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

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Supplementary Materials – Data Handling

Hedge's g effect sizes and the corresponding 95% confidence intervals for all extracted outcomes were calculated whenever possible. In this review, Hedge's g was consistently calculated as the quotient of the difference in the mean score of the treatment group over the mean score of the control group divided by the pooled weight standard deviation incorporating Bessel's correction. Similar to Cohen's d, Hedge's g effects of 0-0.32 were interpreted as small, 0.33-0.55 as moderate and 0.56-1.2 as large. The effect sizes were calculated using the published means and standard deviations. In cases where other measures of central tendency, such as medians (1), or other measures of dispersion, such as 95% confidence intervals (2) and interquartile ranges (1) were reported, means and standard deviations were estimated as following:

$$sd = \frac{(\mu - CI.lb) * \sqrt{n}}{1.96}$$

$$sd = \sqrt{\frac{1}{12} * \left[\frac{(a - 2m + b)^2}{4} + (b - a)^2\right]}$$

, where μ denotes the mean, CI.lb denotes the lower bound of the confidence interval, and a and b the upper and lower ends of the interquartile end respectively (3). Effect sizes were calculated for all extracted outcomes whenever possible. In instances where there was not enough information to estimate the appropriate effect sizes, the lead or senior author were contacted and asked to disclose the necessary statistics from the published papers. Replies were received from Dr Neşe Yorguner-Kupeli, Prof Ellen Frank, and Prof David Miklowitz. In cases were a reply was not received, means and standard deviations were extracted using PlotDigitizer, a tool approved by the Cochrane Collaboration (4). Means and standard deviations were extracted for Benedetti et al. 1997 (5) and Dauphinais et al. 2012 (6) using PlotDigitizer. This method has been previously validated for use in psychopathology questionnaires in RCTs (9). It is worth noting that differences in Steardo et al. 2020 (8) were

interpreted as favouring the experimental over the control group, in line with the interpretations in-text. This comes in contrast with the information the authors provide in Table 2 of their paper, but this is probably due to a mix-up in a correction the authors provided regarding a typo in said table. An email was sent to the first author, but no reply was received.

Following the estimation of the Hedge's g effect sizes and the associated 95% confidence intervals, the resulting significance level was calculated. In all instances, "significant" results denote those where the difference in means was associated with a p of less than 0.05. The formula used for the significance level estimations was derived from Altman and Bland 2011 (10):

$$se = \frac{CI.ub - CI.lb}{2 * 1.96}$$

$$z = |\frac{Hedge's\ g\ effect\ size}{se}|$$

$$p - value = exp * (-0.7178 * z - 0.416 * z^2)$$

, where CI.ub and CI.lb denote the upper and lower bounds of the confidence interval, respectively, and exp denotes the exponential function.

Consistent with pre-registered plans, random-effects models were implemented when at least five studies delivered the same intervention and measured the same outcome. All analyses were performed in the software R, version 3.6.0 using the *tidyverse* and *metafor* packages. All analyses and datasets are available on the following Open Science Framnework page: https://osf.io/gv3pe/

References

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Supplementary Table 1. Safety assessment reporting of the included studies

