Adjunctive Bright Light Therapy for Bipolar Depression: A Randomized Double-Blind Placebo-Controlled Trial

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Objective: Patients with bipolar disorder have recurrent major depression, residual mood symptoms, and limited treatment options. Building on promising pilot data, the authors conducted a 6-week randomized double-blind placebo-controlled trial to investigate the efficacy of adjunctive bright light therapy at midday for bipolar depression. The aims were to determine remission rate, depression symptom level, and rate of mood polarity switch, as well as to explore sleep quality.

Method: The study enrolled depressed adults with bipolar I or II disorder who were receiving stable dosages of antimanic medication (excluding patients with hypomania or mania, mixed symptoms, or rapid cycling). Patients were randomly assigned to treatment with either 7,000-lux bright white light or 50-lux dim red placebo light (N=23 for each group). Symptoms were assessed weekly with the Structured Interview Guide for the Hamilton Depression Scale With Atypical Depression Supplement (SIGH-ADS), the Mania Rating Scale, and the Pittsburgh Sleep Quality Index. Remission was defined as having a SIGH-ADS score of 8 or less.

Results: At baseline, both groups had moderate depression and no hypomanic or manic symptoms. Compared with the placebo light group, the group treated with bright white light experienced a significantly higher remission rate (68.2% compared with 22.2%; adjusted odds ratio=12.6) at weeks 4–6 and significantly lower depression scores (9.2 [SD=6.6] compared with 14.9 [SD=9.2]; adjusted $\beta = -5.91$) at the endpoint visit. No mood polarity switches were observed. Sleep quality improved in both groups and did not differ significantly between them.

Conclusions: The data from this study provide robust evidence that supports the efficacy of midday bright light therapy for bipolar depression.

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Patients with bipolar disorder often have recurrent major depression and residual mood symptoms (1). Despite advances in drug treatment for mania, the development of effective pharmacotherapy for bipolar depression remains a challenge. Antimanic medications reduce depressive symptoms in only one-third of patients (2). Antidepressant monotherapy can induce hypomania and rapid cycling (3). Given the limited treatment options, research to investigate novel therapeutics for bipolar depression is a high-priority public health concern.

Patients with bipolar disorder are susceptible to environmental cues that alter circadian rhythms and trigger relapse. Depressed bipolar patients frequently have delayed sleep phase and atypical features (hypersomnia, hyperphagia, and lethargy), which are predictors of light therapy response (4). We previously conducted a dose-finding, safety, and efficacy pilot study of the effects of light therapy for patients with stable depression in the context of bipolar disorder (5). Morning light therapy induced full response in one of four patients and, unexpectedly, hypomania in the other three patients (5). Other researchers have been unable to demonstrate any effect of morning light therapy compared with placebo in patients with bipolar depression (6). In contrast, some patients with seasonal depression (7–10) or rapid-cycling bipolar illness (11) have experienced antidepressant effects from midday or evening bright light therapy. At midday, bright light exposure can phase-advance and increase the amplitude of nocturnal melatonin production in healthy subjects (12) and in elderly patients with insomnia (13). Sleep parameters (decreased awake time at night, increased sleep efficiency, and reduced wake time after sleep onset) have also been found to be improved with midday light therapy (13). Given the promising findings of improved mood and sleep from midday light therapy and the possible association of therapeutic response with changes in circadian rhythms (9, 12, 13), we adjusted the time of intervention to midday in our pilot study. We enrolled five additional patients; three had a full response, and one who had an initial partial response responded fully after transitioning to morning light.

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Building on those findings, we conducted a 6-week randomized double-blind placebo-controlled trial to investigate the efficacy of bright light therapy at midday for bipolar depression. Our aims were to determine remission rate, the depressive symptom level, and the rate of mood polarity switch in patients treated with 7,000-lux bright white light or 50-lux dim red light. We selected dim red light for the placebo condition because it reversed hypomania induced by morning bright light (5), was a plausible placebo comparator in clinical trials of light therapy for depressive disorders (5, 14, 15), and produced negligible effects on circadian rhythms (16). We hypothesized that the remission rate would be higher and the mean depression score lower in the white-light group compared with the placebo group.

METHOD

We performed the study at Western Psychiatric Institute and Clinic (WPIC), University of Pittsburgh Medical Center, from 2010 to 2014. The Institutional Review Board at the University of Pittsburgh approved the protocol. Our data safety monitoring board, with experts in light therapy, bipolar disorder, and clinical trials, reviewed patient safety data every year. We recruited patients from the WPIC Mood Disorders Program and obtained written informed consent after the study procedures had been fully explained.

Eligibility Criteria

We included patients 18–75 years old with bipolar I or II disorder (confirmed on the Structured Clinical Interview for DSM-IV Axis I Disorders [SCID]) (17), a current moderate or severe episode of major depression (a score ≥20 on the Structured Interview Guide for the Hamilton Depression Rating Scale With Atypical Depression Supplement [SIGH-ADS] and a score ≥1 on SIGH-ADS item H1 or H2) (18), and no hypomania or mixed symptoms (a score ≤4 on the Mania Rating Scale [MRS]) (19). Eligible patients received antimanic medication at stable dosages for at least 4 weeks (20), within the therapeutic dosage range and plasma concentration (3); if applicable, patients received adjunctive antidepressant medication at stable dosages for at least 8 weeks and low-dose sleep aids for mild insomnia. Patients continued the same medications and dosages during the study. We included pregnant women because light therapy presents no additional risk and nonpharmacological treatments are limited (15). We excluded patients who had any manic, hypomanic, or mixed episodes in the past 6 months; rapid cycling in the past year; active suicidal ideation or attempted suicide; acute or chronic psychosis; obsessive-compulsive disorder; uncontrolled thyroid disease; any substance use disorder in the past 6 months; a positive urine drug screen; chronic eye diseases; or treatment with photosensitizing drugs (phenothiazine, antimalarial drugs, propranolol, melatonin, *Hypericum*, stimulants, or chronic treatment with nonsteroidal anti-inflammatory drugs).

