in mania scores remained moderate and non-significant at follow-up (g=-0.55, p=0.084), whereas reductions in depression scores at 6-month post-treatment follow-up were moderate-to-large and statistically significant (g=-0.67, p=0.037). There was a large and significant improvement in insomnia symptoms following treatment (g=-1.36, p<0.001) which was maintained at follow-up (g=-1.01, p=0.002). Similarly, large and significant effects for sleep quality (g=-0.80, p=0.014) and sleep disturbances (g=-1.07, p=0001) were observed at post-treatment and only for sleep disturbances at follow-up (g=-0.68, p=0.034). Further details on sleep measures are presented in Supplementary Table 2.

Sleep Deprivation Therapy

One study reporting an RCT in bipolar depression was included. No significant improvements in depression scores between the treatment and control groups were detected at post-treatment (g=-0.94, p=0.159).

Combination Therapies

Four studies reporting on three RCTs were included. One of the included studies did not provide adequate data for independent effect size calculation (60). One study administered

TSD, BLT and phase advance to BD patients in depression (61), another study administered IPSRT with a family therapy protocol, called Integrated Family and Individual Therapy, to BD patients in a manic, depressed, or mixed phase (62), and the final study recruited a subsample from Harvey et al (2015) and administered a novel sleep-inertia treatment, called RISE-UP, to BD patients in euthymia (63). No significant differences in depression scores were observed in Wu et al (2009), either at post-treatment (g=-0.52, p=0.100) or at a two-month follow up (g=-0.51, p=.107). In Miklowitz et al (2003) the treatment group showed no significant reductions in mania (g=-0.44, p=0.063) or depression symptoms (g=-0.10, p=0.683) compared to the controls. In Kaplan et al (2018) no measures of sleepiness reached statistical significance in either the first hour (g=-0.39, p=0.238) or the first three hours upon awakening (g=-0.31, p=303). Rest-activity findings using actigraphy are presented in Supplementary Table 2.

Registered Clinical Trials

Following the screening of 131 original registration records, five RCT registrations, all from clinicaltrials.gov, were included in this review (Beaulieu, NCT00590265; Jernelöv, NCT04130529; Morken, NCT01704352; Deckersbach, NCT01764035; Olie, NCT02936466). Overall, three out of the five trials plan to investigate euthymia, and recruit patients with a baseline insomnia comorbidity. Two of those trials also plan to administer CBT-I. Future literature in the area might also see the first RCT including polysomnography (one of the five trials), and the wider use of actigraphy (two of the five trials).

Discussion

This review constitutes the first comprehensive appraisal of the effects of psychological and behavioural interventions in BD for sleep and circadian rhythms, as observed in RCTs. Overall, there was limited evidence for the therapeutic capacity of such interventions. This was

primarily due to the small number of studies and sample sizes, as well as the inconsistency in assessed outcomes, diagnostic characterisation, and treatment protocols.

According to the quality appraisal, all studies assessed affective symptomatology, while, surprisingly, only 48% assessed sleep or circadian rhythms. However, it is essential that sleep and circadian outcomes are adequately measured in BD research at large and especially in this research area. First, as a proof of concept, given that the interventions reviewed here are assumed to exert their treatment effects on mood via sleep and circadian pathways. Second, due to the importance of sleep and circadian outcomes on their own right. Sleep, activity, and energy levels are domains particularly salient to patients for the self-monitoring of BD symptoms (14), and to clinicians given their persistence to standard care (64). Finally, sleep and circadian rhythms are presumed mediators of improved psychiatric and functional outcomes in BD. Their integration as endpoints in intervention RCTs will allow researchers to delineate the involvement of sleep and circadian rhythms in the multifactorial causation of BD.

The only therapeutic modality with enough data to meta-analyse was BLT, revealing a medium-to-large difference at post-treatment in depression symptoms (n_c=6; g=-0.74; $p<0.001$). A review of RCTs in non-seasonal depression showed a similar effect size (n_c= 7; standardised mean difference=-0.71; $p<0.001$) in favour of BLT as a single-component treatment (65). Both of these findings contrast with the moderate and non-significant effect of -0.25 reported by a review of RCTs on BLT in bipolar depression (33). This discrepancy is possibly due to Takeshima and colleagues' (2020) choice to extract follow-up as opposed to post-treatment values for one study (47) and to exclude another trial (49) that we included. Findings for blue-light blocking glasses and CBT-I were mostly positive for sleep, morningness, and mood. Only mood symptoms were assessed in IPSRT trials, and results were conflicting. No individual trial containing a TSD element showed any significant effects on any domain examined. This finding is contrary to recent claims in support of the effectiveness

of TSD for bipolar depression (11, 36). However, those claims were based on a literature dominated by non-controlled studies or RCTs that compare TSD plus medication against TSD alone. This inconsistency in findings between RCTs and studies without comparators has previously been highlighted. In a recent review, the significant antidepressant effect of TSD in unipolar depression (66) disappears when non-controlled trials are excluded from the analysis (38, 39). Our review of clinical trial registries suggests that future research might take into account the omission of sleep and circadian outcomes. Recently completed or ongoing trials contain self-report assessments of sleep disruption, and measures of circadian rest-activity rhythms and sleep architecture, with the aim of elucidating the mechanistic role of sleep – and its treatment - in BD. Additionally, there is evidence of a plan to include more comprehensive assessments of functioning and quality of life.

