Case Report

Light therapy for bipolar disorder: a case series in women


Objectives: To perform a dose-ranging safety and efficacy study of bright light therapy for depression in women with bipolar disorder (BD).

Methods: Nine women with DSM-IV BD I or II in the depressed phase were exposed to 50 lux (illuminance at the receiving surface) red light for two weeks, after which they received 7,000 lux light therapy for two-week epochs of 15, 30 and 45 min daily. The Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement and the Mania Rating Scale were used to assess mood symptoms. Four patients received morning light and five patients received midday light.

Results: Three of the four subjects treated with morning light developed mixed states. The fourth subject achieved a full, sustained response. To decrease the risk of inducing mixed episodes, we changed the time of light exposure to midday. Of the five women who received midday light therapy, two achieved full response and two showed early improvement but required a dose increase to sustain response. One woman remained depressed with 45 min of midday light but responded fully to a switch to morning light, 30 min daily.

Conclusions: Women with bipolar illness are highly sensitive to morning bright light treatment; the induction of mixed states is a substantial risk. Initiating treatment with a brief duration (15 min) of midday light for bipolar depression is advisable.

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Treatment interventions for depressed patients with bipolar disorder (BD) have received limited research attention compared to the magnitude of the problem (1). Findings from the largest prospective examination of outcomes in bipolar illness, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), showed recurrent bipolar depression occurred more than twice as often (35%) as recurrence of mania, hypomania or mixed episodes (14%) (2). Despite the advances in somatic therapies for BD, bipolar depression remains a highly recurrent – and mainly depressive – mood disorder (2, 3).

An attractive therapeutic modality is bright light therapy, which is effective for seasonal and
non-seasonal major depression, and not exclusively winter depression with summer hypomania or mania (4). The response rate for light therapy in patients with seasonal bipolar (n = 21) and unipolar (n = 170) depression did not differ significantly (52% and 67% respectively, p > 0.18) (5). Non-seasonally depressed bipolar patients improved more with light therapy (n = 6; 90% reduction in depressive symptoms) compared to their unipolar depressed counterparts (n = 11; 32.8% reduction) (6). These data suggested that patients with bipolar depression respond robustly to light therapy. Lewy et al. (7) observed twice the reduction in plasma melatonin levels among patients with acute bipolar illness who responded to light therapy compared to healthy controls. Separate groups were unable to confirm these findings (8) but have detected other abnormalities, such as low levels of melatonin secretion at baseline in patients with BD I (8, 9) and increased melatonin suppression after light exposure (8, 10).

The efficacy and side effects of light therapy are affected by two important factors, the light dose and the time of day of light exposure. The dose is determined by the intensity emitted from the light source, distance from the light box, and duration of exposure. Most light sources provide 10,000 lux (illuminance at the receiving surface). Although recommendations for the treatment of seasonal affective disorder (SAD; major depressive disorder or BD with a seasonal pattern, according to the DSM-IV) (11) suggest a starting dose of 10,000 lux of morning light for 30 min daily, there are no specific guidelines for the treatment of BD (12) other than the need for anti-manic agent coverage. Investigators have used 2,000 lux of morning light for 2 h daily (6), 400 lux for 2 h daily (6), and 10,000 lux for 45–60 min twice daily (13) with reduction of depressive symptoms in patients with BD. These results could be interpreted as evidence for the efficacy of a wide range of doses of light for patients with BD or as placebo response rates, which average 29% for subjects with bipolar depression (14). Morning light appeared most effective for patients with unipolar depression (4); in contrast, patients with rapid cycling BD responded more favorably to midday light compared to morning or evening (15).

The standard 10,000 lux, ultraviolet-blocked, white fluorescent light box presents minimal risk for adverse outcomes in most patients (5, 16). Commonly reported side effects of light therapy include headache, eyestrain, agitation, and nausea (16–18). Patients with a BD I pattern of SAD are more likely to develop agitation with bright light compared to BD II or unipolar depressed patients (5). Adverse effects usually subside or become tolerable after reduction of the light dose. Insomnia occurred in rapid cycling patients who received 10,000 lux in the evening, while midday light caused no side effects (15). No adverse ocular effects from light therapy were observed after a five-year period (19).