Procedures

At the eligibility visit, we administered the SCID and recorded age, race, sex, marital status, highest level of education, employment, age at onset, number of mood episodes, hospitalizations, medical history, medications and dosages, substance use, body mass index (BMI), and time of year of enrollment. We assessed clinical symptoms with the SIGH-ADS, which provides a benchmark for depression severity, including atypical features (18); the MRS, an 11-item measure derived from the Schedule for Affective Disorders and Schizophrenia for hypomania/mania levels (19); and the Clinical Global Impressions Scale for Bipolar Disorder (CGI-BD). We used the Brief Psychiatric Rating Scale (BPRS) to assess for psychosis; scores ≥31 correspond with active symptoms (21). To monitor side effects, we used the Systematic Assessment for Treatment Emergent Effects (10) and the Beck Scale for Suicide Ideation (22). We evaluated psychosocial functioning with the Global Assessment of Functioning Scale (GAF) and the Social Problems Questionnaire. Response to light therapy is associated with sleep quality and circadian and seasonality traits, which we assessed with the Pittsburgh Sleep Quality Index (23), the Morningness-Eveningness Questionnaire (24), and the Personal Inventory for Depression and Seasonal Affective Disorder (10), respectively. Expectations can moderate outcomes, especially in clinical trials involving light therapy, which test a visible intervention (10). Therefore, we evaluated expectancy on a brief multipoint rating scale at baseline and at the final or endpoint visit.

Randomization, Allocation Concealment, Treatment Blind

Eligible patients were randomly assigned in a 1:1 ratio to active bright white or inactive dim red light and stratified by antidepressant use with a block design (six patients per block). Within each block, patients were independently assigned to each group in equal numbers according to different randomization sequences.

Personnel conducting the visits and performing the clinical ratings were blind to the treatment condition to avoid allegiance effects, and they worked separately from the nonblinded personnel, who dispensed the study light boxes (concealed in numbered sealed containers, away from the blinded team), provided patient training on use of the light box, and regularly checked operation of the units. Ratings of side effects were separated from mood ratings to prevent contamination of the outcome measures. The active and placebo light boxes appeared identical when not illuminated. We implemented the same dosing protocol for both groups (25). Patients agreed not to search for information on light box design. We disclosed the treatment condition to patients only at the final visit and to blinded personnel and statisticians only after the analyses were completed. The study design elements were incorporated to mitigate unbalanced treatment expectations; therefore, we expected the observed treatment response to be related to the active light condition rather than to nonspecific effects.

Dosage Titration and Follow-up

At baseline, eligible patients were randomly assigned to a 7,000-lux, 4,000-K, broad-spectrum white fluorescent

(Carex Day-Light Classic) or a 50-lux red light unit. The unit conforms to stringent standards, including illumination of a broad visual field, lighting from above to avoid glare, and maximal ultraviolet filtration. Participants were provided with standardized instructions on the appropriate use of their light box: optimal placement of the unit on its desk stand 12 inches from the eyes, and facing the light box without directly staring at it (to minimize discomfort) during the daily sessions of light therapy. Patients agreed to use the light box daily at home or work.

Patients began with 15-minute sessions of light therapy between 12:00 p.m. and 2:30 p.m. They attended weekly visits for assessment of mood level, side effects, suicidality, sleep quality, and psychosocial functioning. After each visit, the duration of light therapy was increased by 15 minutes to attain a target dose of 60 minutes per daily session by week 4 or until remission. Upward titration was conditional on having manageable side effects (item scores <3 on the Systematic Assessment for Treatment Emergent Effects) and no hypomania (an MRS score ≤4). Patients with worsening depression, severe suicidal ideation, or emergent hypomania (according to DSM-IV criteria and with an MRS score ≥5) were evaluated by the principal investigator (D.K.S.) and a nonblind monitor (R.S.D., K.L.W.), and appropriate clinical management was provided. To monitor adherence, patients recorded their daily light therapy sessions on the corresponding self-report form and called the time-stamped machine (checked daily by nonblind personnel). At every clinic visit, patients brought in their units; the nonblind personnel performed quality checks and downloaded the light sensor and sensitivity data recorded by the logger device (a HOBO U9 light on/off data logger; sensitivity threshold, 10–100 lumens/m^2) to confirm appropriate, missed, or ill-timed sessions.