Furthermore, there were several limitations in terms of the clinical characterisation of the patient groups in the included studies. First, no study investigated the differential effects of treatment on BD subtypes. This is particularly salient given that BD-I and BD-II differ in their response to sleep loss (67) and their genetic liability to insomnia and hypersomnia (68). Second, most of the included studies recruited BD patients in an acute illness phase (82%), usually depression (71%). This is expected due to the higher frequency, duration, and burden associated with bipolar depression compared to mania (69), as well as practical challenges with recruitment during a manic episode. However, this leads to a limited understanding of the efficacy of behavioural sleep and circadian treatments in acute mania, and their role in the maintenance of euthymic (more stable) mood and relapse prevention. Finally, only three studies (16%) recruited BD patients based on sleep or circadian disruption at baseline, rendering it possible that there was limited scope for improvement to begin with. Future RCTs might apply more rigid clinical characterisation, as the majority of registered trials proclaim the recruitment of euthymic BD patients with a significant sleep disturbance at baseline.

Consensus on the features of the treatment protocols differed depending on intervention type. There were marked differences in the duration and intensity of BLT and the timing of treatment with blue-light blocking glasses. Interestingly, BLT was delivered mostly in the morning, with the only trial delivering BLT at mid-day not yielding significant improvements in depression or sleep quality (51). Although there is arguably no scientific consensus on the protocols of these interventions, recent findings about the neurobiological effects of light are likely to inform future literature in BD. For example, there is suggestive evidence that low intensity or blue-enriched light might be equally effective as bright light in alleviating depressive symptoms (70-73). Regarding other treatment modalities, studies including a TSD element adopted the recommendations of Benedetti and colleagues (1997). All studies in the IPSRT literature followed a standardised treatment protocol. On some occasions, treatment development was informed by advances in experimental work, as evidenced by: the integration of IPSRT components in CBT-I (5), a shift to personalised wake and sleep times for BLT (61), and the combination of single treatments to form the triple-chronotherapy intervention (61). According to the trial registries, two RCTs will look into the effects of CBT-I in BD, so the evidence base for this intervention might change in the near future. Safety of all included interventions was high, albeit based on inconsistent monitoring, and reporting. No serious adverse events were reported, and side-effects were rare. In contrast to the minimal side effect burden of these interventions, pharmacological treatments for BD show notable rates of discontinuation due to adverse events (74), with side-effects being the most common reason for poor treatment compliance (75). Future trials would benefit from standardised and comparable reporting of safety, as well as from direct and prospective safety comparisons between the included interventions and pharmacological treatments.The primary strength of this review is the comprehensive appraisal of all outcomes, diagnostic features, and treatment parameters in RCTs of psychological and behavioural interventions in BD targeting sleep and

circadian rhythms. However, inferences in this review are based on a limited number of studies. Only one meta-analytic model was computed, with all other interpretations in this review being based on single-trial effect sizes. Additionally, the included studies contain a small number of participants, with the median number of recruited participants being 44. This observation is likely linked to the lack of a sample size justification in the included studies, as only 31.5% reported a power analysis. The small number of participants has implications in terms of the findings observed, as trials with low number of participants are only powered enough to detect the largest of effects. Additionally, studies on pharmacological sleep and circadian rhythm interventions, such as melatonin and other hypnotics, were excluded, limiting the inferences that can be made about the general therapeutic modulation of sleep and circadian rhythms in BD. Since only RCTs were included, the evidence base of this review looks notably different to that of other published reviews in the same research area (11, 32-37). Finally, the inclusion of active control groups in four studies (47, 55, 59, 60) limits the extent to which the effects observed can be solely attributed to the action of the intervention under investigation.

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Appendix

Review pre-registration is available at PROSPERO (ID: CRD42019156782). Supplementary materials, data, and analysis scripts are publicly available on Open Science Framework: https://osf.io/gv3pe/

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Declaration of interests

CAE reports being a cofounder, chief medical officer, and shareholder of and receiving a salary from Big Health Ltd and being a developer of an online platform for cognitive behavioural therapy for insomnia, Sleepio. KEAS and SDK reports receiving nonfinancial support from Big Health Ltd in the form of provision of Sleepio for use in clinical trials.

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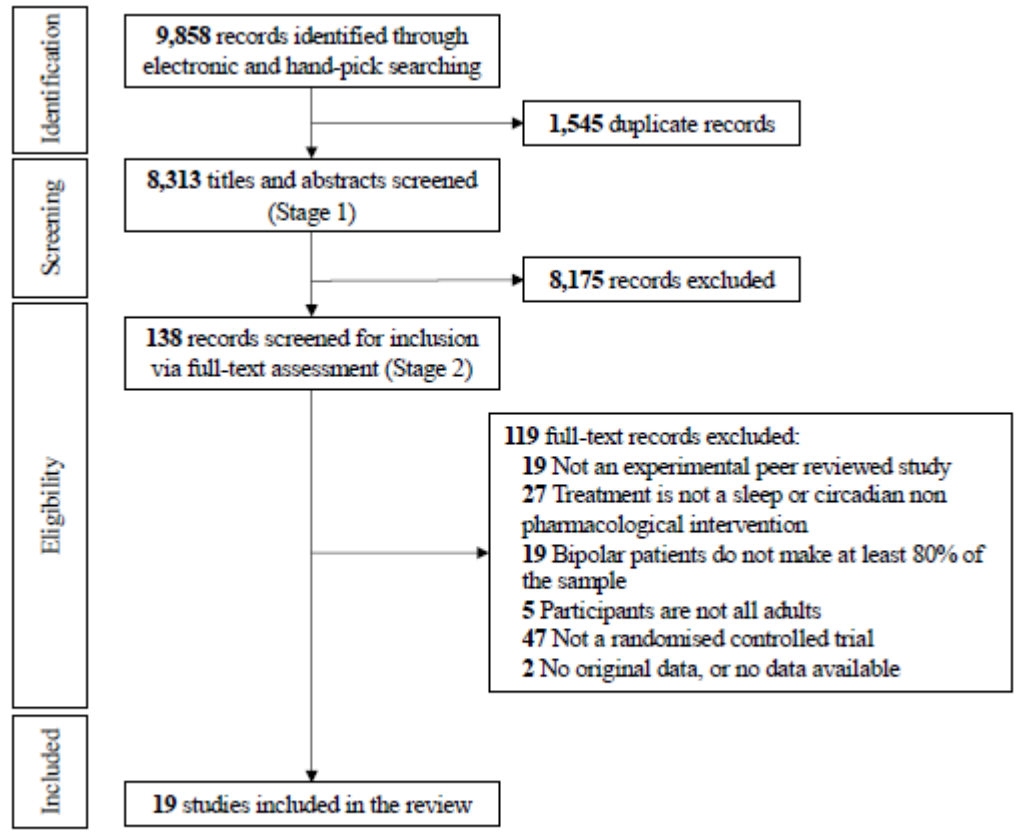

