Randomized Clinical Trial of Bright Light Therapy for Antepartum Depression: Preliminary Findings

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Background: Bright light therapy was shown to be a promising treatment for depression during pregnancy in a recent open-label study. In an extension of this work, we report findings from a double-blind placebo-controlled pilot study.

Method: Ten pregnant women with DSM-IV major depressive disorder were randomly assigned from April 2000 to January 2002 to a 5-week clinical trial with either a 7000 lux (active) or 500 lux (placebo) light box. At the end of the randomized controlled trial, subjects had the option of continuing in a 5-week extension phase. The Structured Interview Guide for the Hamilton Depression Scale-Seasonal Affective Disorder Version was administered to assess changes in clinical status. Salivary melatonin was used to index circadian rhythm phase for comparison with antidepressant results.

Results: Although there was a small mean group advantage of active treatment throughout the randomized controlled trial, it was not statistically significant. However, in the longer 10-week trial, the presence of active versus placebo light produced a clear treatment effect (p = .001) with an effect size (0.43) similar to that seen in antidepressant drug trials. Successful treatment with bright light was associated with phase advances of the melatonin rhythm.

Conclusion: These findings provide additional evidence for an active effect of bright light therapy for antepartum depression and underscore the need for an expanded randomized clinical trial.

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morning light therapy depends on the circadian time of light administration relative to evening melatonin onset.\textsuperscript{14}

**METHOD**

Pregnant depressed women were recruited through the media and referrals from local health care providers. After describing the study to prospective subjects, written informed consent was obtained for this study, which was approved by each institution’s internal review board. Subjects met DSM-IV criteria\textsuperscript{13} for major depressive disorder. The 29-item Structured Interview Guide for the Hamilton Depression Scale-Seasonal Affective Disorder Version (SIGH-SAD)\textsuperscript{16} was designed to measure symptoms from the 21-item Hamilton Rating Scale for Depression\textsuperscript{17} in addition to those from an 8-item scale for atypical (reversed neurovegetative) symptoms. A baseline score of at least 20 on the SIGH-SAD was required for inclusion. Current use of psychotropic medication, recent suicide attempt, presence of another Axis I disorder, current medical or neurologic disorder, or a diagnosed sleep disorder were bases for exclusion. Ten women were enrolled from April 2000 to January 2002.

During a 1-week observation period, patients started a sleep log. In a preparatory adjustment procedure, they were instructed to wake up 30 minutes earlier than usual to accommodate the morning light exposure. With earlier wake-up time established before treatment began, we attempted to control for the possible impact of the shifted sleep schedule on clinical response and/or melatonin secretion phase. Subjects were then to receive daily treatment for 5 weeks using a specially designed 2.7-kg (6.0-lb) light box (modified HealthLight, SphereOne Inc., Silver Plume, Colo.) with a surface area of 55.0 cm $\times$ 37.5 cm (21.7 in $\times$ 14.8 in). Each light box provided a broad field of either bright (7000 lux [active]) or dim (500 lux [placebo]) ultraviolet-screened, diffuse broad-band fluorescent illumination at a distance of 33 cm (13 in). Subjects began their 60-minute treatment sessions within 10 minutes of rising. During clinic visits, which alternated weekly with telephone assessments, subjects were seen by psychiatrists and rated by experienced clinicians using the SIGH-SAD. As a compliance check, subjects called the clinic daily to log the time of treatment. Five weeks after randomization, the nonblinded medical monitor gave all responders the option to continue using the same light box for an additional 5 weeks. Partial responders (25%–49% reduction in SIGH-SAD score) to active light were instructed to increase the duration of daily exposure to 75 minutes for the next 5 weeks. Placebo nonresponders were given the option of treatment with an active light box. Clinicians and the research psychiatrists remained blinded to the subjects’ group assignments and continued to monitor subjects for evidence of clinical deterioration, hypomania, and side effects.