Outcome Measures

The primary outcome measures were the rate of remission (defined as a SIGH-ADS score ≤8) within the week 4–6 period and the continuous SIGH-ADS scores at the endpoint visit. We assumed that patients who were still actively enrolled at weeks 4–6 had fully (or nearly) completed the dose-titration protocol, and those who withdrew early also provided informative outcome data. Secondary outcome measures included the rate of response (the proportion with reductions ≥50% on SIGH-ADS score), frequency of mood polarity switch, clinical severity (based on the CGI-BD severity score), and the continuous ratings of side effects, suicidal thoughts, anxiety symptoms (using the five-item subscale of the 21-item Hamilton Depression Rating Scale [HAM-D]) (26), atypical features, psychosis (based on the BPRS), sleep quality (based on Pittsburgh Sleep Quality Index), and psychosocial functioning (based on the GAF and the Social Problems Questionnaire). To ascertain adherence, we assessed the total number of visits attended, the early withdrawal rate, the maximum light dose (minutes of daily light therapy exposure) to which the patient titrated, and the actual light dose per daily session reported by the patient at the endpoint visit.

Power Analysis

We proposed to enroll two groups of 30 patients for an 80% power to detect group differences in the mean SIGH-ADS score of 2.6 points with a moderate effect size (0.37) and remission rates of 33%−38% (for an odds ratio of 6.9 at an alpha of 0.05, according to the PASS 2002 program [NCSS Statistical Software, Kaysville, Utah]) within the observed range in published trials (65% [SD=24] for active treatment and 29% [SD=12] for placebo treatment) (27). We stopped enrollment at 23 participants per group because funding had ended.

Statistical Analysis

We used a modified intent-to-treat approach whereby all participants were analyzed according to the group to which they were randomized. For the primary outcome measures, we analyzed data from patients who had at least one visit between weeks 4 and 6; for the secondary, longitudinal analyses, we analyzed data from patients who had at least one follow-up visit. We performed unadjusted and adjusted analyses. The adjusted analyses accounted for the potential confounding effects of age, time of enrollment (season), and baseline SIGH-ADS and GAF scores. For continuous outcomes, we performed linear regressions, and for binary outcomes (SIGH-ADS score ≤8, Beck Scale for Suicide Ideation score ≥1, Beck Scale for Suicide Ideation score ≥8, and CGI-BD severity score ≥2), we performed logistic regressions to assess treatment effect. The secondary longitudinal analyses involved a mixed-modeling approach; we assumed fixed effects of intervention group, study week, and group-by-week interaction, and a random patient effect. We conducted the analyses in SAS, version 9.4 (SAS Institute, Cary, N.C.) and R, version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided with the significance threshold set at 0.05. Because of the sample size and numbers per group, we did not make adjustments for multiple hypothesis tests.

RESULTS

Baseline Characteristics

We obtained informed consent from 93 potential participants (see the CONSORT chart in the data supplement that accompanies the online edition of this article). Rapid cycling, substance use disorders or a positive urine screen, mild depression, concurrent hypomania, and psychosis were common reasons for exclusion. Forty-six patients underwent randomized assignment, 23 to bright white light (active treatment) and 23 to dim red light (inactive treatment). The demographic characteristics did not differ significantly between groups (Table 1). Participants were 44.7 years old on average, 40% had completed college, and 67% were women. We enrolled one woman during pregnancy. The sample's racial distribution was 80% white, 11% black, and 9% multiracial. Two-thirds of eligible patients had bipolar I disorder. Age at onset was early on average (mean=16.0 years, SD=8.7 years). The

TABLE 1. Demographic and Clinical Characteristics of Participants in a Study of Active (Bright White Light) and Inactive (Dim Red Light) Light Therapy in Bipolar Depression

Measure	Total Sample (N=46)		Intervention Group			
			Active Treatment (N=23)		Inactive Treatment (N=23)	
	N	%	N	%	N	%
Female	31	67.4	14	60.9	17	73.9
Race						
White	37	80.4	20	87.0	17	73.9
Black	5	10.9	2	8.7	3	13.0
Other	4	8.7	1	4.3	3	13.0
Education level						
High school or less	10	21.7	6	26.1	4	17.4
Some college/training	18	39.1	6	26.1	12	52.2
College	9	19.6	5	21.7	4	17.4
Graduate/professional	9	19.6	6	26.1	3	13.0
Employed	18	39.1	12	52.2	6	26.1
Bipolar subtype						
Bipolar I disorder	31	67.4	13	56.5	18	78.3
Bipolar II disorder	15	32.6	10	43.5	5	21.7
	Mean	SD	Mean	SD	Mean	SD
Age (years)	44.7	14.5	45.7	14.3	43.7	15.0
Age at first episode (years)	16.0	8.7	16.8	8.5	15.3	8.9
Time since first episode (years)	28.5	16.7	28.1	16.3	29.0	17.4
Body mass index	30.9	8.3	30.6	8.9	31.2	7.9
Psychiatric hospitalizations	2.7	7.9	3.4	10.5	1.8	1.70
	N	%	N	%	N	%
First episode type						
Depression	26	56.5	12	52.2	14	60.9
Manic or hypomanic	10	21.7	5	21.7	5	21.7
Mixed	8	17.4	4	17.4	4	17.4
Psychotic mood episode	2	4.3	2	8.7	0	0.0
Seasonal component to bipolar disorder	38	82.6	19	82.6	19	82.6
Any axis I comorbidity	35	76.1	17	73.9	18	78.3
Any axis II comorbidity	6	13.0	2	8.7	4	17.4
Any axis III comorbidity	41	89.1	21	91.3	20	87.0

first episode was usually major depression (56.5%), and many participants had bipolar disorder for decades (the mean duration was 28.5 years [SD=16.7]), complicated by other medical disorders, including obesity (the mean BMI was 30.9 [SD=8.32]).