Like other somatic treatments for depression, light therapy precipitates hypomanic/manic episodes in susceptible patients (6, 20, 21). Severely ill patients with BD have experienced light-induced worsening of depressive symptoms, ultrarapid cycling, mixed states and suicidality (15). New-onset suicidal ideation that required hospitalization occurred in three out of nine rapid cycling patients despite continuation of anti-manic drug treatment during light therapy with 10,000 lux light boxes (15). Rapid onset of suicidal ideation and suicide attempts occurred within two weeks after initiating bright light monotherapy for SAD in one patient with unipolar and two patients with bipolar depression (22). These cases suggested suicidal ideation may be triggered by light-induced mania, mixed symptoms or agitation in the setting of patients with a ‘brittle’ form of BD (15) or inadequate anti-manic therapy. Patients with both BD I and SAD who were maintained on anti-manic agents did not develop suicidal ideation with light therapy (5). Others debated that suicidal behavior developed before the onset of full antidepressant effect of light therapy or other somatic treatments (16).

To establish that the treatment response to light is not merely a placebo response, it is essential to incorporate an inactive control. In mood disorders research, a placebo response rate of 29% (+ 12%; range 13–38%) was observed in studies of drug treatments for patients with BD in the depressed phase (14). Studies of the effects on different light spectra on mood indicated that red light is the least likely wavelength to cause changes in depressive symptoms (23, 24). The colored wavelength range above 600 nm, which appears as red, has negligible effect on melatonin suppression, circadian rhythm phase shifting, and clinical response in patients with SAD (24, 25). Red light seems ‘special’ to subjects and has served well as a placebo in other studies (26). Therefore, it was chosen as the inactive comparator in this study.

Bright light therapy is a potentially valuable modality for patients with bipolar depression (whether seasonal or non-seasonal) because: (i) the light dose can be titrated on a daily basis against emergent side effects and hypomania, (ii) major side effects are rare, (iii) drug–drug interactions are avoided in a group of patients likely to be taking multiple medications, and (iv) the treatment is affordable.
and readily disseminated. Therefore, we designed a dose-ranging safety and efficacy study to explore several doses of light for depression in women with BD. Our objectives were to determine: (i) the efficacious light dose for the treatment of bipolar depression, (ii) the rate of induction of mania or mixed states, and (iii) the side-effect profile. A secondary objective was to evaluate dim red illumination as a reasonable placebo comparator.

**Methods**

Nine women with BD I or II, depressed phase, without seasonal pattern were recruited. Incidentally, all women were referred by their psychiatrists mainly because they had failed numerous trials of conventional treatments for bipolar depression. We chose to study only females because this was a convenience pilot sample to obtain in our research clinic. Our subjects were healthy and had normal ocular health. Women were excluded if they took herbal agents like hypericum, beta-blockers or other drugs for an unstable medical disorder, had uncontrolled thyroid disease, current psychosis or generalized anxiety disorder, suicide attempt within 3 months, or alcohol or substance abuse within 6 months. Informed consent was obtained from all subjects. This study protocol was approved by the University of Pittsburgh Institutional Review Board, in accordance with the Helsinki Declaration of 1975.

Diagnoses were confirmed with the Structured Clinical Interview for DSM-IV (27). Mood severity was determined with the Structured Interview Guide for the Hamilton Depression Scale with Atypical Depression Supplement (SIGH-ADS) (25, 28) score 20 or more, and a Mania Rating Scale (MRS) (29) score of <12. The SIGH-ADS and its predecessor, the Structured Interview for the Hamilton Depression Scale-Seasonal Affective Disorder Version (30), have provided a benchmark for assessment of depression severity in light therapy trials. The SIGH-ADS is a depression questionnaire comprised of the 29-item Hamilton Rating Scale for Depression and an additional set of eight questions to probe for light-sensitive atypical symptoms of depression. The MRS is an 11-item symptom measure derived from the Schedule for Affective Disorders and Schizophrenia (29).

All subjects were required to take at least one antimanic agent at a stable dose for four weeks before enrollment and remain on this drug throughout the study. Two subjects continued antidepressant medications at a constant dose.

