JAMA Psychiatry | Original Investigation

Bright Light Therapy for Nonseasonal Depressive Disorders
A Systematic Review and Meta-Analysis

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IMPORTANCE Seasonal humor disorders are prone to have a link with daylight exposure. However, the effect of external light on nonseasonal disorders remains unclear. Evidence is lacking for the validity of bright light therapy (BLT) as an adjunctive treatment for these patients.

OBJECTIVE To assess BLT effectiveness as an adjunctive treatment for nonseasonal depressive disorders.

DATA SOURCES In March 2024, a comprehensive search was performed of publications in the MEDLINE, Embase, and Cochrane databases for randomized clinical trials (RCTs) evaluating BLT effects in patients with nonseasonal depression.

STUDY SELECTION RCTs published since 2000 were eligible. Comparisons between BLT and dim red light or antidepressant monotherapy alone were considered for inclusion.

DATA EXTRACTION AND SYNTHESIS Using the systematic review approach on RCTs published from January 1, 2000, through March 25, 2024, differences between patients treated with and without BLT were estimated using the Mantel-Haenszel method; heterogeneity was assessed using I^2 statistics.

MAIN OUTCOMES AND MEASURES Remission of symptoms, response to treatment rates, and depression scales were assessed.

RESULTS In this systematic review and meta-analysis of 11 unique trials with data from 858 patients (649 female [75.6%]), statistically significant better remission and response rates were found in the BLT group (remission: 40.7% vs 23.5%; odds ratio [OR], 2.42; 95% CI, 1.50-3.91; P <.001; I^2 = 21%; response: 60.4% vs 38.6%; OR, 2.34; 95% CI, 1.46-3.75; P <.001; I^2 = 41%). With BLT, subgroup analysis based on follow-up times also showed better remission (<4 weeks: 27.4% vs 9.2%; OR, 3.59; 95% CI, 1.45-8.88; P = .005; I^2 = 0% and >4 weeks: 46.6% vs 29.1%; OR, 2.18; 95% CI, 1.19-4.00; P = .01; I^2 = 47%) and response (<4 weeks: 55.6% vs 27.4%; OR, 3.65; 95% CI, 1.81-7.33; P <.001; I^2 = 35% and >4 weeks: 63.0% vs 44.9%; OR, 1.79; 95% CI, 1.01-3.17; P = .04; I^2 = 32%) rates.

CONCLUSIONS AND RELEVANCE Results of this systematic review and meta-analysis reveal that BLT was an effective adjunctive treatment for nonseasonal depressive disorders. Additionally, results suggest that BLT may improve the response time to the initial treatment.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2024.2871
Published online October 2, 2024.

Supplemental content

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Major depressive disorder (MDD) is currently the leading cause of functional disability and one of the most critical mental health issues.[1] The estimated response rate to initial treatment is approximately 50%, requiring alternative treatments when the initial approach is insufficient after 4 to 8 weeks.[2] Given this, bright light therapy (BLT) has been studied as a potential adjunctive treatment for MDD, as light exposure is well understood to affect human mood and cognitive function.[3,4] This effect may arise from retinal ganglion cells, which extend their axons across brain areas involved in mood regulation, including the amygdala, the suprachiasmatic nucleus, and the dorsal raphe nucleus.[5-9] Conversely, the efficacy of BLT as an adjunctive treatment is established only for seasonal depressive disorders. Previous meta-analyses on the subject showed inconclusive results compromised by very small sample sizes and a limited set of statistical analyses.[10,11]

Several trials have been conducted in recent years assessing BLT in nonseasonal depressive disorders.[6,12-21] Seven new relevant studies[6,12-16,18] comprising nearly 3 times the sample size of the most similar previous meta-analyses have been added to the literature, possibly adding important insights to the body of evidence. Because BLT may be able to serve as a low-cost adjunctive treatment option for MDD, we aimed to investigate whether BLT is effective in nonseasonal depressive disorders by assessing its outcomes in a more comprehensive analysis and an extensive subset of statistical analyses.

Key Points

Question Is bright light therapy (BLT) an effective adjunctive treatment for nonseasonal depressive disorders?

Findings In this systematic review and meta-analysis of 11 unique trials with data from 858 patients, statistically significant better remission and response rates were found in the BLT group. Subgroup analysis based on follow-up times also showed better remission and response rates with BLT.

Meaning These findings suggest that BLT was an effective adjunctive treatment for nonseasonal depressive disorders, and the response time to the initial treatment may be improved with the addition of BLT.

Methods

Design

This systematic review and meta-analysis was performed in accordance with the Cochrane Handbook[22] for Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[23,24] reporting guidelines.