Study	Treatment /Control	Safety Assessment
Bright Light Therapy		
Dauphinais et al. 2012 (48)	BLT/Negative ion therapy	No SAEs. 2 drop-outs due to hypomania (1 BLT and 1 Negative ion therapy). No significant* differences in AEs between BLT and negative ion therapy as measured by SAFTEE. AEs included headache (11 BLT and 10 Negative ion therapy), hypomania (4 BLT and 2 Negative ion therapy), and irritability (3 BLT and 1 Negative Ion Therapy)
Franchini et al. 2009 (47)	BLT/Fluvoxamine	No drop-outs due to AEs or side-effects
Kupeli et al. 2018 (49)	BLT/DL	No drop-outs due to AEs or side-effects and no switch to mania or hypomania in either group. Side effects included insomnia (1 BLT), headache (2 BLT 2 DL), and nausea (1 DL). No significant* differences between BLT and DL measures by SERS
Rosenthal et al. 1984 (50)	BLT/DL	*"hypomanic irritability and hyperactivity in a few cases with bright lights"*
Sit et al. 2018 (51)	BLT/DL	No SAEs. Infrequent worsening of symptoms in both groups, but less excessive sleepiness in BLT compared to DL
Zhou et al. 2018 (52)	BLT/DL	No SAEs. No significant* differences in AEs between BLT and DL as measured by SERS. AEs included dizziness (1 BLT), fatigue (1 BLT), and sleep disturbances (2 BLT)
Interpersonal Social Rhythms Therapy		
Frank et al. 2005 (53)	IPSRT/ICM	No information provided
Miklowitz et al. 2007 (54)	IPSRT/CC	No information provided
Steardo et al. 2020 (7)	IPSRT/TAU	No information provided. *"The intervention was well-received by patients…"*
Swartz et al. 2012 (55)	IPSRT/Quetiapine	No information provided
Blue-light Blocking Glasses		
Esaki et al. 2020 (56)	BB/CL glasses	One drop-out because of the intervention in BB glasses, and 4 AEs recorded in the same group. No information provided about CL glasses group
Henriksen et al. 2016 (58)	BB/CL glasses	Side effects included emerging depressive symptoms (2 in BB glasses) but no switch to depressive phase, headache (1 in BB glasses and 3 in CL glasses)
Henriksen et al. 2020 (57)	BB/CL glasses	Safety details reported in Henriksen et al. 2016
Cognitive Behavioural Therapy for Insomnia		
Harvey et al. 2015 (5)	CBT-I/PE	Side effects included increase in depressive symptoms in the mild to moderate range (5 in CBT-I and 12 in PE) or the severe range (3 in CBT-I and 3 in PE), increase in manic symptoms in the severe range (1 in CBT-I and 1 in PE), voluntarily hospitalisation for a transient amnestic episode (1 in CBT-I), and voluntarily hospitalisation for suicide ideation (1 in PE)
Total Sleep Deprivation		
Benedetti et al. 1997 (59)	TSD/Fluoxetine	No information provided
Combination Treatments		
Colombo et al. 2000 (60)	TSD + (no) lithium + red/white/ambient light	No information provided but 7 patients switched polarity (3 in TSD + lithium + red light, 2 TSD + red, and 2 TSD + white)
Kaplan et al. 2018 (63)	RISE-UP/PE	Safety details reported in Harvey et al. 2015
Miklowitz et al. 2003 (62)	IFIT/CM	No information provided
Wu et al. 2009 (61)	TC/TAU	AEs included brief switches to hypomanic episodes (2 in TC)

* significance as reported by the original paper

Abbreviations: AEs, Adverse Events; BB glasses, Blue-light Blocking glasses; BLT, Bright Light Therapy; CBT-I, Cognitive Behavioural Therapy for Insomnia; CC, Collaborative Care; CL glasses, Clear Lenses glasses; CM, Clinical Management; DL, Dim Light; ICM, Intensive Clinical Management; IFIT, Integrated Family and Individual Therapy; IPSRT, Interpersonal and Social Rhythm Therapy, PE, Psychoeducation; SAEs, Serious Adverse Events; SAFTEE, Systematic Assessment for Treatment Emergent Effects; SERS, Side Effects Rating Scale; TAU, Treatment as Usual; TC, Triple Chronotherapy; TSD, Total Sleep Deprivation