Figure 1. PRISMA flowchart of the included studies

Table 1. Characteristics of the included studies

Author year location	**Diagnosis (manual), subtype, phase comorbidities**	**Randomised *n* (completed *n*), *n* female, mean age (sd), recruitment population**	**Treatment type frequency, duration, timing (administrator)**	**Control type frequency, duration, timing (administrator)**	**Medication status**	**Domains examined (measurement tool)**	**Summary of between-groups estimated outcomes**
Bright Light Therapy							
Dauphinais et al. 2012 (48) USA	BD (DSM-IV), I and II, depressed, unclear comorbidities	*BLT:* 18 (10), 13f, 42.9 (12.4), outpatients *Negative Ion Therapy:* 20 (11), 15f, 43.1 (16.0), outpatients	*BLT* 7,000 lux, daily for 8 weeks, 7.5 min upon waking for the first three days with toleration increasing 2 x 7.5 up to 45 min upon waking (self-administered)	*Negative Ion Therapy* Daily for 8 weeks, 7.5 min upon waking for the first three days with toleration increasing 7.5 up to 45 min upon waking (self-administered)	Stable psychotropic medication. Benzodiazepines lorazepam-equivalents and zolpidem were allowed for insomnia	Depression (SIGH-ADS and MADRS), mania (YMRS), quality of life (Q-ES-Q)	No significant difference in depression, mania, or quality of life
Franchini et al. 2012 (47) Italy	BD (DSM-IV-TR), unclear, depressed with psychotic symptoms, no other Axis-I diagnosis	*BLT + Fluvoxamine:* 17 (17), 7f, 42.9 (17.9), inpatients *Fluvoxamine:* 10 (10), 7f, 54.0 (12.2), inpatients	*BLT* 10,000 lux, daily for 40 days, 30 min, between 4.45am-8.45am (nursing staff) *Fluvoxamine* Same as in the control condition	*Fluvoxamine* Titrated at 100mg qid days 1-3, 100mg bid on days 4-7, and 150mg bid on day 8. Participants then remained on 300mg per day for the remaining 5 weeks	As suited fluvoxamine, lithium (prophylactic dose), and/or flurazepam (up to 45mg/day). No other psychotropic medication allowed	Depression (HDRS), delusions (DDERS)	Significant reduction in depression scores for the BLT and fluvoxamine group. Unknown effect on delusion scores
Yorguner Kupeli et al. 2018 (49) Turkey	BD (DSM-IV and HDRS >17), I and II, depressed, no psychotic symptoms	*BLT:* 16 (16), 10f, 42.1 (9.1), outpatients *Dim light:* 16 (16), 16f, 37.1 (8.2), outpatients	*BLT* 10,000 lux, every morning for 30 minutes for 14 days, between 8 and 10 am (clinician)	*Dim light* <500 lux, every morning for 30 minutes for 14 days, between 8 and 10 am (clinician)	Stable medication throughout the study except lorazepam when needed as an add-on treatment	Depression (HDRS and MADRS) and sleep quality (PSQI)	Significant decrease in depression and increase in sleep quality for the BLT group
Rosenthal et al. 1984 (50) USA	Major affective disorder: BD (major affective disorder according to the RDC), I and II, unclear, unclear comorbidities	*BLT:* 4(4), 4f, 31.25(7.63), volunteers *Dim yellow light:* 5 (5), 4f, 44.8 (4.97), volunteers	*BLT* 2,500 lx, 6 hours a day (3 hours before dawn and 3 hours after dusk) for 2 weeks (unclear)	*Dim yellow light* 100 lx, 6 hours a day (3 hours before dawn and 3 hours after dusk) for 2 weeks (unclear)	Unclear but most participants were on some form of medication	Depression (HDRS)	No significant difference in depression between groups at post-treatment
Sit et al. 2018 (51) USA	BD (SCID in DSM-IV), I and II, depressed, no OCD	*BLT:* 23 (22), 14f, 45.7 (14.3), outpatients *Dim red light:* 23 (18), 17f, 43.7 (15.0), outpatients	*BLT* 7,000 lx, start with 15-minute sessions between 12:00 p.m. and 2:30 p.m. Then weekly increase by 15 minutes to attain a target dose of 60 minutes per daily session by week 4 or until remission (research personnel)	*Dim red light* 50 lx, lx, start with 15-minute sessions between 12:00 p.m. and 2:30 p.m. Then weekly increase by 15 minutes to attain a target dose of 60 minutes per daily session by week 4 or until remission (research personnel)	Anti-manic medication for at least 4 weeks prior to enrolment	Depression (SIGH-ADS and HDRS), functioning (GAF), clinical severity (CGI-BP), anxiety and suicidal thoughts (HDRS), sleep quality (PSQI), psychosis (BPRS)	Decrease in psychosis scores and an increase in global functioning in the BLT group were the only significant differences at post-treatment
Zhou et al. 2018 (52) China	BD (DSM-IV), unclear, depressed, no other Axis-I diagnoses	*BLT:* 37 (33), 20f, 35.09 (14.19), volunteers *Dim light:* 37 (30), 14f, 39.73 (13.53), volunteers	*BLT* 5000 lx, 1 hour a day every day for 2 weeks, between 6:30am-9 am (research staff)	*Dim light* 100 lx, 1 hour a day every day for 2 weeks, between 6:30am-9am (research staff)	Stable psychotropic medication for 2 weeks prior to enrollment	Depression (HDRS) and hypomania (YMRS)	Significant reduction in depression in the BLT group

