A controlled study of light therapy in women with late luteal phase dysphoric disorder

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Received 21 December 1998; received in revised form 16 April 1999; accepted 12 May 1999

Abstract

Previous studies suggest that light therapy, as used to treat seasonal affective disorder, may be beneficial for pre-menstrual depressive disorders. We conducted a six-menstrual cycle randomized, double-blind, counter-balanced, crossover study of dim vs. bright light therapy in women with late luteal phase dysphoric disorder (LLPDD). Fourteen women who met DSM-III-R criteria for LLPDD completed two menstrual cycles of prospective baseline monitoring of pre-menstrual symptoms, followed by two cycles of each treatment. During the 2-week luteal phase of each treatment cycle, patients were randomized to receive 30 min of evening light therapy using: (1) 10000 lx cool-white fluorescent light (active condition); or (2) 500 lx red fluorescent light (placebo condition), administered by a light box at their homes. After two menstrual cycles of treatment, patients were immediately crossed over to the other condition for another two cycles. Outcome measures were assessed at the mid-follicular and luteal phases of each cycle. Results showed that the active bright white light condition significantly reduced depression and pre-menstrual tension scores during the symptomatic luteal phase, compared to baseline, while the placebo dim red light condition did not. These results suggest that bright light therapy is an effective treatment for LLPDD. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Premenstrual; Depressive disorders; Seasonal affective disorder; Phototherapy; Circadian rhythms; Premenstrual dysphoric disorder; Serotonin

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1. Introduction

Bright light therapy is an effective treatment for winter seasonal affective disorder (SAD) (Rosenthal et al., 1984). Light therapy has also been studied in other disorders involving disturbances of mood and appetite, including non-seasonal major depression (Kripke et al., 1992; Yamada et al., 1995), bulimia nervosa (Lam et al., 1994; Blouin et al., 1996), and late luteal phase dysphoric disorder (LLPDD) (Parry et al., 1989, 1993). Recent light therapy studies in LLPDD produced equivocal results, but these studies assessed treatment over only one menstrual cycle and used a light treatment protocol that is less convenient. The objective of this study was to examine evening light therapy using a higher intensity light therapy protocol in women with LLPDD treated for two menstrual cycles.

2. Method

2.1. Patients

Patients were recruited from a specialized outpatient Pre-menstrual Syndrome (PMS) Clinic at B.C. Women's Hospital and Health Sciences Centre in Vancouver, Canada, where referrals are made by family physicians. All patients resided within the Greater Vancouver area (latitude 49°N). The clinic patients were assessed using an unstructured clinical interview by one of two psychiatrists with clinical and research expertise in pre-menstrual disorders (DC, SM). The diagnosis of LLPDD, based on DSM-III-R criteria, was made using all available medical information and, when available, review of a prospective, patient-completed daily symptom diary (Reid, 1985). The likelihood of the LLPDD diagnosis was rated as 'low', 'moderate', or 'high' based on the clinical judgement of the interviewers. The descriptor 'high' was used for those diagnoses which could be confirmed by a prospective symptom diary, while the term 'moderate' was applied if retrospective history strongly suggested a diagnosis of LLPDD, but no prospective measures were available. For the purposes of the study, patients assessed as having LLPDD of 'moderate' or 'high' probability were eligible for this study.

Entry criteria included a provisional diagnosis of LLPDD, regular menstrual cycles lasting between 25 and 34 days, and significant symptoms on the Structured Interview Guide for the Hamilton Depression Scale—Seasonal Affective Disorder version (SIGH—SAD, Williams et al., 1988) during the symptomatic luteal phase. The SIGH—SAD comprises the usual 21-item Hamilton Depression Rating Scale (Hamilton, 1967) and an eight-item addendum that assesses atypical symptoms including hypersomnia and hyperphagia. Exclusion criteria for the study were any psychotropic drug use within 2 weeks of study start, use of hormone preparations including oral contraceptives, past hysterectomy (because of difficulty determining timing of menstrual cycle), irregular menstrual cycles, and unstable medical or psychiatric illness. All patients gave written informed consent for the study, and the study was approved by the Human Ethics Committee of the University of B.C.