The dose-ranging phase lasted 8 weeks, and was divided into four, 2-week epochs. The continuation phase to assess durability of response lasted 12 weeks. In the initial study design, the subjects were assigned to morning light therapy. They were asked to awaken 30 min before their usual wake time to use the light box within 10 min of rising. The active light therapy units were 5,000 Kelvin fluorescent light boxes (modified Daylight XL; SphereOne Inc., Silver Plume, CO, USA) that measured 30 × 45 × 36 cm and weighed <2.4 kg. Each subject positioned herself 30–36 cm from the box with her face fully exposed to the box without staring directly at the unit. The first epoch consisted of a placebo lead-in of 70 lux morning dim red light for 30 min daily. Active light therapy was administered in the second, third and fourth epochs. In the second epoch, the subject began with 15 min of active light for two weeks. For each successive epoch, the active light dose was increased by increments of 15 min, until response or a maximum of 45 min daily. Mood, side effects, and treatment compliance were assessed at baseline and weekly during the dose-ranging phase and monthly during the continuation phase. Mood symptoms were evaluated with the SIGH-ADS and the MRS. Compliance with light therapy was tracked on daily sleep logs. An independent evaluator who was blind to the study design completed all follow-up study assessments.

Treatment response was defined as an improvement ≥50% compared to the baseline SIGH-ADS score. Subjects with significant mood worsening, indicated by an increase of SIGH-ADS by ≥10, mania/hypomania MRS ≥12, or suicidal ideation were evaluated for additional intervention. For subjects who developed hypomanic or mixed symptoms, we reduced the light dose immediately and discontinued light therapy in women with significant mood worsening (31). Strategies to manage treatment-emergent hypomania or mixed episodes were recorded. After three of the initial four subjects who received morning light developed mixed episodes, we modified the protocol and implemented active light at midday.

**Results**

Sixty-four women were screened by telephone, 29 completed a baseline assessment, 32 did not meet eligibility criteria for the study or declined participation, and 3 asked to be contacted in the future. Of the 29 subjects who underwent baseline assessment, 12 enrolled in the study, 11 were ineligible, 4 required delays in starting light therapy to address pre-existing medical problems, and 2 declined participation. Three initial study enrollees changed their minds and declined to participate because of
the conservative titration schedule of light dose against emergent side effects over eight weeks. We report data from 9 subjects (Tables 1–3). All women who enrolled in the study had severe BD, but they did not meet criteria for treatment-refractory depression (32).

During the placebo lead-in, women with bipolar depression experienced mild improvement, with a mean SIGH-ADS = 27.2 ± 5.7 at baseline, 24.8 ± 7.2 after one week, and 19.9 ± 6.1 after two weeks of red light. After one and two weeks of red light, the mean SIGH-ADS changes were –2.4 [95% confidence interval (CI) = 1.4 to –5.4; p = 0.26], and –7.3 (95% CI –2.9 to –9.8; p < 0.0001), respectively.

The first four subjects received morning light therapy (Table 2). One patient (subject 2) responded fully at 30 min of daily exposure. Three subjects developed mixed states (subjects 1, 3, and 4), and two required immediate cessation of light therapy (subjects 1 and 3). In subjects 1 and 4, the induction of mixed symptoms happened rapidly after the transition from dim red to morning active light. In subject 3, the mixed state occurred after very brief euthymia under morning light. All three women described irritability, elevated energy, goal-directedness (multi-tasking family- and child-related tasks with own jobs, adding new commitments to an already tight schedule), creativity, aggression, racing thoughts, and pressured speech. Subject 1 was reluctant to stop light therapy due to the rapid onset of elevated mood that she strongly missed during a period of protracted depression preceding the study. Subject 4 noticed grandiose ideations, distractibility, psychomotor agitation, and new onset of auditory hallucinations (vague voices at night) despite ongoing low mood and guilt. She tolerated a light dose reduction that temporarily alleviated her irritable mood. Because of persistent agitation, she requested an open trial of dim red light for an additional three weeks, which she perceived as calming. Eventually, she withdrew due to persistent depression.

