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CME Objective
After studying this article, you should be able to:

- Consider the use of bright light therapy to augment antidepressant effects in the treatment of refractory nonseasonal depressive episodes of major depressive disorder and bipolar disorder

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Bright Light Therapy as Augmentation of Pharmacotherapy for Treatment of Depression:
A Systematic Review and Meta-Analysis

Thomas M. Penders, MS, MD[a,*]; Cornel N. Stanciu, MD[a]; Alexander M. Schoemann, PhD[b]; Philip T. Ninan, MD[a]; Richard Bloch, PhD[a]; and Sy A. Saeed, MD[a]

ABSTRACT

Background: Bright light therapy has demonstrated efficacy and is an accepted treatment for seasonal depression. It has been suggested that bright light therapy may have efficacy in nonseasonal depressions. Also, there is evidence that bright light therapy may improve responsiveness to antidepressant pharmacotherapy.

Data Sources: We searched PubMed/MEDLINE, PsycINFO, PsycARTICLES, CINAHL, EMBASE, Scopus, and Academic OneFile for English-language literature published between January 1998 and April 2016, using the keywords *bright light therapy* AND *major depression*, *bright light therapy* AND *depress**, *bright light therapy* AND *bipolar depression*, *bright light therapy* AND *affective disorders*, *circadian rhythm* AND *major depression*, *circadian rhythm* AND *depress**, and *circadian rhythm* AND *affective disorder*.

Study Selection and Data Extraction: Studies that reported randomized trials comparing antidepressant pharmacotherapy with bright light therapy ≥ 5,000 lux for ≥ 30 minutes to antidepressant pharmacotherapy without bright light therapy for the treatment of nonseasonal depression were included. Studies of seasonal depression were excluded. Following review of the initial 112 returns, 2 of the authors independently judged each trial, applying the inclusionary and exclusionary criteria. Ten studies were selected as meeting these criteria. Subjects in these studies were pooled using standard techniques of meta-analysis.

Results: Ten studies involving 458 patients showed improvement using bright light therapy augmentation versus antidepressant pharmacotherapy alone. The effect size was similar to that of other accepted augmentation strategies, roughly 0.5.

Conclusions: Analysis of pooled data from randomized trials provides evidence for the efficacy of use of bright light therapy ≥ 5,000 lux for periods ≥ 30 minutes when used as augmentation to standard antidepressant pharmacotherapy in the treatment of major depressive disorder and bipolar depression without a seasonal pattern.

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[a]Department of Psychiatry and Behavioral Medicine, Brody School of Medicine, East Carolina University, Greenville, North Carolina
[b]Department of Psychology, East Carolina University, Greenville, North Carolina
**Corresponding author:* Thomas M. Penders, MS, MD, Department of Psychiatry and Behavioral Medicine, Brody School of Medicine, East Carolina University, Ste 400E, 600 Moye Blvd, Greenville, NC 27834 (penderst@ecu.edu).

Depressive disorders are highly prevalent worldwide. Lifetime prevalence is estimated to be 21% of the population of the United States[1] and at least 15% globally. Depression is a strong contributor to disability and burden of disease,[2,3] as well as a risk for death by suicide. Depression is a factor affecting the course, morbidity, and mortality of several common and chronic medical illnesses such as heart disease, cancer, and diabetes. Depression contributes to untold

Clinical Points

- Clinicians should consider prescribing bright light therapy to patients with major depressive disorder when initiating antidepressant pharmacotherapy.
- Clinicians should be aware of the potential of bright light therapy to precipitate a switch to mania when used for treatment of bipolar depression.
- When using bright light therapy, begin with ≥ 5,000 lux for ≥ 30 minutes, preferably in the morning.

suffering for those affected and their loved ones. Analysis of large naturalistic clinical trials[4,5] has shown the limits of current treatments for both major depressive disorder and bipolar disorder. Development of new approaches to treatment of refractory depression has been identified as a significant unmet need among psychiatric clinicians.[6]

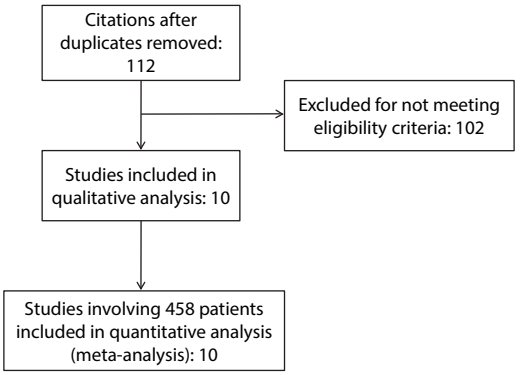
When a single antidepressant agent fails to produce significant improvement or remission in a patient with a depressive disorder, use of multiple pharmacologic agents or psychosocial interventions has been an accepted standard. Such augmentation strategies include addition of lithium carbonate, thyroid hormone, a second antidepressant, or certain second-generation antipsychotics. In the case of bipolar depression, strategies include use of mood stabilizers or antipsychotic medications.[7,8]