Supplementary 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
Activity levels						
Henriksen et al. 2020 (57)	BB/CL glasses	Activity counts per epoch	20	-0.98	-1.91 to -0.05	**0.039**
Kaplan et al. 2018 (63)	RISE-UP/PE	Activity in the first hour upon awakening	38	0.66	0.01 to 1.32	**0.048**
Sleep Onset Latency						
Harvey et al. 2015 (5)	CBT-I/PE	Sleep diaries	41	-0.47	-1.09 to 0.15	0.138
Harvey et al. 2015 (5)	CBT-I/PE	Sleep diaries; *6FU*	41	-0.14	-0.76 to 0.47	0.668
Esaki et al. 2020 (56)	BB/CL glasses	Actigraphy	37	1.32	0.61 to 2.03	**<0.001**
Wake After Sleep Onset						
Henriksen et al. 2020 (57)	BB/CL glasses	Actigraphy	20	-1.12	-2.06 to -0.17	**0.020**
Harvey et al. 2015 (5)	CBT-I/PE	Sleep diaries; *6FU*	41	-0.26	-0.87 to 0.36	0.415
Harvey et al. 2015 (5)	CBT-I/PE	Sleep diaries	41	0.03	-0.58 to 0.65	0.930
Esaki et al. 2020 (56)	BB/CL glasses	Actigraphy	37	0.18	-0.47 to 0.83	0.599
Sleep Efficiency						
Henriksen et al. 2020 (57)	BB/CL glasses	Actigraphy	20	1.00	0.07 to 1.93	**0.035**
Harvey et al. 2015 (5)	CBT-I/PE	Sleep diaries; *6FU*	41	0.66	0.03 to 1.29	**0.040**
Harvey et al. 2015 (5)	CBT-I/PE	Sleep diaries	41	0.34	-0.28 to 0.96	0.286
Esaki et al. 2020 (56)	BB/CL glasses	Sleep diaries	37	-0.83	-1.50 to -0.16	**0.015**
Total Sleep Time						
Henriksen et al. 2020 (57)	BB/CL glasses	Actigraphy	20	0.68	-0.22 to 1.58	0.139
Esaki et al. 2020 (56)	BB/CL glasses	Actigraphy	37	0.25	-0.40 to 0.89	0.456
Harvey et al. 2015 (5)	CBT-I/PE	Sleep diaries; 6*FU*	41	0.08	-0.54 to 0.69	0.811
Harvey et al. 2015 (5)	CBT-I/PE	Sleep diaries	41	-0.06	-0.68 to 0.55	0.859
Total Wake Time						
Harvey et al. 2015 (5)	CBT-I/PE	Sleep diaries	41	-0.48	-1.11 to 0.14	0.132
Harvey et al. 2015 (5)	CBT-I/PE	Sleep diaries; *6FU*	41	-0.48	-1.10 to 0.15	0.132
Time in bed						
Harvey et al. 2015 (5)	CBT-I/PE	Sleep diaries	41	-0.33	-0.95 to 0.28	0.297
Harvey et al. 2015 (5)	CBT-I/PE	Sleep diaries; *6FU*	41	-0.21	-0.83 to 0.40	0.514
Sleep inertia						
Kaplan et al. 2018 (63)	RISE-UP/PE	Sleep diaries	38	0.22	-0.42 to 0.86	0.511
Psychosis						
Sit et al. 2018 (51)	BLT/DL	BPRS	40	-0.85	-1.50 to -0.20	**0.010**
Anxiety						
Sit et al. 2018 (51)	BLT/DL	HDRS-anxiety	40	-0.49	-1.13 to 0.14	0.131