Due to the induction of mixed episodes in three out of our first four subjects, similar to the observations of Leibenluft et al. (15) in their patients with rapid cycling BD on light therapy, we adjusted the timing for light exposure to midday (within the range of 12:00–14:00 hours). Of the five subjects receiving midday light, two experienced full response (subjects 8 and 9). One individual (subject 5) responded partially, but achieved full response after a change to 37.5 min of morning light (Table 2). Two individuals (subjects 6 and 7) experienced early, but unsustained response to midday light (Table 3).

Of all full responders, subject 2 completed the entire dose-ranging phase (eight weeks) but was unable to enter the continuation phase because of family commitments; subjects 5, 8 and 9 completed the entire protocol. Both partial responders (subjects 6 and 7) completed the dose-ranging and continuation phases. Subjects 1, 3, and 4, who experienced manic or mixed symptoms after morning light, only completed 5, 4 and 8 weeks, respectively, of the dose-ranging phase.

Subjects 5 and 8 were permitted to remain on antidepressant treatment, along with anti-manic treatment for the study duration. They had been on a stable dose of venlafaxine XL 150 mg daily and paroxetine 20 mg daily, respectively, for >12 weeks prior to their enrollment in the study with stable bipolar depression (no evidence of mixed/manic symptoms while on antidepressant treatment).

Two individuals (subjects 7 and 8) described the onset of pain in their small joints. Three women (subjects 4, 7, and 8) had dysfunctional uterine bleeding with active light therapy. One woman (subject 4) was menopausal and two women (subjects 7 and 8) had pre-existing irregular menstrual periods. Each developed heavy and persistent bleeding unrelated to menses that required uterine biopsy. Their gynecologists detected no evidence of malignancy.

Discussion

We found the optimal response was at 7,000 lux midday light for 45 or 60 min. For midday light non-responders, trials of morning light were offered to two individuals (subjects 5 and 7). Subject 5 achieved full response with 37.5 min of morning light. Subject 7 reached only partial response after a switch to 30 min of morning light; at the final assessment, she preferred pharmacologic intervention to address her ongoing symptoms over further titration of the light dose. Morning light was associated with development of mixed states in three of the four initial subjects (subjects 1, 3 and 4) despite continuation of anti-manic drugs. Both women who responded fully to bright morning light without complications (subjects 2 and 5) had stable bipolar depression and mostly non-seasonal mood episodes; subject 5 had a distant history of SAD. Subject 1, who had past seasonal and non-seasonal bipolar episodes, responded to morning light with rapid onset of mixed symptoms. The onset of action began during the first two weeks of active light therapy similar to the time of onset of action of antidepressant drugs (33) and light therapy for chronic depression (34).
<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Menstrual status</th>
<th>Time of year in study</th>
<th>Bipolar drugs</th>
<th>Episode length</th>
<th>Illness history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>Regular menses by history</td>
<td>Winter–Spring</td>
<td>Lithium 900 mg qd, Lorazepam 1 mg qd</td>
<td>4 months</td>
<td>BD I; recurrent non-seasonal depression and SAD from age 14 years. 2001: bipolar psychosis; mixed episodes. Failed trials: lithium or divalproex sodium combined with SSRI or TCA.</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>Regular menses by history</td>
<td>Winter–Spring</td>
<td>Lithium 300 mg bid</td>
<td>4 weeks</td>
<td>BD II from age 16 years. 1987: mania in pregnancy; began lithium. Recurrent depression – variable response to lithium or combined with fluoxetine.</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>Menopause</td>
<td>Winter</td>
<td>Lithium 900 mg qd, Oxcarbazepine 150 mg qd, Lorazepam 0.5 mg qd</td>
<td>2 weeks</td>
<td>BD I diagnosed in 1994. 2000: florid mania; psychiatric admission. Failed trials: fluoxetine, carbamazepine, amitriptyline, paroxetine.</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>Menopause</td>
<td>Winter–Spring</td>
<td>Aripiprazole 15 mg qd, Lamotrigine 50 mg qd, Venlafaxine XL 150 mg qd, Topiramate 200 mg qd</td>
<td>3 months</td>
<td>BD II with recurrent non-seasonal depression and SAD since age 18 years. Failed trials: aripiprazole, topiramate, venlafaxine.</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>Menopause</td>
<td>Spring–Summer</td>
<td>Ziprasidone 60 mg bid, Divalproex sodium 250 mg bid, Gabapentin 600 mg tid</td>
<td>5 months</td>
<td>BD I; recurrent depression from 1970. 2003–2004: 3 hospitalizations for depression, psychosis, and medication overdose; began divalproex sodium. Failed trials: bupropion, venlafaxine, olanzapine, aripiprazole.</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>Ovulatory (mid-cycle LH tests)</td>
<td>Spring–Summer</td>
<td>Lithium 1500 mg qd, Lamotrigine 400 mg qd, Zolpidem 10 mg qhs, Clonazepam 0.5 mg qd</td>
<td>3 months</td>
<td>BD I; recurrent depression from 1990. 1990–2001: 7 hospitalizations for mania, psychosis, and depression. Failed trials: citalopram, venlafaxine, bupropion, fluoxetine, paroxetine, aripiprazole, topiramate.</td>
</tr>
<tr>
<td>8</td>
<td>43</td>
<td>Ovulatory (mid-cycle LH tests)</td>
<td>Spring–Fall</td>
<td>Lithium 1200 mg daily, Aripiprazole 10 mg qd, Paroxetine 20 mg qd, Fish oil 2000 mg qd</td>
<td>2 months</td>
<td>BD I; &gt;50 depressive episodes in lifetime. 1990–1998: multiple hospitalizations. Failed trials: fluoxetine, bupropion, imipramine, sertraline, fluvoxamine, clobazamine, lithium, ziprasidone, olanzapine, risperidone.</td>
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</table>