Search Strategy

The research protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024531310).[23] MEDLINE, Embase, SCOPUS, Web of Science, PsycINFO, and Cochrane Central Register of Controlled Trials were systematically searched from inception to March 25, 2024, with the following search strategy: "bright light" AND ("unipolar" OR "bipolar" OR "depression" OR "depressive") AND ("augmentation" OR "adjunctive" OR "adjunct" OR "add-on"). More information on search strategy is available in eTable 1 in Supplement 1. The chosen databases provide comprehensive coverage across various disciplines and study designs pertinent to the research question. MEDLINE and Embase offer medical and biomedical literature, SCOPUS and Web of Science cover multidisciplinary fields, the Cochrane Library is crucial for identifying clinical trials, and PsycINFO focuses on psychological and behavioral sciences. After removing duplicates, 2 authors (F.T. and C.M.) independently screened titles and abstracts. They evaluated the studies in full for eligibility, while 1 author (A.M.A.) screened titles to resolve possible disagreements. We also reviewed the references of selected articles to identify any relevant additional publications.

Selection Criteria and Data Extraction

Eligibility criteria were as follows: (1) randomized clinical trials; (2) comparison of BLT alone or BLT plus antidepressant with placebo, antidepressant monotherapy, or dim red light; (3) patients with any type of nonseasonal depressive disorders; and (4) a report of at least 1 relevant outcome (eTable 2 in Supplement 1). We only included studies published after the year 2000. Exclusion criteria were (1) absence of a control group, (2) non-English language, and (3) conference abstracts. Patient race and ethnicity information was not included in the analysis, as not all of the included studies provided these data.

Three authors (A.M.A., M.E.C., and J.H.C.O.C.) independently conducted data extraction, collecting the following information from each study: study population, number of patients, sex distribution, age (years), control group, and BLT characteristics of the intervention group. Quality control was applied to check if the generated raw data were in accordance with the original data provided in each study to reduce biases in data extraction.

End Points and Definitions

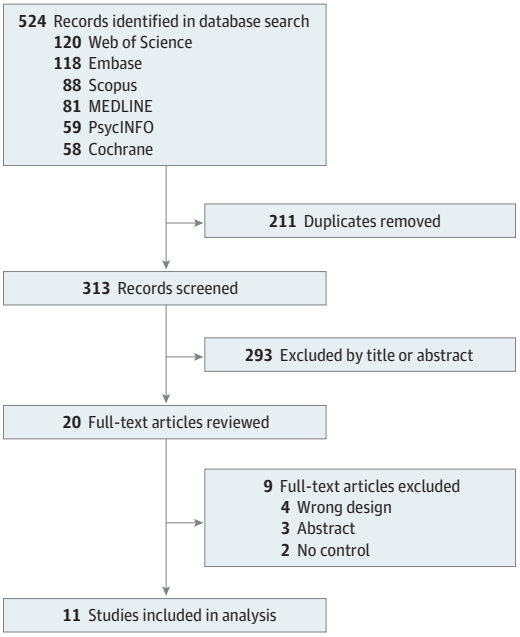
The primary outcome was the response to treatment and the remission of the symptoms. Secondary outcomes were composed of scales, including the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Clinical Global Impressions Scale (CGI). Additionally, we performed a subgroup analysis stratified by different follow-up times for both remission and response rates.

BLT was defined as using a fluorescent light box that produces white light for at least 30 minutes, the commonly used range is 10 000 lux.

Quality Assessment

Assessment of risk of bias in individual studies was conducted using the Cochrane Risk of Bias tool for randomized trials. Two independent authors (A.M.A. and M.E.C.) evaluated the bias risk of each study and documented their observations. This dual approach enhances the credibility of the results by reducing the likelihood of assessment bias and promoting a comprehensive and impartial analysis. Disagreements were resolved through discussion and consensus.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram With Systematic Review of Detailed Searches



Statistical Analysis

We used R Studio software, version 4.3.2 (R Project for Statistical Computing) and extension package meta for all statistical analyses. Binary outcomes were analyzed using odds ratio (OR), whereas continuous outcomes were assessed through mean difference (MD) or standard mean difference (SMD), both using 95% CIs to reduce potential bias. Statistical significance was set as *P* values <.05. Heterogeneity was examined using the I^2 statistics with 95% CIs, and significance was attributed to cases with I^2 >25%.[25] For all outcomes, the Mantel-Haenszel random-effects model was applied. Meta-regression analysis was assessed to evaluate a possible link between the age at onset of MDD or duration of MDD and remission and response rates.

Results

Search Results and Baseline Characteristics

As shown in the PRISMA flow diagram (**Figure 1**), the initial search yielded 257 results. After the removal of duplicate records and exclusions based on title and abstract, 114 articles were fully reviewed. A total of 13 RCTs were initially included. Of these studies, 11 reported comparable outcomes, comprising 858 patients, and the remaining 2 studies were excluded for not matching outcomes with the other included studies. In this systematic review and meta-analysis of 11 unique trials[6,12-21] with data from 858 patients (649 female [75.6%]; 209 male [24.4%]), a total of 426 patients (52.3%) received BLT, and 389 patients (47.7%) constituted the control group. Study characteristics are reported in the **Table**; 9 studies[6,12-19] exposed the intervention group to 10 000 lux 30 to 60 minutes daily, 1 study[21] used 7000 lux, and 1 study[20] used 5000 lux BLT.