Bright light therapy is an accepted modality for treatment of major depressive disorder with a seasonal pattern, commonly referred to as seasonal affective disorder.[9] Studies[10] have also suggested that bright light monotherapy may have some efficacy in the treatment of depressive illnesses with no seasonal pattern. Also, several studies[11] have suggested that bright light therapy may augment the efficacy of established pharmacotherapies in the treatment of nonseasonal depression. A comprehensive review[11] published in 2005 of literature relating to the use of bright light therapy for treatment of mood disorders concluded that "bright light for nonseasonal depression is efficacious, with effect sizes equivalent to those in most antidepressant pharmacotherapy trials."(p31) Despite the very limited risks and costs associated with the use of bright light therapy, there has been little utilization in clinical practice outside treatment for seasonal affective disorder.[12] This systematic review and meta-analysis was conducted to assess the current state of evidence favoring use of bright light therapy as an augmentation to antidepressant pharmacotherapy in the treatment of depressive disorders with no seasonal pattern.

METHODS

This meta-analysis complies with the criteria provided in the Preferred-Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Two members of the research team (T.M.P. and C.N.S.) reviewed initial returns and selected trials on the basis of predefined inclusionary and exclusionary criteria.[13–23]

Figure 1. Flow Diagram for Study Selection



Data Sources

We searched PubMed/MEDLINE, PsycINFO, PsycARTICLES, CINAHL, EMBASE, Scopus, and Academic OneFile for English-language medical literature published between January 1998 and April 2016 using the search terms *bright light therapy* AND *major depression*, *bright light therapy* AND *depress**, *bright light therapy* AND *bipolar depression*, *bright light therapy* AND *affective disorders*, *circadian rhythm* AND *major depression*, *circadian rhythm* AND *depress**, and *circadian rhythm* AND *affective disorder*. Search results were supplemented by references gleaned from recent reviews and citations of searched returns.

Inclusion and Exclusion Criteria and Study Selection

All studies that reported randomized trials comparing antidepressant pharmacotherapy with bright light therapy ≥ 5,000 lux for ≥ 30 minutes to antidepressant pharmacotherapy without bright light therapy for the treatment of nonseasonal depression were included. Studies that included subjects with seasonal depression, subsyndromal symptoms, dementia, eating disorders, bright light therapy alone, or premenstrual dysphoric disorder were excluded. The original search yielded 112 reports. After elimination of studies with exclusionary criteria, 10 studies[13–22] met our original search criteria (Figure 1, Table 1). In the case of 2 disputed exclusions, 1 reviewer (S.A.S.) mediated an agreement on proper allocation.

Data Extraction and Analysis

Our statistician (A.M.S.) extracted the number of subjects and the outcomes by trial arm. All studies meeting inclusion criteria that reported the statistical information necessary to compute an effect size were included in all analyses. We used standard meta-analytic methods based on Lipsey and Wilson.[23] On the basis of the reported results for each study, we computed a standardized mean effect size and its 95% confidence interval, with small sample size corrections when appropriate.[24] Across the 10 studies, the weighted mean of the effect sizes and the variance of the effect sizes were computed using inverse variance weights from each study (Figure 2). All analyses were conducted with the metafor[25] package using the statistical software R.[26]