Clinical Measures at Randomization

As shown in Table 2, at baseline patients assigned to active treatment and inactive treatment had moderate depression levels (mean SIGH-ADS scores, 24.22 and 27.70, respectively; (Mann-Whitney U=5.68, p=0.017), moderate clinical severity (CGI-BD severity score ≥2), no hypomania or psychosis, increased social problems, and moderate impairment in global functioning (mean GAF score, 57.05 and 53.48, respectively; U=4.83, p=0.028). Despite randomization, the active and inactive treatment groups differed significantly on baseline depression and functioning. The frequency of suicidal thoughts (23.9% for the sample) did not differ significantly between groups. Patients in both conditions had prominent anxiety (mean HAM-D subscale score, 5.6 [SD=2.01]), reduced sleep quality (mean Pittsburgh Sleep Quality Index score, 8.3 [SD=3.4]), an intermediate morning-evening preference (mean Morningness-Eveningness Questionnaire score, 46.9 [SD=9.7]), and moderate levels of seasonal sensitivity (mean Personal Inventory for Depression and Seasonal Affective Disorder, part 2 score, 11.1 [SD=5.8]) and winter exacerbation of atypical neurovegetative symptoms (part 4 score, 6.1 [SD=2.1]). The majority enrolled in the fall (39.1%) or winter (34.8%). Three patients were randomly assigned to active treatment and seven to inactive treatment in February or March (the months that immediately precede remission of seasonal affective disorder). We enrolled 78.3% patients who were receiving combined treatment with a mood stabilizer and an antidepressant and 21.7% who were receiving treatment only with a mood stabilizer. Baseline expectancy was not significantly different between groups at randomization, when the light units were dispensed.

Primary Outcome Measures

Forty-five patients attended one or more postbaseline visits (median=6 visits), and 40 patients (87%) completed the study (Table 3). The active treatment group, compared with the

TABLE 2. Baseline Clinical Measures in a Study of Active (Bright White Light) and Inactive (Dim Red Light) Light Therapy in Bipolar Depression

Measure	Total Sample (N=46)		Intervention Group			
			Active Treatment (N=23)		Inactive Treatment (N=23)	
	N	%	N	%	N	%
Clinical Global Impressions Scale for Bipolar Disorder, severity score ≥2	46	100.0	23	100.0	23	100.0
Expectation about light therapy						
Minor improvement	13	28.3	8	34.8	5	21.7
Moderate improvement	23	50.0	12	52.2	11	47.8
Major improvement	7	15.2	2	8.7	5	21.7
Full improvement	3	6.5	1	4.3	2	8.7
	Mean	SD	Mean	SD	Mean	SD
Brief Psychiatric Rating Scale	36.6	4.1	36.0	4.1	37.3	4.1
Global Assessment of Functioning Scale[a]	55.2	5.6	57.1	5.5	53.5	5.3
Morningness-Eveningness Questionnaire	46.9	9.7	49.2	9.5	44.7	9.5
Personal Inventory for Depression and Seasonal Affective Disorder						
Degree seasonal	11.1	5.8	11.0	4.4	11.3	7.0
Winter symptoms	6.1	2.1	6.3	2.3	5.9	2.0
Pittsburgh Sleep Quality Index	8.3	3.4	8.5	3.6	8.2	3.3
SIGH-ADS[b]	26.0	5.2	24.2	4.6	27.7	5.2
Hamilton Depression Rating Scale (21-item)	17.4	5.0	16.4	4.7	18.4	5.3
Hamilton Depression Rating Scale, anxiety subscale	5.6	2.0	5.1	2.1	6.1	1.8
Atypical symptoms	10.7	4.0	9.7	3.4	11.7	4.5
Social Problems Questionnaire	16.2	8.2	14.4	9.0	18.1	7.0
Beck Scale for Suicide Ideation	0.8	2.0	0.7	2.0	0.8	2.0
	N	%	N	%	N	%
Beck Scale for Suicide Ideation score ≥1	11	23.9	6	26.1	5	21.7
Medications[c]						
Mood stabilizer stratification						
Mood stabilizer only	10	21.7	6	26.1	4	17.4
Mood stabilizer and antidepressant	36	78.3	17	73.9	19	82.6
Mood stabilizers						
>1 mood stabilizer	23	50.0	10	43.5	13	56.5
Anticonvulsant	27	58.7	12	52.2	15	65.2
Lithium	10	21.7	6	26.1	4	17.4
Antipsychotic	31	67.4	14	60.9	17	73.9
Antidepressants						
>1 antidepressant	6	13.0	3	13.0	3	13.0
SSRI or SNRI	30	65.2	13	56.5	17	73.9
MAO inhibitor	2	4.3	2	8.7	0	0.0
Bupropion (sustained release)	10	21.7	5	21.7	5	21.7
Sleep aid	27	58.7	12	52.2	15	65.2
Other medications	25	54.3	13	56.5	12	52.2
Season of randomization[d]						
Winter	16	34.8	8	34.8	8	34.8
Spring	5	10.9	2	8.7	3	13.0
Summer	7	15.2	3	13.0	4	17.4
Fall	18	39.1	10	43.5	8	34.8

[a] Significant difference between active and inactive treatment groups, Mann-Whitney U test=4.83, p=0.028.
[b] SIGH-ADS=Structured Interview Guide for the Hamilton Depression Scale With Atypical Depression Supplement. Significant difference between active and inactive treatment groups, Mann-Whitney U test=5.68, p=0.017.
[c] Mood stabilizers included anticonvulsants (lamotrigine, valproate, carbamazepine, and oxcarbazepine) and antipsychotics (quetiapine, aripiprazole, risperidone, ziprasidone, lurasidone, and olanzapine). Sleep aids included low-dose benzodiazepines, trazodone, and zolpidem. Other medications included agents for hypertension, diabetes mellitus, and lipid control. MAO=monoamine oxidase; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.
[d] Season was defined according to the National Oceanic and Atmospheric Administration (NOAA).