BD I = bipolar I disorder; BD II = bipolar II disorder; SAD = seasonal affective disorder; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; LH = luteinizing hormone.
These findings contrast with earlier data that suggested the onset of therapeutic effects from light therapy within 2–4 days after starting bright light therapy in patients with bipolar SAD (35). Two subjects remained on their antidepressant drugs along with anti-manic therapy (subjects 5 and 8) because they did not tolerate a complete taper and withdrawal of their antidepressant drugs.

The response rates that we observed were similar to those of other investigators who have used bright light for treatment-resistant depression in patients with BD. In our study, 44% of patients were full responders (subjects 2, 5, 8, and 9) and 22% were partial responders (subjects 6 and 7). In non-treatment-resistant patients, Benedetti et al. (36) reported a response rate of 44% in patients who had failed to respond to adequate trials of one or more antidepressant drugs. Patients with BD often struggle with persistent subsyndromal or syndromal depressive symptoms that negatively impact function (37). Light therapy, therefore, is an attractive and possibly effective augmentation strategy to improve the likelihood of full treatment response.

We ascertained the frequency of treatment resistance in our patients and excluded all rapid cycling patients due to concerns about the induction of worsening illness with light therapy (15). Although our patients did not meet criteria for treatment resistance (32), their histories indicated lengthy illnesses punctuated with numerous hospitalizations and multiple medication trials with lasting functional impairment. Once they were appropriately diagnosed with BD, our subjects responded well to anti-manic agents, and suffered few recurrences of manic or hypomanic episodes. However, these treatments failed to eliminate depressive episodes.

Our experience with morning light sustained and extended the preliminary findings of Leibenluft et al. (15), who reported mood-destabilizing effects in three of five patients with rapid cycling bipolar illness. One of their patients developed worsening depression, another switched to hypomania and ultra-rapid cycling (from mania to depression within the same day) and the third experienced a switch to hypomania followed by acute depression. In contrast, midday light restored mood stability in two patients by eliminating both depressive and hypomanic symptoms. Leibenluft et al. (15) hypothesized that midday light could increase the amplitude of nighttime melatonin secretion and prevent endogenous circadian rhythm phase advances, which casts doubt on the hypothesis that phase advances are essential for achieving therapeutic response (38). Such circadian rhythm stabilization could increase the likelihood that