Pooled Analysis of All Studies

Remission and Response

Eight RCTs[12,14-19,21] reported the remission rate of symptoms. Among patients with nonseasonal depressive disorders, the estimated remission rate was statistically significantly higher in the BLT group (40.7% vs 23.5%; OR, 2.42; 95% CI, 1.50-3.91; *P* <.001; I^2 = 21%) (**Figure 2**A). The response rate showed a similar tendency toward the BLT group (60.4% vs 38.6%; OR, 2.34; 95% CI, 1.46-3.75; *P* <.001; I^2 = 41%) (Figure 2B).

Subgroup Analysis Based on Duration of Follow-Up

Remission in Less Than 4 Weeks and Greater Than 4 Weeks

In the subgroup of studies reporting data on remission rate in up to 4 weeks of follow-up after treatment, BLT was favored with statistically significant differences between groups (<4 weeks: 27.4% vs 9.2%; OR, 3.59; 95% CI, 1.45-8.88; *P* = .005; I^2 = 0%) (**Figure 3**A). The same tendency was observed in a follow-up time of more than 4 weeks (>4 weeks: 46.6% vs 29.1%; OR, 2.18; 95% CI, 1.19-4.00; *P* = .01; I^2 = 47%) (Figure 3B).

Response in Less Than 4 Weeks and Greater Than 4 Weeks

The response rate in up to 4 weeks of follow-up also favored the BLT group (<4 weeks: 55.6% vs 27.4%; OR, 3.65; 95% CI, 1.81-7.33; *P* <.001; I^2 = 35%) (Figure 3C). Similarly, the subgroup with more than 4 weeks of follow-up significantly tended toward the BLT group concerning response rate (>4 weeks: 63.0% vs 44.9%; OR, 1.79; 95% CI, 1.01-3.17; *P* = .04; I^2 = 32%) (Figure 3D).

Depression Assessment Scales

HAM-D score had a significantly greater reduction in the BLT group than in the control group (MD, −1.44; 95% CI, −2.40 to −0.48; *P* = .003; I^2 = 0%) (**Figure 4**A). CGI and MADRS scores did not show statistically significant differences between groups (MD, −0.06; 95% CI, −0.29 to 0.16; *P* = .56; I^2 = 0%) (Figure 4B) and (MD, 0.36; 95% CI, −2.60 to 3.31; *P* = .81; I^2 = 23%) (Figure 4C), respectively.

Meta-Regression of Age at Onset of MDD vs Remission Rate

The meta-regression evaluating the relationship between remission rate and the age at onset of MDD reached a threshold *P* value in the test of moderators (*P* = .06), meaning that there is a possibility of a true link between the covariate and the outcome, even though the available data are insufficient to determine this connection. Figure 4D details the bubble plot generated by this analysis. The following meta-regression analysis did not reach significant or threshold *P* values: (1) age at onset of MDD and response rate, (2) duration of MDD and response rate, and (3) duration of MDD and remission rate.

Quality Assessment

The individual assessment of each of the RCTs included in the meta-analysis is depicted in eFigure 1 in Supplement 1. Overall, all RCTs were deemed at low risk of bias. The mostly symmetrical distribution of comparable studies depicted in the fun-