Table 1. Characteristics of the included studies

Author year location	**Diagnosis (manual), subtype, phase comorbidities**	**Randomised *n* (completed *n*), *n* female, mean age (sd), recruitment population**	**Treatment type frequency, duration, timing (administrator)**	**Control type frequency, duration, timing (administrator)**	**Medication status**	**Domains examined (measurement tool)**	**Summary of between-groups estimated outcomes**
Interpersonal and Social Rhythm Therapy							
Frank et al. 2005 (53) USA	BD (SCID-P for DSM-IV) or schizoaffective disorder manic type (SCID-P DSM-IV or schedule for affective disorders and schizophrenia), I, manic, depressed or mixed, no BPD, APD, bulimia or anorexia	*IPSRT:* 87 (49), 26f, 36.4 (10.6) in- and outpatients *ICM:* 88 (44), 22f, 39.4 (10.8), in- and outpatients	*IPSRT (acute)/IPSRT (chronic)* Weekly until stabilisation then biweekly for 12 weeks, then monthly, 45-55min, not stated (social worker, nurse, or psychologist)	*ICM (acute)/ICM (chronic)* Weekly until stabilisation then biweekly for 12 weeks, then monthly, 20 min, not stated (social worker, nurse or psychologist)	For manic pahses: lithium to serum 0.8/1.0 mEq/L, or sodium divalproex or carbamazepine as required. For depressive phases: lithium, and tranylcypromine sulphate, imipramine hydrochloride and SSRI as required	Recurrence of acute mania ore depression episodes (clinical evaluation using the RDC), social rhythms (SRM)	No adequate data for an independent appraisal of the results
Miklowitz et al. 2007 (54) USA	BD (Affective Disorders Evaluation adapted from SCID-P from DSM-IV), I and II, depressed, unclear comorbidities	*IPSRT:* 62 (42), volunteers *CC:* 130 (90), volunteers	*IPSRT*	*CC* Three 50-minute individual sessions in the six weeks post randomisation, an educational videotape, and workbook	Mood stabiliser (lithium, valproate, or carbamazepine) plus antidepressant in some cases	Mania and depression relapse	No significant differences between groups in either depression or mania scores
Steardo et al. 2020 (7) Italy	BD (SCID-5-CV for DSM-V), I and II, unclear, unclear comorbidities	*IPSRT:* 22 (22), 12f, 49.1 (12.6), outpatients *TAU:* 22 (22), 13f, 46.7 (12.8), outpatients	*IPSRT* 12 weekly sessions, 90 min (psychiatrist)	*TAU*	Stable treatment with mood stabilizers for at least a year prior to recruitment	Depression (IDSSR and MADRS), anxiety (HAM-A), mania (MRS), functioning (GAF and AMI), and response to mood stabilizers (ALDA)	Significant improvements in the IPSRT group for both depression and mania scores
Swartz et al. 2012 (55) USA	BD (SCID for DSM-IV-clinician-version), II, depressed, no BPD or APD	*IPSRT:* 14 (12), 7f, 40.1 (11.7), volunteers *Quetiapine:* 11 (9), 3f, 32.1 (12.8), volunteers	*IPSRT* 12 weekly sessions, 45 min (master's level therapists)	*Quetiapine* Daily for 12 weeks. Start dose of 50 mg a day, increased weekly by 50 mg a day, as tolerated, to a maximum of 300 mg a day.	No psychotropic medication allowed prior to the study, but low doses of lorazepam if they experienced sleep problems	Depression (HDRS-25, HDRS-17 and MADRS), mania (YMRS), functioning (CGI-BP), and anxiety (BAI)	No significant differences between groups in either depression or mania scores
Blue-Light Blocking Glasses							
Esaki et al. 2020 (56) Japan	BD (DSM-V), and Insomnia (ISI ≥8), I and II, euthymic, unclear comorbidities	*BB glasses:* 21 (19), 9f, 44.1 (11.8), outpatients *Placebo:* 22 (18), 14f, 41.1 (10.4), outpatients	*BB* Orange-tinted glasses worn every night for 14 consecutive nights, 8pm-bedtime (unclear)	*Placebo* Clear glasses worn every night for 14 consecutive nights, 6pm-8pm-dedtime (unclear)	Medication as usual (stable throughout the study)	Sleep (actigraphy, sleep diaries, VAS for sleep quality and ISI), chronotype (MEQ), mania (YMRS), depression (MADRS)	Significant reduction in depression scores and phase advance (MEQ) in the BB glasses group
Henriksen et al. 2016 (58) Norway	BD (MINI-Plus for DSM-IV-TR), I, manic, unclear comorbidities	*BB glasses:* 18 (12), 5f, 43.0 (11.0), inpatients	*BB*	*Placebo*	Medication as usual (stable throughout the study)	Mania (YMRS)	Significant decline in manic symptoms for the BB glasses group