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mood severity</th>
<th>Light dose</th>
<th>Baseline</th>
<th>Hours sleep; sleep onset/wake time</th>
<th>Mood severity</th>
<th>Light dose</th>
<th>Baseline</th>
<th>Hours sleep; sleep onset/wake time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SIGH-ADS = 30</td>
<td>15 min AM light</td>
<td>9.75 h; 23:15–09:00 hours</td>
<td>SIGH-ADS = 9</td>
<td>MRS = 0</td>
<td>5 h; 00:00–09:00 hours</td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>SIGH-ADS = 27</td>
<td>30 min AM light</td>
<td>6 h; 00:30–09:00 hours</td>
<td>SIGH-ADS = 6</td>
<td>MRS = 10</td>
<td>7.25 h; 23:35–07:00 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SIGH-ADS = 25</td>
<td>15 min AM light</td>
<td>7.25 h; 00:00–07:15 hours</td>
<td>SIGH-ADS = 4</td>
<td>MRS = 15</td>
<td>7 h; 22:00–07:00 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>SIGH-ADS = 20</td>
<td>15 min AM light</td>
<td>11.5 h; 20:00–07:00 hours</td>
<td>SIGH-ADS = 9</td>
<td>MRS = 9</td>
<td>7.25 h; 22:30–07:30 hours</td>
<td></td>
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</tbody>
</table>

SIGH-ADS = The Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement; MRS = Mania Rating Scale. Some patients suffered insomnia and spent several min-hours awake during the night. Therefore, the total hours slept was not derived from the subtraction of the wake time from the sleep onset.
Table 3. Response to midday light therapy

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mood severity</th>
<th>Baseline</th>
<th>Red light</th>
<th>Response</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Hours sleep; sleep onset/wake time&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mood severity</td>
<td>Hours sleep; sleep onset/wake time&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Full responders</td>
<td>5</td>
<td>SIGH-ADS = 25</td>
<td>10.5 h; 20:30-07:00 hours</td>
<td>SIGH-ADS = 17</td>
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<td></td>
<td></td>
<td>MRS = 0</td>
<td></td>
<td>MRS = 0</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>SIGH-ADS = 31</td>
<td>8.5 h; 22:00-08:30 hours</td>
<td>SIGH-ADS = 19</td>
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<td></td>
<td></td>
<td>MRS = 0</td>
<td></td>
<td>MRS = 0</td>
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<tr>
<td></td>
<td>9</td>
<td>SIGH-ADS = 29</td>
<td>10 h; 23:30-10:15 hours</td>
<td>SIGH-ADS = 25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRS = 0</td>
<td></td>
<td>MRS = 0</td>
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<tr>
<td>Partial responders</td>
<td>6</td>
<td>SIGH-ADS = 29</td>
<td>8 h; 03:00-11:00 hours</td>
<td>SIGH-ADS = 19</td>
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<tr>
<td></td>
<td></td>
<td>MRS = 2</td>
<td></td>
<td>MRS = 0</td>
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<tr>
<td></td>
<td>7</td>
<td>SIGH-ADS = 21</td>
<td>8 h; 03:00-11:00 hours</td>
<td>SIGH-ADS = 20</td>
</tr>
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<td></td>
<td></td>
<td>MRS = 0</td>
<td></td>
<td>MRS = 0</td>
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SIGH-ADS = The Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement; MRS = Mania Rating Scale.

<sup>a</sup>Some patients suffered insomnia and spent several min-hours awake during the night. Therefore, the total hours slept was not derived from the subtraction of the wake time from the sleep onset.
patients with rapid cycling or difficult-to-treat BD I disorder would respond to the activating or antidepressant effects of light therapy without hypomania or mood cycling. Further research of women and men is required to confirm the differential response to light therapy timing across both genders.

The induction of mania or mixed states has been reported as a relatively rare phenomenon in the light therapy literature (5, 36). However, these protocols rarely have included a formal mania rating scale. It is possible that such states occurred but were captured as non-responders with worsening depression or early withdrawals from treatment. Mania or mixed symptoms can be managed with a reduction in the patient’s dose of light. Leibenluft et al. (15) recommended against the use of light therapy on days that a person has hypomania. Symptoms of mania emerged only after implementation of bright morning light. Parallel trials are needed to assess the efficacy of dim red light as a placebo control for treatment of bipolar depression; no side effects emerged during dim red light exposure in our study.