Table. Baseline Characteristics of Included Studies

Source	IG/CG		Type of depressive disorder	Intervention treatment	Control treatment	Disease severity	Criteria for response	Criteria for remission
	No. of participants	Age, mean (SD), y						
Chan et al,[16] 2022	47/46	47.4 (11.4)/45.4 (12.0)	Unipolar major depressive disorder	10 000-lux BLT 30 min/daily (in habitual baseline wake time of the patient) for 5 wk	50-lux Dim red light	Only moderate	NA	17-HDS ≤7
Chen et al,[15] 2022	22/21	47.1 (15.0)/42.8 (14.3)	Major depressive disorder	10 000-lux BLT 30 min/daily (after being awake and before 09:00) for 4 wk	70-lux Dim red light	Mild, moderate, or severe	≥50% Reduction on HAM-D 17	HAM-D 17 ≤7
Chojnacka et al,[17] 2016	52/43	53.7 (14.5)/51.9 (12.9)	Major depressive disorder	10 000-lux BLT 30 min/daily (after awake and between 08:00 and 09:00) for 2 wk	Negative ion generator	Moderate or severe	≥50% Reduction on HDRS-21	HDRS-21 ≤8
Fregna et al,[13] 2024	55/29	56.84 (11.22)/ 59.65 (14.86)	Major depressive disorder	10 000-lux BLT 30 min/daily for 4 wk	Negative ion generator (sham BLT)	Mild, moderate, or severe	≥50% Reduction on HDRS	NA
Ioannou et al,[18] 2021	16/17	31.3 (13.1)/29.0 (8.6)	Major depressive disorder and bipolar disorder	10 000-lux BLT 30 min/daily for 1 wk	Antidepressant	Only high severity	≥50% Reduction on MADRS-S	MADRS-S ≤10
Martiny et al,[19] 2005	48/54	43.1 (15.8)/45.9 (16.1)	Major depressive disorder	10 000-lux BLT 60 min/daily for 5 wk	50-lux Dim red light	Only severe	≥50% Reduction on HAM-D6	HAM-D 6 ≤4
Sit et al,[21] 2018	23/23	45.7 (14.3)/43.7 (15.0)	Bipolar depressive disorder	7000-lux BLT 60 min/daily for 6 wk	50-lux Dim red light	Only moderate	≥50% reduction on SIGH-ADS	SIGH-ADS ≤8
Yorguner Küpeli et al,[14] 2018	16/16	42.1 (9.1)/37.1 (8.2)	Bipolar depressive disorder	10 000-lux BLT 30 min/daily for 2 wk	<500-lux Dim red light	Moderate or severe	HAM-D scores (not specified)	HAM-D scores (not specified)
Zhou et al,[20] 2018	33/30	35.09 (14.19)/ 39.73 (13.53)	Bipolar depressive disorder	5000-lux BLT 30 min/daily for 2 wk	<100-lux Dim red light	Moderate or severe	≥50% Reduction on HAM-D 17	NA
Legenbauer et al,[12] 2024	114/110	15.5 (1.4)/<18y	Major depressive disorder	10 000-lux BLT 30 min/daily for 4 wk	100-lux Dim red light	Moderate or severe	50% Reduction on BDI-II	BDI-II ≤19 and CGI ≤2
Huang et al,[6] 2022	22/21	47.09 (15.03)/ 42.76 (14.30)	Major depressive disorder	10 000-lux BLT 30 min/daily for 4 wk	70-lux Dim red light	Mild, moderate, or severe	NA	NA

Abbreviations: BLT, bright light therapy; CG, control group; HAM-D, Hamilton Rating Scale for Depression; HDRS, Hamilton Rating Scale for Depression; HDS, Hamilton Depression Score; IG, intervention group; MADRS-S, Montgomery-Åsberg Depression Rating Scale–Self-Assessment; NA, not available; SIGH-ADS, Structured Interview Guide for the Hamilton Depression Rating Scale With Atypical Depression.

nel plot in eFigure 2 in Supplement 1 suggests a low probability of publication bias affecting the general results of remission and response rates.

Discussion

In this systematic review and meta-analysis, the estimated response rate to treatment with BLT in patients with nonseasonal depressive disorders was 40%, whereas that of the control group was 23%. Patients treated with BLT had a significantly higher remission rate, as well as a greater reduction in HAM-D score. Differences regarding follow-up time were examined in subgroup analysis of remission and response rates based on the duration of follow-up (<4 weeks; >4 weeks), which also favored the BLT group.

Seasonal affective disorders comprise a subgroup of affective disorders with a considerable reactivity to environmental factors, eg, climate, luminous exposure, and latitude, and all have been found to be treatable with BLT.[26-30] Although the effectiveness of BLT in nonseasonal depressive disorders has previously been explored in meta-analyses,[10,11] to our knowledge, none of them had sufficient power to derive a formal recommendation. Additionally, this is the first study, to our knowledge, to derive a more comprehensive review including the 2 subtypes of MDD, the unipolar form and the bipolar type. Despite reporting general results tending in favor of BLT, previous studies had insufficient statistical power to ascertain a strong conclusion due to restricted sample size and poor analytical methods. Recent studies have proposed new approach techniques to investigate the BLT mechanism of action. Huang et al[6] are notable to be the only study in our meta-analysis that linked depression score outcomes to imaging methods. A combination of measuring outcomes by assessing HAM-D change from baseline and magnetic resonance imaging scans at the end of the follow-up demonstrated an increased intranetwork functional connectivity in various pathways mentioned in studies of psychiatric disorders to be responsible for detecting, integrating, and filtering emotional information.[6,31] Their results strengthen the correlation between BLT and mood modulation and impact directly on our general results conclusion.