Table 1. Characteristics of the included studies

Author year location	**Diagnosis (manual), subtype, phase comorbidities**	**Randomised *n* (completed *n*), *n* female, mean age (sd), recruitment population**	**Treatment type frequency, duration, timing (administrator)**	**Control type frequency, duration, timing (administrator)**	**Medication status**	**Domains examined (measurement tool)**	**Summary of between-groups estimated outcomes**
		Placebo: 14 (11), 2f, 49.8 (13.8), inpatients	Orange-tinted glasses worn every night for 7 consecutive nights, 6pm-8am (nurses)	Clear glasses worn every night for 7 consecutive nights, 6pm-8am (nurses)			
Henriksen et al. 2020 (57) Norway	BD (MINI-Plus for DSM-IV-TR), I, manic, unclear comorbidities	*BB glasses:* 18 (10), 4f, 43.9 (11.8), inpatients *Placebo:* 14 (10), 2f, 48.8 (14.1), inpatients	*BB* Orange-tinted glasses worn every night for 7 consecutive nights, 6pm-8am (nurses)	*Placebo* Clear glasses worn every night for 7 consecutive nights, 6pm-8am (nurses)	Medication as usual (stable throughout the study)	Rest-activity and sleep (actigraphy)	Higher SE, lower activity counts per epoch, lower WASO, and decreased sleep fragmentation for the BB group
Cognitive Behavioural Therapy for Insomnia							
Harvey et al. 2015 (5) USA	BD (SCID for DSM-IV-TR, YMRS<12 and IDS-C<24) and Insomnia (general insomnia by ICSD-2 and primary insomnia by DSISD), I, inter-episode, no PTSD, other sleep disorder, or alcohol and substance abuse/dependency over the past 3 months	*CBT-I:* 30 (22), 19f, 37.7 (12.4), outpatients *PE:* 28 (19), 17f, 35.5 (9.3), outpatients	*CBT-I* 8 weekly sessions, 50-60 min (doctoral or master's level therapists) The behavioural components included: stimulus control, SRT, psychoeducation, relaxation therapy in dim-light conditions, and a wake-up routine. The cognitive components included: targeting unhelpful beliefs about sleep and reducing sleep-anxiety and rumination. The daytime functioning component included: behavioural activities to allow patients to experience the effects of being active, and identification of energy-generating activities in order to tackle daytime tiredness	*PE* 8 weekly sessions, 50-60 min (doctoral or master's level therapists)	Medication as usual (stable throughout the study)	Relapse rate and days spent in acute episodes (clinical evaluation using the SCID for DSM-IV-TR), depression (IDS-C), mania (YMRS), insomnia (ISI and clinical evaluation by the DSISD), sleep quality (PSQI), sleep disturbances (PROMIS-SD), and sleep (sleep diaries), functionality (SDS), quality of life (Q-LES-Q-SF), percentage of patients taking mood or sleep medications	No significant differences in mania, depression or sleep efficiency at post-treatment. Significant improvements in depression and sleep efficiency at FU but not for mania. Lower insomnia, and fewer sleep disturbances at post-treatment and FU. Higher sleep quality at post-treatment but not FU. No significant differences for most sleep diary measures (i.e. SOL, WASO, TIB, and TST), and for quality of life at post-treatment or FU
Sleep Deprivation							
Benedetti et al. 1997 (59) Italy	BD (DSM-III-R), I and II, depressed, unclear comorbidities	*TSD & fluoxetine:* 5 (5), 3f, 40.0 (12.1), outpatients *Fluoxetine only:* 5 (5), 4f, 42.0 (9.7), outpatients	*TSD* 36 hours awake for 3 nights, from 7.00 to 19.00 the following day (nursing staff) *Fluoxetine* 20mg once daily, 8am (nursing staff)	*Fluoxetine* 20mg once daily, 8am (nursing staff)	Free of all psychotropic medication for at least 1 week before admission	Depression (HDRS)	No significant reduction in depression scores for the TSD group compared to the control
Combination Treatments							