TABLE 3. Summary of Visits and Dosing in a Study of Active (Bright White Light) and Inactive (Dim Red Light) Light Therapy in Bipolar Depression[a]

Measure	Total Sample (N=46)		Intervention Group: Active Treatment (N=23)		Intervention Group: Inactive Treatment (N=23)		Analysis	
	Median	IQR	Median	IQR	Median	IQR	U	p
Postbaseline visits	6	6–6	6	6–6	6	5–6	185	0.003
	Mean	SD	Mean	SD	Mean	SD	U	p
Maximum dose (minutes)	45.7	16.1	46.3	14.9	45.0	17.5	<0.01	0.944
Last dose (minutes)	44.7	17.1	45.3	16.7	44.0	17.9	0.03	0.862
Systematic Assessment for Treatment Emergent Effects[b]								
Worsening, n	37.7	25.8	38.0	27.3	37.4	24.7	<0.01	0.971
Worsening, sum	47.9	34.7	46.0	35.3	50.2	34.8	0.34	0.559
Worsening, mean	1.27	0.23	1.24	0.23	1.30	0.24	1.02	0.312
	N	%	N	%	N	%	TP	p
Early withdrawal rate[c]	6	19.0	1	4.3	5	21.7	0.18	0.187

[a] IQR=interquartile range; TP=table probability from Fisher's exact test.
[b] "Worsening" indicates that the item score increased from the previous visit; "n" indicates the number of times this happened during the study; "sum" indicates the total score of the "worsening" events; and "mean" is the sum divided by the n.
[c] Early withdrawal is defined as dropout before week 4.

inactive treatment group, had a significantly higher remission rate at weeks 4–6 (SIGH-ADS scores ≤8, 68.2% and 22.2%, respectively; odds ratio=7.50, 95% CI=1.80, 31.28, p=0.003; adjusted odds ratio=12.64, 95% CI=2.16, 74.08, p=0.004) and a lower mean depression score at the endpoint visit (SIGH-ADS score, mean=9.18 [SD=6.57] compared with mean=14.94 [SD=9.16]; β=−5.76, p=0.026; adjusted β=−5.91, p=0.023) (Table 4, Figure 1). No hypomania or mood polarity switch was observed. One patient enrolled during pregnancy; the analyses with and without her indicated no differences in outcomes.

Secondary Outcome Measures

As shown in Table 4, patients in the active treatment group, compared with those in the inactive treatment group, had significantly better global functioning (GAF score, mean=74.77 [SD=9.70] and mean=67.65 [SD=9.86], respectively; β=7.13, p=0.030; adjusted β=7.61, p=0.042) and a significantly larger percent reduction in SIGH-ADS score (mean=−62.23% [SD=24.45] and mean=−46.21% [SD=29.67], respectively; adjusted β=−21.06, p=0.027). The active treatment group also experienced a higher response rate, lower clinical severity, less anxiety, fewer social problems, fewer neurovegetative symptoms, and better sleep quality compared with the inactive treatment group, but the differences were not significant. We encountered no serious adverse effects. Patients in both conditions experienced infrequent side effect worsening and, rarely, thoughts of suicide (see Tables 3 and 4). On the Systematic Assessment for Treatment Emergent Effects, patients in the active treatment group, compared with those in the inactive treatment group, had significantly less excessive sleep (21.7% compared with 52.2%; χ^2=4.57, df=1, p=0.033) and less trouble concentrating (52.2% compared with 78.3%; χ^2=3.45, df=1, p=0.063).

The maximum dose of light therapy exposure (46.3 minutes/day [SD=14.9] and 45.0 minutes/day [SD=17.5], for the active and inactive treatment groups, respectively), and the actual light dose per daily session reported by the patient at the endpoint visit (45.3 minutes/day [SD=16.7] and 44.0 minutes/day [SD=17.9], respectively) did not differ significantly between groups (Table 3). Although the median number of postbaseline visits (median=6 [interquartile range=6–6] for the active treatment group, compared with median=6 [interquartile range=5–6] for the inactive treatment group; U=185, p=0.003) differed significantly between groups, the early withdrawal rate (4.3% and 21.7%, respectively; see Table 3) did not differ significantly between groups. The one patient who withdrew from the active treatment group indicated that she was not permitted to use the light box at her new job. In the inactive treatment group, one patient returned the light unit after 3 weeks and did not complete another visit; others withdrew for one or more reasons: stopped using the light box for undefined reason, job, or school (N=4); preferred medication change (N=2); and missed two or more visits (N=1). Expectations at endpoint were not significantly different between groups. The secondary longitudinal analyses were not significant (not reported here).