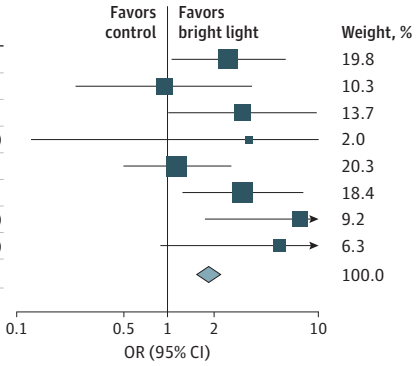
The primary supportive argument in favor of using bright light as an adjunctive treatment is the cost. Even though out-

Figure 2. Forest Plot of Remission Rate and Response to Treatment Outcomes

A Remission rate

Source	Bright light, No. Events	Bright light, No. Total	Control, No. Events	Control, No. Total	OR (95% CI)	Weight, %
Chan et al,[16] 2022	32	47	21	46	2.54 (1.09-5.91)	19.8
Chen et al,[15] 2022	6	22	6	21	0.94 (0.25-3.56)	10.3
Chojnacka et al,[17] 2016	15	52	5	43	3.08 (1.02-9.34)	13.7
Ioannou et al,[18] 2021	1	16	0	17	3.39 (0.13-89.37)	2.0
Legenbauer et al,[12] 2024	16	52	16	57	1.14 (0.50-2.60)	20.3
Martiny et al,[19] 2005	20	48	10	54	3.14 (1.28-7.69)	18.4
Sit et al,[21] 2018	15	22	4	18	7.50 (1.80-31.28)	9.2
Yorguner Küpeli et al,[14] 2018	7	16	2	16	5.44 (0.92-32.31)	6.3
Total	112	275	64	272	2.42 (1.50-3.91)	100.0

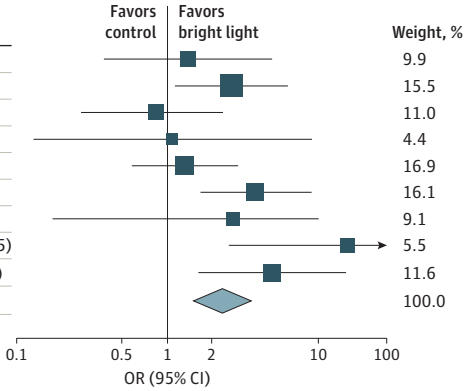
Heterogeneity: $\tau^2 = 0.1144$; $\chi^2_7 = 8.89$ ($P = .26$); $I^2 = 21\%$
Test for overall effect: $z = 3.64$ ($P < .001$)



B Response to treatment

Source	Bright light, No. Events	Bright light, No. Total	Control, No. Events	Control, No. Total	OR (95% CI)	Weight, %
Chan et al,[16] 2022	9	22	7	21	1.38 (0.40-4.80)	9.9
Chojnacka et al,[17] 2016	26	52	12	43	2.58 (1.09-6.10)	15.5
Fregna et,[13] 2024	55	66	29	34	0.86 (0.27-2.72)	11.0
Ioannou et al,[18] 2021	2	16	2	17	1.07 (0.13-8.67)	4.4
Legenbauer et al,[12] 2024	19	53	18	60	1.30 (0.59-2.87)	16.9
Martiny et al,[19] 2005	34	48	21	54	3.82 (1.67-8.74)	16.1
Sit et al,[21] 2018	16	22	9	18	2.67 (0.71-9.95)	9.1
Yorguner Küpeli et al,[14] 2018	11	16	2	16	15.40 (2.50-95.05)	5.5
Zhou et al,[20] 2018	26	33	13	30	4.86 (1.61-14.64)	11.6
Total	198	328	113	293	2.34 (1.46-3.75)	100.0

Heterogeneity: $\tau^2 = 0.1798$; $\chi^2_8 = 13.46$ ($P = .10$); $I^2 = 41\%$
Test for overall effect: $z = 3.54$ ($P < .001$)



A, Remission rate. B, Response to treatment. The size of the data markers (squares) corresponds to the weight of the study in the meta-analysis. OR indicates odds ratio.

patient treatment costs with antidepressants are widely variable, exposure to external light generally involves no costs or limitations, which reinforces the need to firm BLT as an efficient adjunctive treatment for nonseasonal depressive disorders. In contrast, geographic location may impact photoperiod daylight and thus compromise the utilization of natural light after seasonal changes. Regardless of the majority of included trials being conducted in the northern hemisphere, there are crescent data of studies enrolled in a subtropical environment, which experiences unequal daylight duration throughout the year in comparison to those in a temperate zone.[6,15,16,20] Additionally, each study defined response and remission rates using different depression scores, the most frequently seen was the HAM-D variations, in addition to the inclusion of variable disorder severity. Consequently, the pooled analysis evaluating remission and response rates was expected to result in some level of resultant heterogeneity. Overall, ORs on remission and response rates tended to reveal greater effectiveness in the BLT group, with low and moderate heterogeneity among trials (21% and 41%, respectively). In general, these differences regarding the study location of enrollment did not seem to have a great impact on patients' comparability, which also contributes to strengthening the positive association of BLT in MDD; BLT may be able to serve as an adjunctive treatment in several locations around the globe and, consequently, in the more diverse economic environments.