Table 1. Included Studies and Characteristics

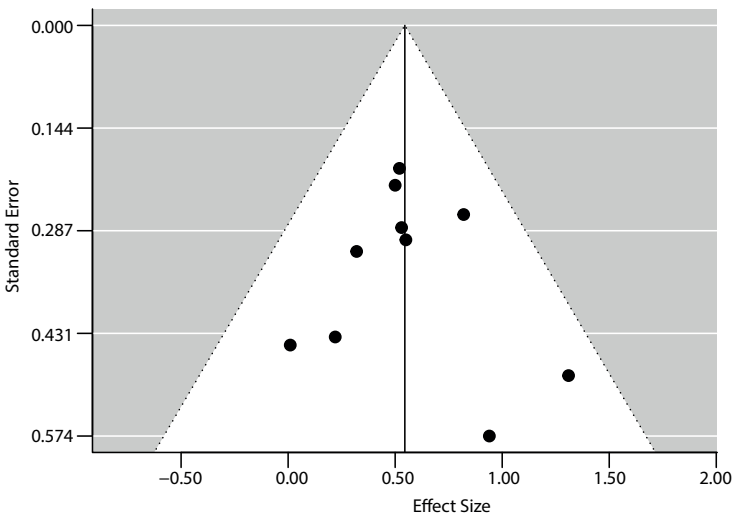
Study	Trial Length	Experimental				Control				Effect Size
		Condition	Illumination (lux)	Time (min/d)	Patients	Condition	Illumination (lux)	Time (min/d)	Patients	
Beauchemin and Hays[13]	7 d	Bright light therapy	10,000	30	n = 11 Male: 4 Female: 7 Mean age: 36 y	White	2,500	30	n = 8 Male: 4 Female: 4 Mean age: 43 y	1.38
Martiny et al[19]	5 wk	Bright light therapy	10,000	60	n = 54 Male: 23 Female: 31 Mean age: 45 y	Dim red	100	30	n = 48 Male: 17 Female: 31 Mean age: 46 y	0.41
Loving et al[14]	7 d	Bright light therapy	10,000	30	n = 7 Male: 1 Female: 44 Mean age: 44 y	Dim red	100	30	n = 6 Male: 1 Female: 5 Mean age: 44 y	1.02
Dauphinais et al[15]	8 wk	Bright light therapy	7,000	45	n = 18 Male: 5 Female: 13 Mean age: 42 y	Ion generator	None	45	n = 20 Male: 5 Female: 15 Mean age: 43 y	0.32
Wu et al[16]	3 d	Bright light therapy	5,000	120	n = 32 Male: 22 Female: 10 Mean age: 39 y	None	None	None	n = 17 Male: 7 Female: 10 Mean age: 40 y	0.56
Prasko et al[17]	21 d	Bright light therapy	5,000	120	n = 11 Male: 3 Female: 8 Mean age: 41 y	Dim red	500	120	n = 9 Male: 3 Female: 6 Mean age: 43 y	0.23
Lieverse et al[18]	3 wk	Bright light therapy	7,500	60	n = 42 Male: 14 Female: 28 Mean age: 70 y	Dim red	50	60	n = 47 Male: 17 Female: 30 Mean age: 69 y	0.51
Leibenluft et al[20]	3 mo	Bright light therapy	10,000	45	n = 9 Male: 1 Female: 8 Mean age: 42 y	None	None	None	n = 9 Male: 1 Female: 8 Mean age: 42 y	0.01
Lam et al[21]	8 wk	Bright light therapy	10,000	30	n = 29 Male: 14 Female: 15 Mean age: 39 y	Ion generator	None	30	n = 31 Male: 9 Female: 22 Mean age: 37 y	1.11
Güzel Özdemir et al[22]	8 wk	Bright light therapy	7,000	60	n = 25 Male: 11 Female: 14 Mean age: 33 y	None	None	None	n = 25 Male: 12 Female: 13 Mean age: 38 y	0.54

RESULTS

Publication bias was assessed with a visual inspection of a funnel plot and a rank correlation test of funnel plot asymmetry.[27] Neither the funnel plot (Figure 2) nor the rank correlation test (Kendall $\tau = -0.022$, $P = .999$) showed evidence of publication bias among the studies.

Across the 10 studies that met inclusion criteria, bright light therapy had a positive and significant effect ($g = 0.545$, $P < .001$; 95% CI, 0.385–0.732). The variance of the effect sizes was not significantly different from zero ($\tau^2 = 0.00$; 95% CI, 0.000–0.170), and there was no significant heterogeneity in effect sizes ($Q_9 = 6.54$, $P = .685$) (Figure 3).

Figure 2. Funnel Plot of Effect Sizes and Corresponding Standard Errors



Quality of Studies

Two reviewers (P.T.N. and R.B.) independently evaluated the quality of each study using guidelines

Figure 3. Effect Sizes of Bright Light Therapy (> 0 favors treatment)