Table 1. Characteristics of the included studies

Author year location	**Diagnosis (manual), subtype, phase comorbidities**	**Randomised *n* (completed *n*), *n* female, mean age (sd), recruitment population**	**Treatment type frequency, duration, timing (administrator)**	**Control type frequency, duration, timing (administrator)**	**Medication status**	**Domains examined (measurement tool)**	**Summary of between-groups estimated outcomes**
Colombo et al. 2000 (60) Italy	BD (DSM-IV), unclear, depressed, no other axis 1 diagnosis	*TSD + red BLT + lithium:* 14 (14), 9f, 45.6 (14.6), inpatients *TSD + red BLT:* 19 (19), 13f, 41.6 (12.9), inpatients *TSD + white BLT + lithium:* 17 (17), 10f, 42.6 (12.1), inpatients *TSD + white BLT:* 23 (23), 19f, 45.1 (12.8), inpatients *TSD + ambient light + lithium:* 15(15), 10f, 51.1(13.2), inpatients *TSD + ambient light:* 15(15), 11f, 49.5 (10.5), inpatients	*TSD* 36 hours awake for 3 nights, from 7am to 7pm the following day (unclear) *Red BLT* 150 lux of red light given for 30 min on each TSD night at 3am (unclear), on the morning after the recovery sleep and half an hour after awakening between 8am and 9am *White BLT* 2,500 lux of white light given for 30 min on each TSD night at 3am (unclear), on the morning after the recovery sleep and half an hour after awakening between 8am and 9am *Lithium* Same lithium carbonate dosage as usual	*TSD* 36 hours awake for 3 nights, from 7am to 7pm the following day (unclear) *Ambient light* Room monitored at 80 lux with no additional light exposure *Lithium* Same lithium carbonate dosage as usual	No other long-term medication besides lithium. If treated with benzodiazepines a progressive dose reduction prior to the run-in period was conducted	Subjective mood (VAS from very happy to very sad), and sleepiness (SSS)	No adequate data for an independent appraisal of the resultsc
Kaplan et al. 2018 (63) USA	BD (SCID for DSM-IV-TR, YMRS<12 and IDS-C<24) and Insomnia (general insomnia by ICSD-2 and primary insomnia by DSISD), I, inter-episode, no PTSD, other sleep disorder, or alcohol and substance abuse/dependency over the past 3 months	*RISE-UP:* 20 (19), 14f, 39.3 (14.2), outpatients *PE:* 20 (19), 13f, 35.4 (8.9), outpatients	*RISE-UP* One 60-minute therapy session at the start of CBT-I (doctoral student). The components of the treatment included: refraining from snoozing, increasing activity in the first hour upon awakening, showering or washing face with cold water, expose to sunlight, upbeat music and phoning a friend	*PE* One session, 50-60 min (doctoral or master's level therapists)	Medication as usual (stable throughout the study)	Sleep (actigraphy and sleep diaries), sleepiness (SSS)	RISE-UP group was significantly more active in the first hour upon awakening. No other significant differences were detected
Miklowitz et al. 2003 (62) USA	BD (SCID-P for DSM-IV), I and II, (hypo)manic, depressed and mixed, no DSM-IV drug or alcohol disorder	*IFIT:* 31 (24), 18f, 35.7 (9.2), inpatients and outpatients *CM:* 70 (54), 46f, 35.6 (10.6), inpatients and outpatients	*IFIT* 21 one-hour sessions, 12 of them weekly, then 6 of them biweekly and finally 3 monthly sessions (trained therapists)	*CM* 2 home-based BD information sessions within 2 months of entry to the study, emergency counselling also available (clinician)	Medication as usual	Survival time, mood disorder symptom severity, depression, and mania (all from SADS-C)	No significant differences between groups in either depression or mania scores

Table 1. Characteristics of the included studies

Author year location	Diagnosis (manual), subtype, phase comorbidities	Randomised *n* (completed *n*), *n* female, mean age (sd), recruitment population	Treatment type frequency, duration, timing (administrator)	Control type frequency, duration, timing (administrator)	Medication status	Domains examined (measurement tool)	Summary of between-groups estimated outcomes
			One session per week for 12 months, alternating between IPSRT and FT (optimally 25 IPSRT and 25 FT). Flexibility when designing each therapeutic protocol, not all therapists took all 50 sessions available (one therapist for IPSRT and one for FT, therapists were graduate and postdoctoral researchers)				
Wu et al. 2009 (61) USA	BD (SCID in DSM-IV), I and II, depressed, unclear comorbidities	*TSD + BLT + Phase Advance:* 32 (27), 10f, 39 (13.31), outpatients *TAU:* 17 (17), 10f, 40 (14.1), outpatients	*TSD* 33 hours awake, from 9am to 6pm the day after (nursing staff) *BLT* 5000 lux for 2 hours over 3 days in the morning following a night of TSD, exact timing was calculated based on individual MEQ scores *Phase advance* for 3 nights the evening after the first TSD night	*Medication treatment as usual* (nursing staff)	Everyone on mood stabilizers, antidepressants and sertraline administered on the same time schedule. Lithium (or other mood stabilizers if intolerant) initiated 1 week before the SD night to minimize the risk of switches into hypomania/mania	Depression (HDRS)	No significant differences in depression scores either at post-treatment or at a two-month FU

Abbreviations: AMI, Attitude to Mental Illness Questionnaire ; APD, Antisocial Personality Disorder; BAI, Beck Anxiety Inventory; BB glasses, Blue-light Blocking glasses; BD, Bipolar Disorder; BLT, Bright Light Therapy; BPD, Borderline Personality Disorder; BPRS, Brief Psychiatric Rating Scale; CBT-I, Cognitive Behavioural Therapy for Insomnia; CC, Collaborative Care; CGI-BP, Clinical Global Impression for use in Bipolar disorder; CI, Confidence Intervals; CM, Clinical Management; DDERS, Dimensions of Delusional Experience Rating Scale; DSISD, Duke Structured Clinical Interview for Sleep Disorders; DSM, Diagnostic and Statistical Manual for mental disorders; FU, Follow-Up (the precipitating number indicates months); GAF, Global Assessment of Functioning; HAM-A, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; ICM, Intensive Clinical Management; ICSD, International Classification of Sleep Disorders; IDS-C, Inventory of Depressive Symptomatology- Clinician version; IFIT, Integrated Family and Individual Therapy; IPSRT, Interpersonal and Social Rhythm Therapy; ISI, Insomnia Severity Index; MADRS, Montgomery–Åsberg Depression Rating Scale; MEQ, Morningness-Eveningness Questionnaire; MRS, Mania Rating Scale; N, number of participants; OCD, Obsessive-Compulsive Disorder; PE, Psychoeducation; PROMIS-SD, Patient-Reported Outcomes Measurement Information System- Sleep Disturbance; PSQI, Pittsburgh Sleep Quality Index; PTSD, Posttraumatic Stress Disorder; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; RDC, Research Diagnostic Criteria; SADS-C, Schedule for Affective Disorders and Schizophrenia- Change in symptomatology; SCID, Structured Clinical Interview for the DSM; SD, Standard Deviations; SE, Sleep Efficiency; SIGH-ADS, Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement; SRM, Social-Rhythm Metric; SSS, Stanford Sleepiness Scale; TAU, Treatment As Usual; TC, Triple Chronotherapy; VAS, Visual Analogue Scale; WASO, Wake After Sleep Onset; YMRS, Young Mania Rating Scale