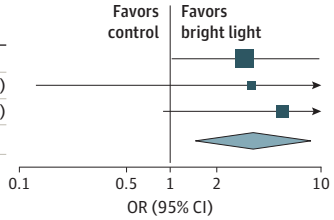
One trial can be seen as an outlier; Legenbauer et al[12] proposed an investigation of BLT effectiveness as an inpatient treatment for adolescents with MDD, whereas all other included studies were conducted in an outpatient setting, which may directly impact their results. Their findings, therefore, do not support group differences regarding depressive symptoms treated with BLT. Additionally, despite randomizing the largest sample size to date in a trial with the referred purpose, the discontinuation of participants during the follow-up time accounted for more than 50% of the initial randomized population. Certainly, this discrepancy may be correlated with the characteristics of included patients, which were mainly composed of inpatient adolescents with severe depression, differing from most of the included studies that included patients with moderate or mild depression in the outpatient setting. In contrast with adult literature, previous studies focusing on younger patients have underpowered generalizability due to poor evidence base owing to small sample sizes, reports, and trials with no control group.[32-34] Conversely, inpatient stud-

Figure 3. Forest Plot of Remission Rate and Response to Treatment Less Than and Greater Than 4 Weeks

A Remission rate in <4 wk

Source	Bright light, No. Events	Bright light, No. Total	Control, No. Events	Control, No. Total	OR (95% CI)	Weight, %
Chojnacka et al,[17] 2016	15	52	5	43	3.08 (1.02-9.34)	66.6
Ioannou et al,[18] 2021	1	16	0	17	3.39 (0.13-89.37)	7.6
Yorguner Küpeli et al,[14] 2018	7	16	2	16	5.44 (0.92-32.31)	25.8
Total	23	84	7	76	3.59 (1.45-8.88)	100.0

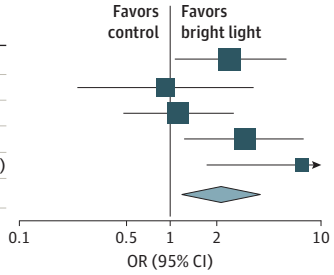
Heterogeneity: $\tau^2 = 0$; $\chi^2_2 = 0.28$ ($P = .87$); $I^2 = 0\%$
Test for overall effect: $z = 2.77$ ($P = .006$)



B Remission rate in >4 wk

Source	Bright light, No. Events	Bright light, No. Total	Control, No. Events	Control, No. Total	OR (95% CI)	Weight, %
Chan et al,[16] 2022	32	47	21	46	2.54 (1.09-5.91)	24.5
Chen et al,[15] 2022	6	22	6	21	0.94 (0.25-3.56)	14.3
Legenbauer et al,[12] 2024	16	52	16	57	1.14 (0.50-2.60)	25.0
Martiny et al,[19] 2005	20	48	10	54	3.14 (1.28-7.69)	23.1
Sit et al,[21] 2018	15	22	4	18	7.50 (1.80-31.28)	13.0
Total	89	191	57	196	2.18 (1.19-4.00)	100.0

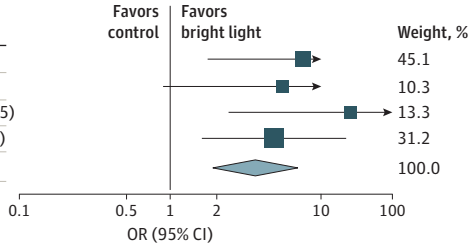
Heterogeneity: $\tau^2 = 0.2063$; $\chi^2_4 = 7.54$ ($P = .11$); $I^2 = 47\%$
Test for overall effect: $z = 2.51$ ($P = .01$)



C Response to treatment in <4 wk

Source	Bright light, No. Events	Bright light, No. Total	Control, No. Events	Control, No. Total	OR (95% CI)	Weight, %
Chojnacka et al,[17] 2016	26	52	12	43	2.58 (1.09-6.10)	45.1
Ioannou et al,[18] 2021	2	16	2	17	1.07 (0.13-8.67)	10.3
Yorguner Küpeli et al,[14] 2018	11	16	2	16	15.40 (2.50-95.05)	13.3
Zhou et al,[20] 2018	26	33	13	30	4.86 (1.61-14.64)	31.2
Total	65	117	29	106	3.65 (1.81-7.33)	100.0

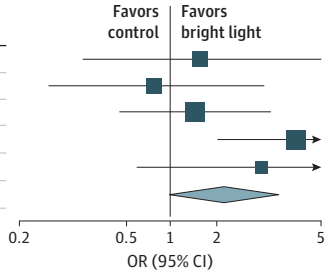
Heterogeneity: $\tau^2 = 0.0890$; $\chi^2_3 = 4.59$ ($P = .20$); $I^2 = 35\%$
Test for overall effect: $z = 3.63$ ($P < .001$)