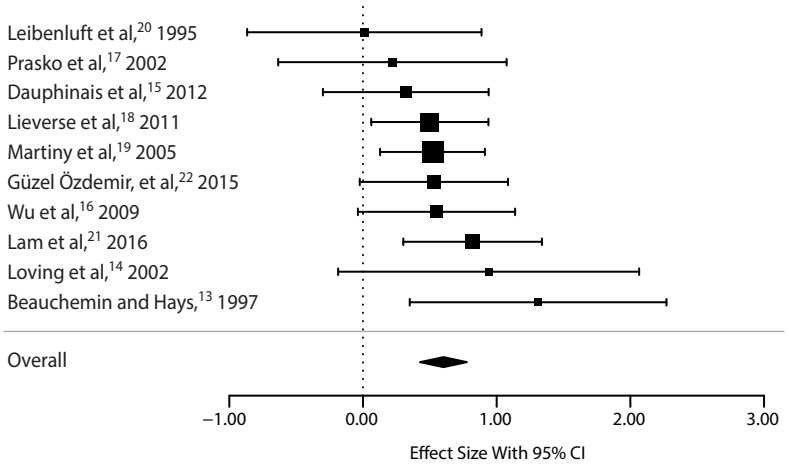


Table 2. Grading of Quality Divided Into High, Medium, and Low

Beauchemin and Hays[13]	Low
Loving et al[14]	Low
Dauphinais et al[15]	Low
Wu et al[16]	Low-medium
Prasko et al[17]	Medium
Lieverse et al[18]	High
Martiny et al[19]	High
Leibenluft et al[20]	Low
Lam et al[21]	High
Güzel Özdemir et al[22]	Medium

established by the GRADE[28] (Grading of Recommendations, Assessment, Development, and Evaluation) method. Only 3 studies[18,19,21] were judged to be of high quality. Three others[16,17,22] were rated as medium or low to medium. The remaining studies[13,14,15,20] were rated as low quality (Table 2). Studies included subjects with bipolar and major depressive disorder, introducing a possible bias on the basis of this selection.

DISCUSSION

Many patients with depressive disorder fail to respond to standard antidepressant pharmacotherapy, psychotherapy alone, or the combination. Augmentation strategies improve outcome in many cases, but treatment resistance remains common, leaving many patients with disabling or distressing residual symptoms. Adoption of bright light therapy for treatment of nonseasonal depression by psychiatric clinicians remains quite limited despite a recommendation for use by the American Psychiatric Association.[29] Insurance coverage for bright light therapy for nonseasonal depression is also severely limited. However, the quality of current evidence supports a recommendation for efficacy. This meta-analysis supports conclusions reached by others,[10] suggesting that bright light therapy is effective and can add to the armamentarium of interventions available to patients with refractory depressive disorders. Recently reported studies[30] add substantially to evidence in support of bright light therapy to augment the therapeutic actions of antidepressant agents.

The studies meeting criteria for inclusion in this analysis varied substantially in their design, measured outcomes for improvement in depression, length of light exposure, type of placebo, and lengths of the trials. Antidepressant treatments varied from study to study. The study[19] with the largest number of subjects utilized a single antidepressant and controlled dosing. Another study[16] provided outcomes after only 3 days and also included an additional intervention, wake therapy, introducing additional significant confounds. Leibenluft et al[20] reported a study of a limited number of subjects with rapid-cycling bipolar disorder, a group substantially different from those of most other included studies.

Limitations

The resultant heterogeneity in the studies included in this pooled analysis somewhat confounds interpretation of the data. However, all included studies were consistent in reporting antidepressant action of bright light therapy for depressions with no seasonal pattern. Future trials will benefit from designs that limit these confounds as attempts are made to better define the effect of bright light therapy in the several subtypes of depressive disorders. There also may be a potential for development of markers and predictors of response to bright light therapy when used as an augmentation strategy.

CONCLUSION

Analysis of pooled data from randomized trials provides evidence for the efficacy for use of bright light therapy administered at ≥5,000 lux for periods ≥30 minutes when used as augmentation to standard antidepressant treatment. Methodological flaws, small sample sizes, and heterogeneity of published studies have resulted in strength of evidence that is moderate overall.

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Drug names: lithium (Lithobid and others).
Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, lithium is not approved by the US Food and Drug Administration for augmentation of antidepressant action.
Financial disclosure: **Dr Ninan** has served as a consultant to Lundbeck. **Drs Penders**, **Stanciu**, **Schoemann**, **Bloch**, and **Saeed** have no personal affiliations or financial relationships with any commercial interest to disclose relevant to the activity.
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POSTTEST

To obtain credit, go to http://www.cmeinstitute.com/activities/Pages/PCC.aspx to complete the Posttest and Evaluation.

1. **Bright light therapy is already an accepted treatment modality for which psychiatric condition?**
   a. Social anxiety disorder
   b. Generalized anxiety disorder
   c. Recurrent major depressive disorder (MDD) with seasonal pattern
   d. Bipolar depression

2. **Ms A has MDD that you have treated with an antidepressant for an adequate time at an optimized dose, but she still has some mild mood symptoms. She is reluctant to add another medication. According to this meta-analysis, moderate evidence suggests that augmenting Ms A's antidepressant with bright light therapy at a minimum of 5,000 lux for at least 30 minutes/day would have ___.**
   a. No effect
   b. A significantly positive effect
   c. A significantly harmful effect