DISCUSSION

This clinical trial demonstrated that adjunctive bright light therapy at midday induced a potent and stable antidepressant response in depressed bipolar patients. After 6 weeks of bright light therapy, 68.2% experienced remission, and patients reported low levels of depression, significantly better global functioning, and no mood polarity switch. With dim red light, only 22.2% remitted; patients still had moderate depression levels and persistent impairment in functioning. The findings

TABLE 4. Outcome Measures in a Study of Active (Bright White Light) and Inactive (Dim Red Light) Light Therapy in Bipolar Depression[a]

Measure	Total Sample (N=40)		Active Treatment (N=22)		Inactive Treatment (N=18)		Analysis[b]					
							Unadjusted			Adjusted[c]		
Continuous outcome measures	Mean	SD	Mean	SD	Mean	SD	Beta	95% CI	p	Beta	95% CI	p
Brief Psychiatric Rating Scale	26.89	7.84	24.00	6.77	30.29	7.82	−6.29	−11.16, −1.43	0.013	−8.04	−13.57, −2.51	0.006
Global Assessment of Functioning Scale	71.67	10.28	74.77	9.7	67.65	9.86	7.13	0.74, 13.52	0.030	7.61	0.30, 14.93	0.042
Pittsburgh Sleep Quality Index	5.97	3.26	5.80	3.25	6.19	3.35	−0.39	−2.64, 1.86	0.728	−0.93	−3.06, 1.21	0.380
SIGH-ADS	11.78	8.26	9.18	6.57	14.94	9.16	−5.76	−10.81, −0.72	0.026	−5.91	−10.97, −0.86	0.023
Hamilton Depression Rating Scale (21-item)	8.32	6.31	6.82	6.04	10.17	6.29	−3.35	−7.31, 0.61	0.095	−4.01	−7.97, −0.06	0.047
Hamilton Depression Rating Scale, anxiety subscale	3.23	2.22	2.73	1.96	3.83	2.43	−1.11	−2.51, 0.30	0.119	−1.38	−2.94, 0.18	0.082
Atypical symptoms	4.42	4.00	3.32	2.44	5.78	5.08	−2.46	−4.94, 0.02	0.052	−1.85	−4.51, 0.81	0.166
SIGH-ADS, percent reduction	−55.02	27.76	−62.23	24.45	−46.21	29.67	−16.03	−33.34,1.28	0.069	−21.06	−39.59, 2.52	0.027
Social Problems Questionnaire	12.12	9.35	11.05	10.17	13.44	8.34	−2.40	−8.44, 3.65	0.427	−2.14	−8.57, 4.29	0.501
Beck Scale for Suicide Ideation[d]	0.45	1.58	0.64	1.97	0.22	0.94						
Binary outcome measures	N	%	N	%	N	%	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Clinical Global Impressions Scale for Bipolar Disorder, severity score ≥2	17	42.5	8	36.4	9	50.0	0.57	0.16, 2.03	0.398	0.47	0.10, 2.30	0.371
SIGH-ADS score ≤ 8	19	47.5	15	68.2	4	22.2	7.50	1.80, 31.28	0.003	12.64	2.16, 74.08	0.004
SIGH-ADS score ≥50% percent reduction	25	62.5	16	72.7	9	50.0	2.67	0.71, 9.95	0.147	4.28	0.80, 22.98	0.097
Beck Scale for Suicide Ideation score ≥1[d]	4	10.0	3	13.6	1	5.56						
Beck Scale for Suicide Ideation score ≥8[d]	1	2.50	1	4.55	0	0.00						

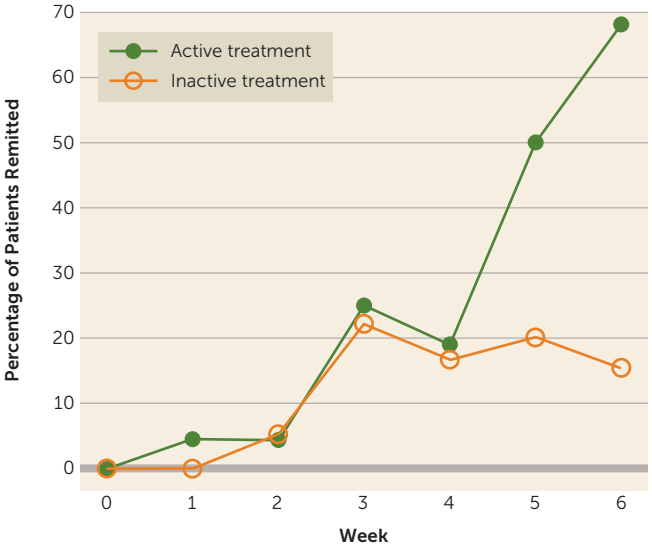
[a] SIGH-ADS=Structured Interview Guide for the Hamilton Depression Rating Scale With Atypical Depression Supplement.
[b] The referent for betas and odds ratios is intervention=inactive.
[c] Adjusted for age, season at enrollment, and baseline scores on the Global Assessment of Functioning Scale and the SIGH-ADS.
[d] Too few cases and an extremely nonnormal distribution required modeling as a cumulative logit.

contrast with an earlier report by Dauphinais et al. (6) suggesting that 8 weeks of morning light therapy (compared with a low-density negative ionization placebo condition) was not effective for bipolar depression. The main difference between our study and this earlier study was the timing of light therapy. For this reason, the time of day when patients use the light box is potentially an important determinant in the response.