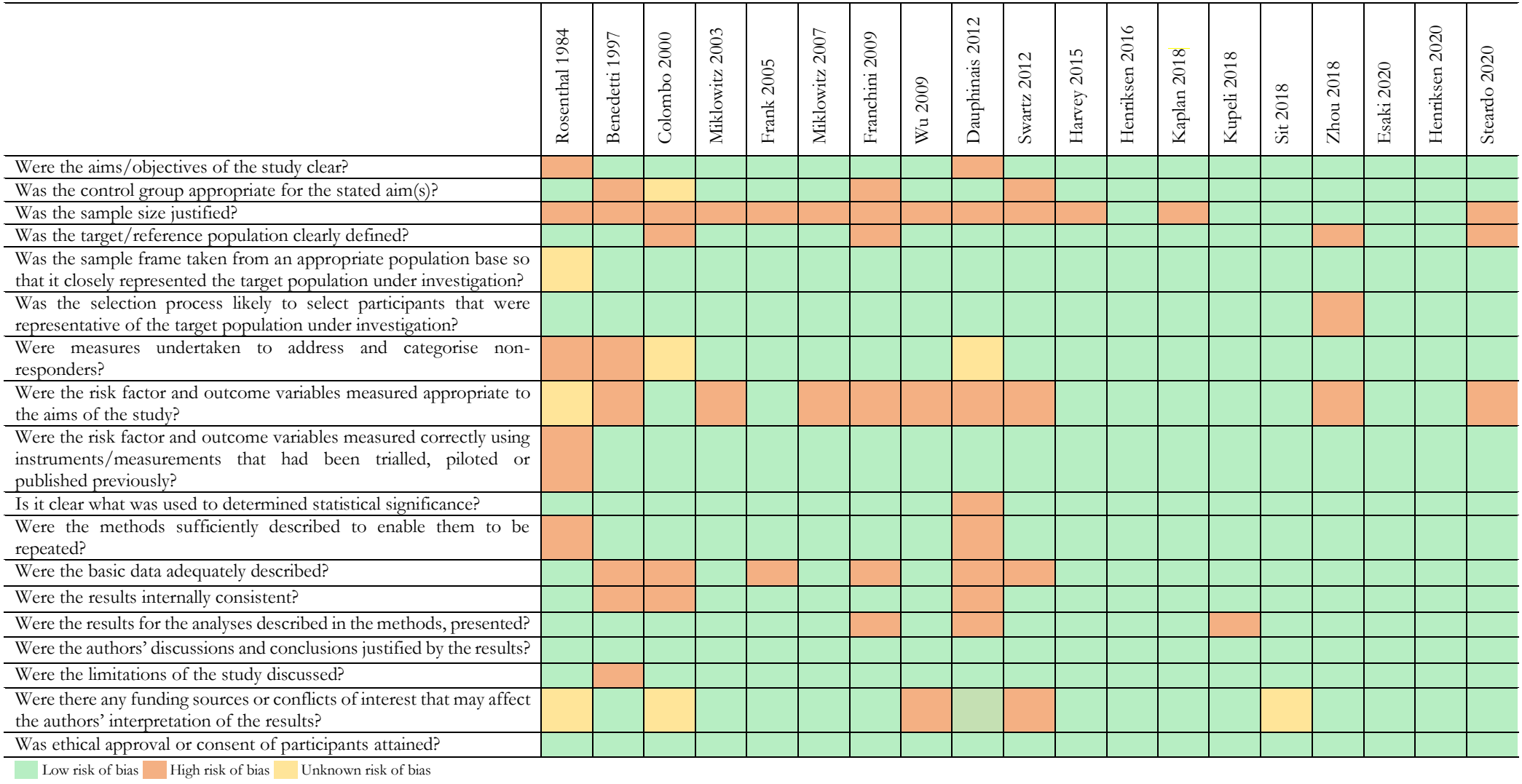
Abbreviations: BB glasses, Blue-light Blocking glasses; BLT, Bright Light Therapy; BPRS, Brief Psychiatric Rating Scale; CBT-I, Cognitive Behavioural Therapy for Insomnia; CI, Confidence Intervals; CL glasses, Clear Lenses glasses; DL, Dim Light; FU, Follow-Up (the precipitating number indicates months); HDRS, Hamilton Depression Rating Scale; N, number of participants; PE, Psychoeducation

Supplementary Table 3. AXIS risk of bias appraisal - total percentage scores

Were the aims/objectives of the study clear?	10.5		89.5
Was the control group appropriate for the stated aim(s)?	15.5	5	
Was the sample size justified?	68.5		31.5
Was the target/reference population clearly defined?	21		79
Was the sample frame taken from an appropriate population base so that it closely represented the target population under investigation?		5	95
Was the selection process likely to select participants that were representative of the target population under investigation?	5		95
Were measures undertaken to address and categorise non-responders?	10.5	10.5	79
Were the risk factor and outcome variables measured appropriate to the aims of the study?	47.5	5	47.5
Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?	5		95
Is it clear what was used to determined statistical significance?		5	95
Were the methods sufficiently described to enable them to be repeated?	10.5		89.5
Were the basic data adequately described?	31.5		68.5
Were the results internally consistent?	15.5		84.5
Were the results for the analyses described in the methods, presented?	15.5		84.5
Were the authors' discussions and conclusions justified by the results?			100
Were the limitations of the study discussed?		5	95
Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	10.5	15.5	74
Was ethical approval or consent of participants attained?			100

Low risk of bias | High risk of bias | Unknown risk of bias

Supplementary Table 4. Quality assessment table using the AXIS tool (Downess 2010)



Supplementary Figure 1. Funnel plot for studies examining the effect of Bright Light Therapy in bipolar depression