D Response to treatment in >4 wk

Source	Bright light, No. Events	Bright light, No. Total	Control, No. Events	Control, No. Total	OR (95% CI)	Weight, %
Chen et al,[15] 2022	9	22	7	21	1.38 (0.40-4.80)	15.4
Fregna et al,[13] 2024	55	66	29	34	0.86 (0.27-2.72)	17.2
Legenbauer et al,[12] 2024	19	53	18	60	1.30 (0.59-2.87)	27.4
Martiny et al,[19] 2005	34	48	21	54	3.82 (1.67-8.74)	25.9
Sit et al,[21] 2018	16	22	9	18	2.67 (0.71-9.95)	14.1
Total	133	211	84	187	1.79 (1.01-3.17)	100.0

Heterogeneity: $\tau^2 = 0.1486$; $\chi^2_4 = 5.89$ ($P = .21$); $I^2 = 32\%$
Test for overall effect: $z = -2.00$ ($P = .045$)

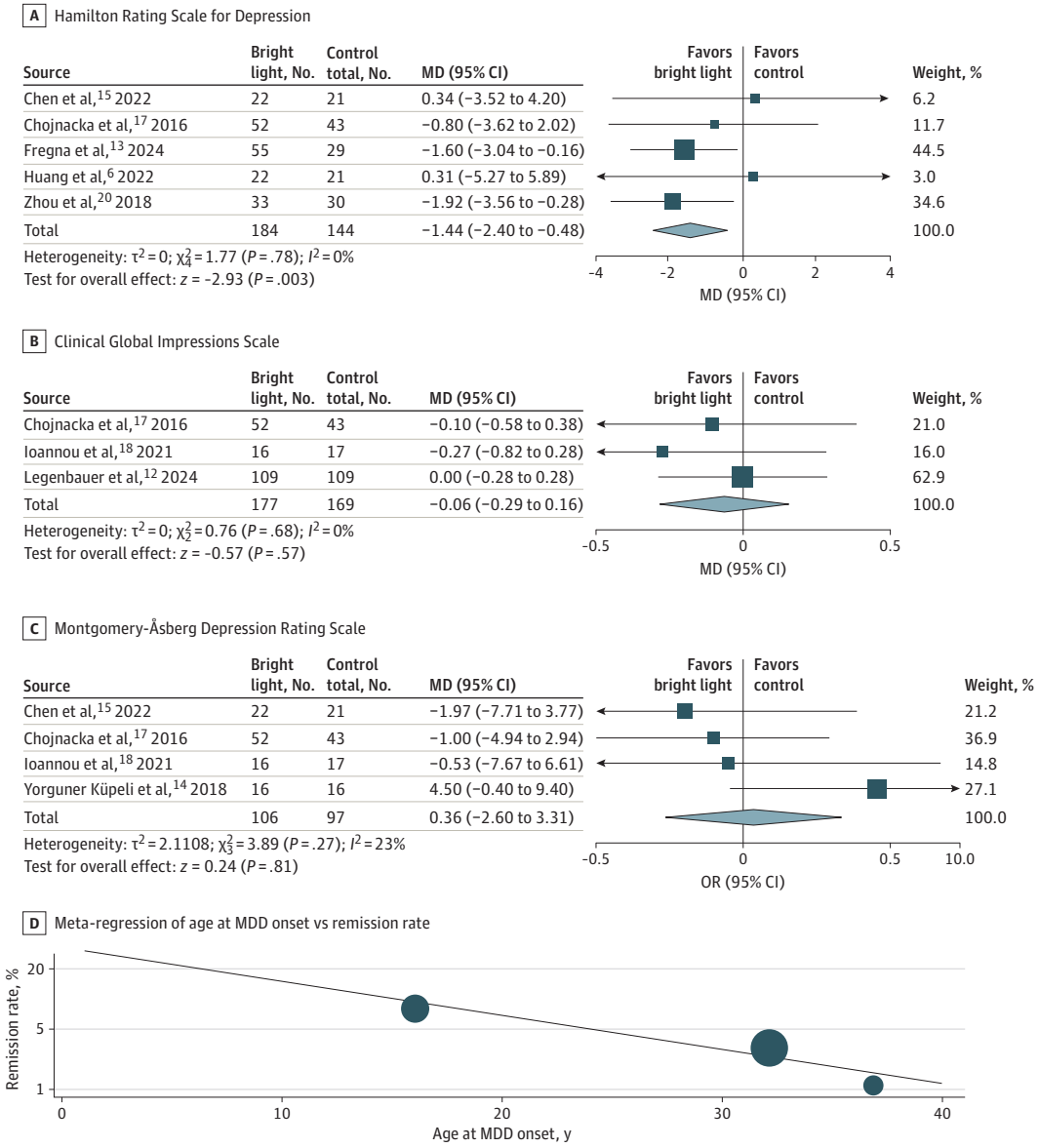


A, Remission rate in less than 4 weeks. B, Remission rate in greater than 4 weeks. C, Response to treatment in less than 4 weeks. D, Response to treatment in greater than 4 weeks. The size of the data markers (squares) corresponds to the weight of the study in the meta-analysis. OR indicates odds ratio.