In seasonal affective disorder (27, 28) and nonseasonal depression (29), the response to morning light therapy is typically attributed to the phase-resetting effects (28). However, the mechanism of response is unclear in bipolar disorder. Combined with a prior night of sleep deprivation, morning (and possibly midday) light therapy can quickly reverse severe bipolar depression in carefully supervised chronotherapeutic protocols (30–32). Compared with morning light therapy, implementing bright light therapy at midday induced robust antidepressant effects and possibly subtle effects on the circadian system (12, 13) that might have mitigated the risk for hypomania or mixed symptoms, as observed in our earlier report (5). But whether the circadian effects of midday light therapy are detectable in bipolar depressed patients and correspond with an antidepressant response requires further investigation. Even so, this novel finding of a significant antidepressant effect from midday bright light therapy offers a real clinical advance and contributes an additional treatment option for bipolar depression.

We detected the large effect of bright light therapy between weeks 4 and 6 (see Figure 1). Because we implemented

FIGURE 1. Remission Rates Across Study Weeks for Patients With Bipolar Depression Treated with Active (Bright White Light) or Inactive (Dim Red Light) Light Therapy[a]



[a] Significant difference in remission rates between the active treatment group (68.2%) and the inactive treatment group (22.2%) (odds ratio=7.50, 95% CI=1.80, 31.28, p=0.003; adjusted odds ratio=12.64, 95% CI=2.16, 74.08, p=0.004).

the dose-titration protocol as a precaution against inducing hypomania or mixed symptoms, we postponed exposure to the full daily light dose (60 minutes) until week 4. The need to reach the maximum light dose to experience a full response might explain the delayed separation of effect of bright light from placebo until weeks 4–6. Most other light studies have implemented full-dose, nontitration protocols and similarly detected remission after 5 weeks for antepartum depression (15) and after 4, 6, and 8 weeks for nonseasonal depression (29). This suggests that our novel dose-titration approach still produced a cumulative therapeutic effect within the same time frame as other protocols and possibly prevented the emergence of hypomania or mania. Given the trajectory of the remission rate curve (see Figure 1), a longer protocol might produce higher rates of remission and response and a larger treatment effect.

The inclusion of patients on concurrent antidepressant treatment was a potential source of heterogeneity; but tapering antidepressants can result in an unacceptable risk of worsening (5). To address this concern, we ensured that patients treated with antidepressants were equally distributed in the two groups. Both groups titrated to the same maximum light dose and the same actual light dose at endpoint, and both indicated similar levels of expectancy. Therefore, the lack of treatment response and the increased withdrawal rate with dim red versus bright white light was probably unrelated to expectancy but rather to the experience of limited therapeutic effect from dim red light. To ensure that responses of both groups were represented, we examined all available data from patients. By examining selected outcomes within the period of weeks 4–6, we were able to consider the patients who completed the dosing protocol and likely received the appropriate exposure to light therapy; however, we were unable to consider the patients who withdrew before then, many of whom were in the placebo comparator group.

Block randomization should mitigate the need for seasonality adjustment. By randomly assigning patients to active or placebo light therapy, the degree of seasonality distributed equally to both treatment groups, as expected. Given that the number of participants enrolled in February and March was unbalanced despite randomization, this actually would bias against the active intervention. Even so, we adjusted for time of enrollment. The unadjusted and adjusted analyses still indicated significant treatment effects with the bright white light intervention as compared with dim red light. We did not explore the responses in patients with or without seasonal affective disorder because subanalyses would be underpowered and would provide inconclusive results. Moreover, the participants had only a moderate level of winter seasonality. This implicates a vulnerability to both seasonal and nonseasonal depression, which is consistent with published reports on the phenomenology of bipolar disorder (33). Given that participants had a SCID-confirmed current major depressive episode (minimum duration of 2 weeks), it is possible that the patients who enrolled in the fall and winter experienced the onset of depression weeks or months earlier and did not have a purely seasonal or winter depression. Even so, further study of the efficacy of midday light therapy for spring- and summer-onset episodes and the long-term prevention of recurrent episodes would be indicated.

We implemented careful design features and enrolled community-based patients with bipolar disorder to better mirror clinical practice and improve the generalizability of the results. Even so, the sample size and the final numbers per group may have constrained our capacity to detect treatment effects and contributed to the wide confidence limits in some outcome measures. Unexpectedly, baseline depression and global functioning scores differed significantly between groups, despite randomization. Because both groups had moderate levels of depression and impaired functioning, categorically, and no other demographic or clinical differences, we judged the groups to be comparable at baseline.

In summary, the study findings provide evidence that confirms the efficacy of add-on bright light therapy for treatment of bipolar depression. The novel use of a dose-titration protocol, implementation of bright light therapy at midday, and the requirement for concurrent antimanic treatment mitigated the risks for emergent mania or hypomania. For this reason, we recommend this conservative approach for indicated patients with bipolar depression. Given its efficacy, ease of use, and tolerability, midday light therapy is ideally suited for depressed patients with bipolar disorder, and it may eventually gain widened acceptance with improved practitioner awareness. Important questions that need further investigation include strategies for maintenance light treatment to

prevent relapse; the biological mechanisms and potential predictors of response; treatment individualization with biomarker identification; and applications in special populations, such as pregnant women and children, who may prefer nonpharmacological, somatic agents.