Gynecologic side effects arose in three women (subjects 4, 7, and 8) after starting active light. Further investigation indicated no underlying pathology for these participants; one patient (subject 8) elected to begin hormonal contraception to regulate a pre-existing problem of irregular menstrual cycles. One case of menometrorrhagia within the first month of active light for a patient with SAD has been reported. Her bleeding ceased when she discontinued use of the light box (39). One year later, she attempted a second trial of light therapy, and quickly developed menometrorrhagia again. Two women experienced mild uterine bleeding after beginning light treatment at midcycle, but this did not recur on subsequent menstrual cycles (16). The impact of light therapy on the hypothalamic–pituitary–ovarian axis may have led to disruptions in the menstrual cycle. In mild cases, these complications resolve spontaneously, but certain patients may not be able to tolerate light therapy if heavy vaginal bleeding occurs. Such patients should receive a medical workup to exclude a pre-existing gynecologic disorder.

The efficacy of somatic treatments for bipolar depression remains very limited. Our pilot findings highlight the potential benefit of bright light therapy for bipolar depression and the importance of future research using a randomized placebo-controlled design to explore the effectiveness of midday light therapy in men and women. The incorporation of a parallel placebo group could reduce our titration phase by 25% (eliminating the

first treatment epoch), and control for the possible confounding effect of spontaneous remission.

For physicians who face the challenge of managing patients with bipolar depression who have not responded to conventional therapies, we recommend the following approach for implementing light therapy (40):

(i) Maintain patients on a stable dose (or serum drug level) of anti-manic drug.

(ii) Most commercially available light boxes are able to provide up to 10,000 lux. Criteria for the selection of apparatus are outlined on websites that include the Center for Environmental Therapeutics (http://www.cet.org) and the Society for Light Treatment and Biological Rhythms (http://www.sltr.org). Close monitoring of the individual patient treatment response to purchased light boxes is critical since our intervention was based on 7,000 lux units.

(iii) Perform an opthalmologic assessment if patients develop eye problems after beginning light therapy or if they have pre-existing eye diseases. Specifically include individuals with past or current retinal disease, cataract surgery and lens removal, macular degeneration, or who are taking photosensitizing drugs such as lithium, phenothiazines (e.g., chlorpromazine), antimalarial drugs, melatonin and hypericum (9).

(iv) Monitor side effects, including headache, eye strain or discomfort, nausea, agitation, insomnia. If a patient develops intolerable side effects, hypomania or mixed symptoms, light treatment may need to be temporarily discontinued. Alternatively, the dose could be discontinued or reduced by 7–15 min (or more) until the side effect has lessened, and before considering dose advancement. Patients should not use the light box on days when they have symptoms of hypomania (15). If the patient has suicidal ideation, psychosis, or intolerable agitation, the patient should stop light therapy and hospitalization should be considered (15).

(v) Begin with midday light therapy between 12:00–14:00 hours at a daily dose of 15 min and increase by 15 min every two weeks until the patient has reached a euthymic mood state. The upper limit of midday light is 45–60 min, beyond which patients are more likely to have difficulty with adherence.

(vi) For treatment responders, it is reasonable to continue light therapy for 12 months after remission to prevent relapses, similar to the
recommendations for antidepressant therapy (41). Without continuation light therapy, Benedetti et al. (36) found that only 57% (13/23) of medication responders and 17% (2/12) of medication-resistant patients with bipolar depression remained depression-free at 9-month follow up. Our study was an 8-week acute therapy trial and the subjects who responded to light remained euthymic for the 12-week follow-up period with continuation light therapy. The guidelines for treatment of SAD, with discontinuation in late spring (16) are not generalizable to patients with non-seasonal BD.

(vii) Consider a change to morning light at a starting dose of 15 min for patients who respond partially or minimally to 45–60 min of midday light without side effects. This should be undertaken with close monitoring since patients with bipolar illness are very sensitive to morning light. Therefore, morning light should be increased by increments no faster than every other week by an additional 7–15 min.

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