ies like Legenbauer et al[12] are prone to demonstrate significant discontinuation rates or shorter duration possibly due to disorder severity, which may provide a confounding factor in the study results. Besides this, when considering the general analysis of remission and response, the present study showed a low to moderate resultant heterogeneity accompanied by a very significant *P* value. In general, all studies considered only outpatient treatment with BLT, but all of them were rigorous when determining the criteria for considering when a patient acquired or did not acquire remission and response. Becker and Hamilton Depression Scales were the main scales that used cutoffs for these outcomes.

The choice of the best follow-up time to quantify the treatment effects of BLT is controversial.[35] In contrast to the present study, a previous meta-analysis by Takeshima et al[36] included a small number of RCTs with a small total sample size and concluded that it was not possible to demonstrate any efficacy of BLT in patients with bipolar depression due to a lack of statistical significance. Juruena et al[35] critically pointed out that this result was possibly influenced by the inclusion of stud-

Figure 4. Forest Plot of Rating Scales and Meta-Regression of Age at Onset of Major Depressive Disorder (MDD)



A, Hamilton Rating Scale for Depression. B, Clinical Global Impressions Scale. C, Montgomery-Åsberg Depression Rating Scale. D, Meta-regression of age at onset of MDD vs remission rate. The size of the data markers (squares) corresponds to the weight of the study in the meta-analysis. MD indicates mean difference.

ies with follow-up time less than 6 weeks.[21,37,38] Even though only Sit et al[21] matched our inclusion criteria when compared with the studies included in the referred study, we also included similar RCTs with a follow-up period varying from 1 to 2 weeks.[14,17,18,20] Considering this gap in the literature, we performed a subgroup analysis of studies with up to 4 weeks of follow-up separated from studies with more than 4 weeks of follow-up. In both analyses, remission and response rates continued to favor the BLT group with statistically significant differences between groups with low or moderate heterogeneity. Our results do not underscore the need for RCTs with larger follow-up periods but strengthen the theory that patients treated with BLT acquire remission of symptoms and response rate more rapidly than patients treated only with antidepressants.

Future Research

Conducting trials in a multicentric manner around the globe would help determine whether seasonal differences regarding photoperiod daylight time impact or do not impact the outcomes of BLT treatment for nonseasonal depressive disorders. Similarly, it would be useful to clarify whether the duration of follow-up reflects the time to remission and response rates. If this was the case, this may suggest that BLT

adjunctive treatment leads patients to respond to the initial treatment more rapidly. Enrollment of various grades of MDD in trials assessing BLT effects could complement statistical analysis by providing sufficient data to compare subgroups according to MDD severity. Further research is also indicated to explore imaging studies for elucidation of the intricate mechanism of action of light in mood regulation.

Limitations

Our study has several limitations. First, there were slight differences between the mean follow-up time of each included RCT. However, the low heterogeneity observed in the pooled analysis of nearly all continuous outcomes suggests that this difference had no significant impact on the final result. Also, the subgroup analysis based on reported follow-up time underscores a negative impact on the general analysis of the primary outcome. Second, Legenbauer et al[12] had an important discontinuation of participants during the follow-up time. However, the resultant heterogeneity in outcomes including this study possibly suggests a small impact on the pooled analysis. Third, the available data did not enable us to analyze separately each included depressive disorder, nor bipolar or unipolar subtypes of MDD. Conversely, the general pooled analysis supports high comparability between studies following the low resultant heterogeneity. Fourth, each included study defined remission rate and response to treatment using different parameters, in addition to including different disorder severities. Despite this, all studies considered variants of the HAM-D score, which possibly balanced the resultant heterogeneity. Fifth, the moderate number of included studies may have affected the I^2 statistics and, consequently, the generalizability. However, most resultant I^2 were deemed as moderate, and the mainly homogenous funnel plot strengthened the primary outcome result.

Conclusions

This systematic review and meta-analysis assessed the effectiveness of BLT for nonseasonal depressive disorders. Our study results suggest that BLT offers significant benefits as an adjunctive treatment for these conditions. In addition, different follow-up times assessed in the subgroup analysis suggest that BLT not only increases remission and response rates but also accelerates the time to respond to initial treatment.

ARTICLE INFORMATION

Accepted for Publication: July 16, 2024.

Published Online: October 2, 2024. doi:10.1001/jamapsychiatry.2024.2871

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Conflict of Interest Disclosures: None reported.

Data Sharing Statement: See Supplement 2.

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