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REFERENCES

1. Perlis RH, Ostacher MJ, Patel JK, et al: Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2006; 163:217–224
2. Sachs GS, Nierenberg AA, Calabrese JR, et al: Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007; 356:1711–1722
3. Post RM, Altshuler LL, Leverich GS, et al: Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion, and sertraline. Br J Psychiatry 2006;189:124–31
4. Terman M, Amira L, Terman JS, et al: Predictors of response and nonresponse to light treatment for winter depression. Am J Psychiatry 1996; 153:1423–1429
5. Sit D, Wisner KL, Hanusa BH, et al: Light therapy for bipolar disorder: a case series in women. Bipolar Disord 2007; 9:918–927
6. Dauphinais DR, Rosenthal JZ, Terman M, et al: Controlled trial of safety and efficacy of bright light therapy vs negative air ions in patients with bipolar depression. Psychiatry Res 2012; 196:57–61
7. Terman M, Terman JS, Quitkin FM, et al: Light therapy for seasonal affective disorder: a review of efficacy. Neuropsychopharmacology 1989; 2:1–22
8. Wirz-Justice A, Graw P, Kräuchi K, et al: Light therapy in seasonal affective disorder is independent of time of day or circadian phase. Arch Gen Psychiatry 1993; 50:929–937
9. Terman JS, Terman M, Lo ES, et al: Circadian time of morning light administration and therapeutic response in winter depression. Arch Gen Psychiatry 2001; 58:69–75
10. Terman M, Terman JS, Ross DC: A controlled trial of timed bright light and negative air ionization for treatment of winter depression. Arch Gen Psychiatry 1998; 55:875–882
11. Leibenluft E, Turner EH, Feldman-Naim S, et al: Light therapy in patients with rapid cycling bipolar disorder: preliminary results. Psychopharmacol Bull 1995; 31:705–710
12. Hashimoto S, Kohsaka M, Nakamura K, et al: Midday exposure to bright light changes the circadian organization of plasma melatonin rhythm in humans. Neurosci Lett 1997; 221:89–92
13. Mishima K, Okawa M, Shimizu T, et al: Diminished melatonin secretion in the elderly caused by insufficient environmental illumination. J Clin Endocrinol Metab 2001; 86:129–134
14. Oren DA, Brainard GC, Johnston SH, et al: Treatment of seasonal affective disorder with green light and red light. Am J Psychiatry 1991; 148:509–511
15. Wirz-Justice A, Bader A, Frisch U, et al: A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. J Clin Psychiatry 2011; 72:986–993
16. Brainard GC, Hanifin JP, Greeson JM, et al: Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. J Neurosci 2001; 21:6405–6412
17. First MB, Spitzer RL, Gibbon M, et al: Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition. New York, New York State Psychiatric Institute, Biometrics Research, 1996
18. Williams JBW, Terman M: Structured Interview Guide for the Hamilton Depression Rating Scale With Atypical Depression Supplement (SIGH-ADS). New York, New York State Psychiatric Institute, 2003
19. Endicott J, Spitzer RL: A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978; 35:837–844
20. Lam RW, Levitt AJ: Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder. Vancouver, Canada, Clinical and Academic Publishing, 1999
21. Leucht S, Kane JM, Kissling W, et al: Clinical implications of Brief Psychiatric Rating Scale scores. Br J Psychiatry 2005; 187:366–371
22. Beck AT, Kovacs M, Weissman A: Assessment of suicidal intention: the Scale for Suicide Ideation. J Consult Clin Psychol 1979; 47: 343–352
23. Buysse DJ, Reynolds CF 3rd, Monk TH, et al: The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989; 28:193–213
24. Horne JA, Ostberg O: A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1976; 4:97–110
25. Martiny K: Adjunctive bright light in non-seasonal major depression. Acta Psychiatr Scand Suppl 2004; 110(425):7–28
26. Sit D, Luther J, Buysse D, et al: Suicidal ideation in depressed postpartum women: associations with childhood trauma, sleep disturbance, and anxiety. J Psychiatr Res 2015; 66-67:95–104
27. Terman M, Lewy AJ, Dijk DJ, et al: Light treatment for sleep disorders: consensus report, IV: sleep phase and duration disturbances. J Biol Rhythms 1995; 10:135–147
28. Lewy AJ, Lefler BJ, Emens JS, et al: The circadian basis of winter depression. Proc Natl Acad Sci USA 2006; 103:7414–7419
29. Lam RW, Levitt AJ, Levitan RD, et al: Efficacy of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder: a randomized clinical trial. JAMA Psychiatry 2016; 73:56–63
30. Wu JC, Kelsoe JR, Schachat C, et al: Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. Biol Psychiatry 2009; 66:298–301
31. Benedetti F, Riccaboni R, Locatelli C, et al: Rapid treatment response of suicidal symptoms to lithium, sleep deprivation, and light therapy (chronotherapeutics) in drug-resistant bipolar depression. J Clin Psychiatry 2014; 75:133–140
32. Gottlieb JF, Terman M: Outpatient triple chronotherapy for bipolar depression: case report. J Psychiatr Pract 2012; 18:373–380
33. Merikangas KR, Akiskal HS, Angst J, et al: Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 2007; 64:543–552