Subjects collected 9 saliva samples at 30-minute intervals under dim light conditions at home preceding bedtime during baseline and at the end of the first 5 weeks of light therapy. Saliva samples were assayed for melatonin using a highly specific radioimmunoassay (Bühlmann Laboratories A.G., Allschwil, Switzerland). Melatonin onset phase was defined as the time the rising concentration curve crossed 3.0 pg/mL.

Due to the small sample size in this pilot investigation, differences in categorical variables (responder/nonresponder) were evaluated descriptively. Comparisons of the subjects’ response to bright and dim light were made with 2 measures of response and at 2 time points. The first measure of response was the continuous SIGH-SAD score; the second was a variable that dichotomized the sample into 2 groups: those who achieved or failed to achieve a $\geq 50\%$ reduction in baseline SIGH-SAD score (responders and nonresponders, respectively). The analysis of response at week 5 most directly tests the impact of being assigned to bright light compared with dim light therapy during the randomized controlled trial. Analysis of the responses for the entire 10-week trial with the presence of bright light as a time-dependent variable tested whether the increases and decreases in the light duration and intensity, made as part of our clinical management of subjects, had a significant impact on depressive symptoms. Analysis at week 5 was completed with a t test for the continuous measure and Fisher exact test for the dichotomized measure. Analysis across the 10-week period was done with a mixed-effect linear regression model that tested the significance of assigned condition, week in study, and intensity and duration of light as time-dependent covariates.\textsuperscript{18}

**RESULTS**

Ten women underwent baseline observation and were randomly assigned to receive daily bright light (N = 5) or dim light (N = 5). Eight women were white, 1 was African American and 1 was Hispanic. Their mean age was 32.1 years (range, 24–37 years) and mean gestational age was 19.5 weeks (range, 8–32 weeks). There were no significant differences between groups in age (p = .15) or gestational week (p = .88) (Table 1). Although the presence of seasonality was not exclusionary, only 1 subject (#4) met DSM-IV criteria for the seasonal pattern specifier. Even so, half of the subjects (3 in the active group, 2 in the placebo group) showed Global Seasonality Scores (GSS)\textsuperscript{19} between 11 and 21, and 8 of 10 patients received treatment between October and February, which is typical for patients with seasonal affective disorder (SAD). Episode onsets, however, generally preceded the fall/winter season. Baseline SIGH-SAD scores (mean $\pm$ SD score = 27.6 $\pm$ 5.6 [active] and 28.6 $\pm$ 8.7 [placebo]) were not significantly different. Eight women

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Table 1. Subject Characteristics and Clinical and Circadian Response to Active or Placebo Bright Light Therapy for Antepartum Depression

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (y)</th>
<th>Gestation, wk</th>
<th>Month of Episode Onset</th>
<th>Global Seasonality Score</th>
<th>Enrolled Months</th>
<th>Baseline SIGH-SAD Score</th>
<th>Treatment Assignment</th>
<th>5-Week Endpoint SIGH-SAD Score</th>
<th>Status at 10 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>16</td>
<td>Nov</td>
<td>26</td>
<td>16</td>
<td>222</td>
<td>Active</td>
<td>4</td>
<td>Open continuation, remitted</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>11</td>
<td>Nov</td>
<td>26</td>
<td>16</td>
<td>222.2</td>
<td>Active</td>
<td>4</td>
<td>Open continuation, remitted</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>16</td>
<td>Nov</td>
<td>18</td>
<td>20</td>
<td>243.5</td>
<td>Active</td>
<td>4</td>
<td>Open continuation, remitted</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>18</td>
<td>Dec</td>
<td>16</td>
<td>20</td>
<td>207</td>
<td>Active</td>
<td>4</td>
<td>Open continuation, remitted</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>19</td>
<td>Jan</td>
<td>20</td>
<td>20</td>
<td>204.1</td>
<td>Active</td>
<td>4</td>
<td>Open continuation, remitted</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>19</td>
<td>Dec</td>
<td>18</td>
<td>19</td>
<td>1837</td>
<td>Active</td>
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<td>19</td>
<td>Nov</td>
<td>20</td>
<td>20</td>
<td>2004</td>
<td>Placebo</td>
<td>4</td>
<td>Withdrawn (placebo responder)</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>35</td>
<td>Aug</td>
<td>35</td>
<td>32</td>
<td>33</td>
<td>Placebo</td>
<td>4</td>
<td>Withdrawn (placebo responder)</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>30</td>
<td>Mar</td>
<td>30</td>
<td>29</td>
<td>23</td>
<td>Placebo</td>
<td>4</td>
<td>Withdrawn (placebo responder)</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>31</td>
<td>Feb</td>
<td>31</td>
<td>30</td>
<td>33</td>
<td>Placebo</td>
<td>4</td>
<td>Withdrawn (placebo responder)</td>
</tr>
</tbody>
</table>