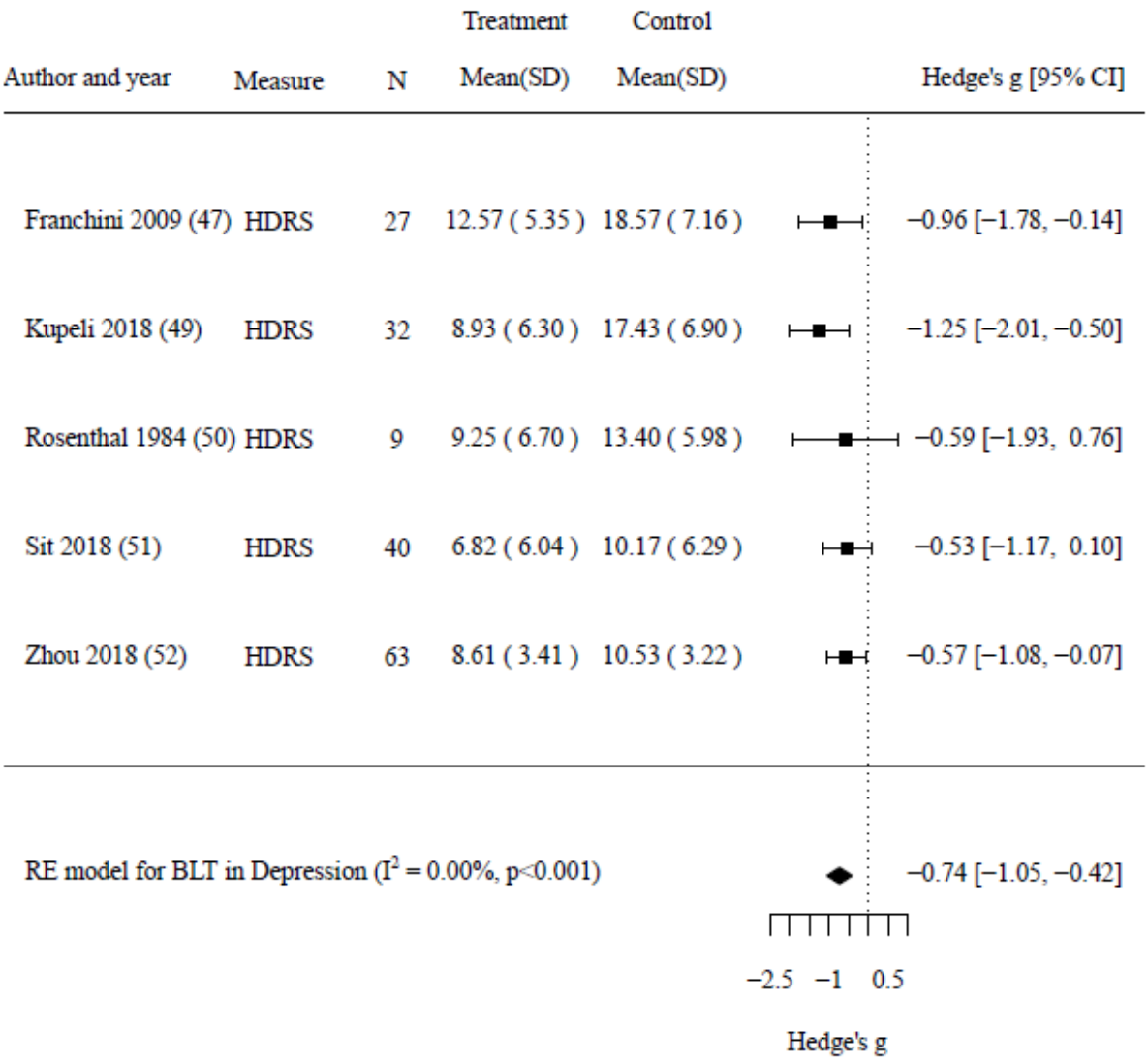

Figure 2. Forest plot showing individual study and global effect size estimates for post-treatment comparisons between bright light therapy and control in depression outcomes

Table 2. Effect sizes classified by symptom outcome and ordered from improvement to worsening