Table notes:
- 5 pg/mL criterion based on salivary radioimmunoassay.
- Mean ± SD.
- t = statistical significance, which could indicate an underpowered trial with small sample size.
- t with unequal variances = 0.16, p = .86.
- With response to light defined as a ≥ 50% reduction in SIGH-SAD score, at 5 weeks there were 2 responders in each group. Subject 5 responded at week 4; however, her depressive symptoms worsened in week 5 when light exposure duration was decreased to 45 minutes because of emerging hypomanic symptoms. Thus, if we include her treatment response at week 4, 3 (60%) of the 5 subjects in the active group responded, compared with 2 (40%) of 5 subjects in the placebo group. At the end of week 5, however, there was no significant difference in mean change in SIGH-SAD scores (active group = 17.3 vs. placebo group = 16.6; t with unequal variances = 0.16, p = .88).

Figure 1 illustrates a gradual trend toward improvement according to the SIGH-SAD in both groups across the 5 weeks of acute treatment. There was a consistent mean advantage of bright light exposure. Notably, the bright light group showed a 10-point improvement at week 1, while the placebo group improved by only 5 points. The group differences, however, were not statistically significant, which could indicate an underpowered trial with small sample size.

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Figure 2 presents 10-week data for the 3 subjects in whom the light dose was manipulated given initial nonresponse or, in the case of subject 5, overresponse. This subject showed steady improvement toward remission (SIGH-SAD score = 6) when an irritable hypomania (with racing thoughts, marked increase in physical activity, decreased need for sleep, and elevated self-esteem) led us to shorten her exposure duration to 45 minutes. Symptoms resolved within 2 days; however, there was subsequent relapse to a SIGH-SAD score of 23 in week 6. After a small increment in exposure duration to 50 minutes, she rapidly regained remission and remained euthymic. Subject 2 showed no clinical improvement under bright light at a 60-minute duration, with weekly SIGH-SAD scores of ≥ 20. She improved, however, when duration was increased to 75 minutes after week 5, with remission (SIGH-SAD score = 4) at week 10. Subject 9, a placebo nonresponder, was switched to active light after week 5, with an improvement to a SIGH-SAD score of 11 (52% relative to baseline) by week 10.

In the random-effects regression analysis across the 10 weeks, with the presence of bright light as a time-dependent variable, we found a significant effect for the presence of active light (β-coefficient = –8.16, 95% confidence interval [CI] = –12.84 to –3.48, p = .001). This translates to an effect size of 0.43 for bright light therapy. An equivalent analysis for the 5-week randomized controlled trial showed no such significance (β-coefficient = –2.21, 95% CI = –8.99 to 4.57, p = .52), which may indi-
cate the importance of individualized dosing of light for achieving successful treatment.

The clinical response to light therapy and the circadian timing of light exposure are interconnected. Patients with SAD respond most strongly to morning light given 7.5 to 9.5 hours after melatonin onset, while light treatment later in the morning produces half the remission rate.\textsuperscript{14} Earlier treatment also produces larger phase advances of melatonin secretion than does later treatment. Likewise, in the present study, 2 bright light responders with more than 85% improvement in their SIGH-SAD score received treatment less than 9.6 hours after melatonin onset, while 2 nonresponders with less than 40% improvement received treatment more than 11.0 hours after melatonin onset. The probability of such an orderly outcome is 0.042 when gauged against chance pairings of the 2 variables.

At baseline, melatonin onset phase ranged from 1857 to 2222 hours (mean $\pm$ SD = 2052 $\pm$ 1:08 hours; see Table 1). By far, the earliest melatonin onset was shown by subject 5, who showed a hypomanic response to light. Subjects who received bright light showed a mean melatonin phase advance of 0.99 $\pm$ 0.17 hours (range, 0.74–1.14 hours), similar to that seen in treatment of SAD.\textsuperscript{14} Unfortunately, posttreatment placebo data were available for only 1 subject (#9) who, however, showed a smaller phase advance of 0.42 hours with partial clinical response.\textsuperscript{14}

**DISCUSSION**

These data from a small, randomized controlled trial provide further clinical evidence that light therapy may be an effective treatment for antepartum depression. Certainly, one limitation of this study is the small sample size, which likely contributed to the lack of difference between placebo and active light groups at the end of week 5. Whether the effectiveness of bright light therapy, which was demonstrated at the end of week 10, is due to enhanced statistical power or adjustments of the daily light dose is unclear. We chose 500 lux, which lies within the upper range of normal room light, as our dim light condition rather than a lower intensity in order to reduce the chance that the light would be perceived as a placebo. Intensities up to 500 lux have served well as controls for bright light exposure in SAD trials.\textsuperscript{20} However, 500
lux might have added an active factor to the placebo response, considering that studies have demonstrated that white light intensity as low as 40 to 80 lux can suppress melatonin secretion, and light only slightly higher, approximately 100 lux, can phase-shift human circadian rhythms. The relevance of these studies to clinical treatment is still unclear, however, because antidepressant effects have never been demonstrated at such low levels.

One intriguing aspect of the study was the effectiveness of dose manipulation, similar to that of medications. Dosing of light is flexible and can be changed daily if untoward effects such as hypomania occur, which enhances the clinical safety of this intervention. Every active antidepressant carries some risk of hypomania, and light appears to be no exception.

Our subjects were carefully screened, and women with clinical complications such as comorbidity (including bipolar disorder) and suicidality were excluded because of an increased risk for decompensation. Aside from the reported transient hypomania in a woman with no such previous history, there were no clinically significant side effects. Although we entered subjects from September through April (there happened to be no enrollments in summer, and only 1 subject enrolled met DSM-IV criteria for seasonal pattern), we cannot rule out a winter seasonal dependency for the treatment effect. All 3 responders in the active group had a GSS of ≥16 and were treated in winter (Table 1). By contrast, there was no correlation between GSS and treatment response in our open-label study.

Animal studies suggest that melatonin secretion is unaffected by stage of pregnancy. In our study, both baseline and posttreatment melatonin onset phases were similar to that seen in patients with SAD. The magnitude of improvement under treatment was related to the time of morning light administration relative to melatonin secretion onset phase (“internal,” circadian time). This result is consistent with the phase shift hypothesis of the antidepressant effect of light therapy, as originally articulated for patients with SAD. A question remains about whether the phase advances to light shown by our antepartum patients were tied to a seasonal mechanism, since the most successful clinical responses in this small study occurred in winter.

These data are consistent with our previous open-label findings that morning bright light therapy has antidepressant effects in depressed pregnant women. The relative dearth of studies that focus on the neurodevelopmental impact of in utero exposure to other somatic antidepressant therapies, taken with the encouraging nature of these findings, underscores the need for a full-scale clinical trial to determine whether light therapy can be added to the antidepressant armamentarium for depressed pregnant women.

REFERENCES