Author (year)	Treatment /Control	Measure	N analysed	Hedge's g	95% CI	p-value
Depression symptom severity						
Kupeli et al. 2018 (49)	BLT/DL	HDRS	32	-1.25	-2.01 to -0.50	**0.001**
Kupeli et al. 2018 (49)	BLT/DL	MADRS	32	-1.24	-2.00 to -0.48	**0.001**
Esaki et al. 2020 (56)	BB/CL glasses	MADRS	37	-1.00	-1.69 to -0.32	**0.004**
Franchini et al. 2009 (47)	BLT/Fluvoxamine	HDRS	27	-0.96	-1.78 to -0.14	**0.022**
Steardo et al. 2020 (7)	IPSRT/TAU	MADRS	44	-0.94	-1.56 to -0.32	**0.003**
Rosenthal et al. 1984 (50)	BLT/DL	HDRS	9	-0.59	-1.93 to 0.76	0.397
Sit et al. 2018 (51)	BLT/DL	SIGH-ADS	40	-0.72	-1.36 to -0.08	**0.027**
Harvey et al. 2015 (5)	CBT-I/PE	IDS-C; *6FU*	41	-0.67	-1.30 to -0.04	**0.037**
Zhou et al. 2018 (52)	BLT/DL	HDRS	63	-0.57	-1.08 to -0.07	**0.027**
Sit et al. 2018 (51)	BLT/DL	HDRS	40	-0.53	-1.17 to 0.10	0.102
Wu et al. 2009 (61)	TC/TAU	HDRS	44	-0.52	-1.14 to 0.10	0.100
Benedetti et al. 1997 (59)	TSD/Fluoxetine	HDRS	10	-0.51	-1.77 to 0.75	0.436
Wu et al. 2009 (61)	TC/TAU	HDRS; *2FU*	44	-0.51	-1.13 to 0.11	0.107
Harvey et al. 2015 (5)	CBT-I/PE	IDS-C	41	-0.38	-1.00 to 0.24	0.232
Miklowitz et al. 2007 (54)	IPSRT/CC	MADRS	132	-0.15	-0.52 to 0.22	0.435
Miklowitz et al. 2003 (62)	IFIT/CM	SADS-C	82	-0.10	-0.56 to 0.36	0.683
Dauphinais et al. 2012 (48)	BLT/Negative ion therapy	SIGH-ADS	21	0.35	-0.51 to 1.21	0.433
Swartz et al. 2012 (55)	IPSRT/Quetiapine	MADRS	21	0.74	-0.16 to 1.63	0.105
Mania symptom severity						
Henriksen et al. 2016 (58)	BB/CL glasses	YMRS	23	-1.81	-2.78 to -0.84	**<0.001**
Harvey et al. 2015 (5)	CBT-I/PE	YMRS	41	-0.62	-1.24 to 0.01	0.051
Steardo et al. 2020 (7)	IPSRT/TAU	YMRS	44	-0.62	-1.22 to -0.01	**0.044**
Harvey et al. 2015 (5)	CBT-I/PE	YMRS; *6FU*	41	-0.55	-1.17 to 0.08	0.084
Swartz et al. 2012 (55)	IPSRT/Quetiapine	YMRS	21	-0.50	-1.38 to 0.38	0.269
Miklowitz et al. 2003 (62)	IFIT/CM	SADS-C	82	-0.44	-0.90 to 0.03	0.063
Esaki et al. 2020 (56)	BB/CL glasses	YMRS	37	0.04	-0.60 to 0.69	0.911
Dauphinais et al 2012 (48)	BLT/negative ion therapy	YMRS	21	0.17	-0.69 to 1.03	0.712
Miklowitz et al. 2007 (54)	IPSRT/CC	YMRS	132	0.19	-0.18 to 0.55	0.312
Insomnia symptom severity						
Harvey et al. 2015 (5)	CBT-I/PE	ISI	41	-1.35	-2.03 to -0.67	**<0.001**
Harvey et al. 2015 (5)	CBT-I/PE	ISI; *6FU*	41	-1.00	-1.65 to -0.35	**0.003**
Esaki et al. 2020 (56)	BB/CL glasses	ISI	37	-0.24	-0.88 to 0.41	0.475
Chronotype						
Esaki et al. 2020 (56)	BB/CL glasses	MEQ	37	1.03	0.35 to 1.72	**0.003**
Sleep quality and disturbances						
Harvey et al. 2015 (5)	CBT-I/PE	PROMIS-SD	41	-1.07	-1.72 to -0.41	**0.001**
Kupeli et al. 2018 (49)	BLT/DL	PSQI	32	-0.81	-1.53 to -0.09	**0.027**
Harvey et al. 2015 (5)	CBT-I/PE	PSQI	41	-0.80	-1.44 to -0.16	**0.014**
Harvey et al. 2015 (5)	CBT-I/PE	PROMIS-SD; *6FU*	41	-0.68	-1.31 to -0.05	**0.034**
Harvey et al. 2015 (5)	CBT-I/PE	PSQI; *6FU*	41	-0.33	-0.94 to 0.29	0.297
Esaki et al. 2020 (56)	BB/CL glasses	VAS	37	0.30	-0.58 to 1.18	0.514
Sit et al. 2018 (51)	BLT/DL	PSQI	40	-0.12	-0.74 to 0.51	0.720
Sleepiness						

Kaplan et al. 2018 (63)	RISE-UP/PE	Sleepiness in the first hour upon awakening	38	-0.39	-1.04 to 0.25	0.238
Kaplan et al. 2018 (63)	RISE-UP/PE	Sleepiness in the first three hours upon awakening	38	-0.31	-0.95 to 0.33	0.348
Quality of life and Functioning						
Sit et al. 2018 (51)	BLT/DL	GAF	40	0.71	0.07 to 1.36	**0.031**
Harvey et al. 2015 (5)	CBT-I/PE	Q-LES-Q-SF; *6FU*	41	0.24	-0.38 to 0.85	0.453
Harvey et al. 2015 (5)	CBT-I/PE	Q-LES-Q-SF	41	0.001	-0.61 to 0.62	0.998

Abbreviations: BB glasses, Blue-light Blocking glasses; BLT, Bright Light Therapy; CBT-I, Cognitive Behavioural Therapy for Insomnia; CC, Collaborative Care; CI, Confidence Intervals; CL glasses, Clear Lenses glasses; CL, Clinical Management; DL, Dim Light; FU, Follow-Up (the precipitating number indicates months); HDRS, Hamilton Depression Rating Scale; IDS-C, Inventory of Depressive Symptomatology- Clinician version; IFIT, Integrated Family and Individual Therapy; IPSRT, Interpersonal Social Rhythm Therapy; ISI, Insomnia Severity Index; MADRS, Montgomery–Åsberg Depression Rating Scale; MEQ, Morningness-Eveningness Questionnaire; N, number of participants; PE, Psychoeducation; PROMIS-SD, Patient-Reported Outcomes Measurement Information System- Sleep Disturbance; PSQI, Pittsburgh Sleep Quality Index; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SADS-C, Schedule for Affective Disorders and Schizophrenia- Change in symptomatology; SIGH-ADS, Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement; TC, Triple Chronotherapy; VAS, Visual Analogue Scale; YMRS, Young Mania Rating Scale

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