2.2. Methods

This study used a double-blind, randomized, counter-balanced, crossover design. Patients were followed prospectively for two menstrual cycles as a baseline period. They were then randomized to two menstrual cycles of treatment with either bright white light, or dim red light. After two treatment cycles, they were immediately crossed-over to the other condition for another two menstrual cycles. During the baseline period and throughout the study, patients were asked to keep a regular sleep schedule and to avoid unnecessary outdoor exposure.

For the treatment conditions, patients were instructed on the use of a light box, and used the light box at home for 30 min daily during the 2-week luteal phase (2 weeks prior to the expected beginning of their menstrual period). Patients used the light box between 19.00 and 21.00 h. Patients kept a daily log of their light box use that was reviewed at the assessment visit. For the active bright light condition, the light box consisted of cool-white fluorescent tubes rated at...
10,000 lx at the level of the cornea, and fitted with an ultraviolet filter. This protocol has been found to be effective in patients with SAD (Terman et al., 1990; Magnusson and Kristbjarnarson, 1991; Terman et al., 1998). For the dim light condition, red gel filters were installed in identical light boxes, so that they emitted 500 lx at the level of the cornea with the patient sitting in the same position.

Dim light treatment was used to control for non-specific effects in this study. A 500-lx intensity was chosen because it has not had significant therapeutic effects in light box studies (Terman et al., 1989; Lam et al., 1991) and does not appear to affect human circadian rhythms. Although termed ‘dim’ light, use of a light box rated at 500 lx is still brighter than office lighting and thus is a plausible treatment for patients. To further enhance plausibility, a red gel filter was used for the 500-lx condition. Red wavelengths were found to be less active compared to green and white light in a light box study in SAD (Oren et al., 1991). In addition, patients more readily believe that a red light is an active treatment (Kripke et al., 1992). Deception was used to obscure study objectives, by explaining to patients that the wavelength (color) of light was being studied, and by presenting the potential effectiveness of each condition in a neutral manner. The success of the deception and the pre-treatment expectation of benefit was assessed using a questionnaire modeled after Borkovec and Nau (1972) and used in other light therapy studies (Joffe et al., 1993; Lam et al., 1994). Following completion of the study, all patients were debriefed and the deception was revealed.

Subjects were assessed twice per month throughout the course of the study. One visit was scheduled during the mid-follicular phase (days 6–13) and the other visit during the symptomatic luteal phase of the cycle (days 21–28). During these visits, raters blind to treatment condition completed the SIGH–SAD and the Clinical Global Impression (CGI) severity and improvement scales (Guy, 1976), and recorded side effects. The patients completed the Beck Depression Inventory (BDI) (Beck, 1978) and the Premenstrual Tension Scale (PMTS), a 35-item self-rated questionnaire that includes assessment of physical symptoms associated with pre-menstrual syndrome (Steiner et al., 1980). Patients also completed the Seasonal Pattern Assessment Questionnaire (SPAQ, Rosenthal et al., 1987) at initial assessment. The SPAQ is widely used as a screening questionnaire for seasonality and seasonal affective disorder (Kasper et al., 1989).

For data analysis, a difference score for each outcome measure was calculated, for each menstrual cycle, by subtracting the score during the mid-follicular phase assessment from the score during the luteal phase. The difference score was then summed over the two menstrual cycles of each condition (baseline, dim light, bright light). These data were analyzed using non-parametric statistics including Friedman’s two-way ANOVA. Post hoc pairwise comparisons between conditions (baseline, bright white light, dim red light) were conducted using Nemenyi’s Tests for ordered data (Linton and Gallo, 1975) to control for multiple comparisons. The frequency of response as determined by the CGI-Improvement scale for each treatment condition was compared using McNemar’s \( \chi^2 \), Wilcoxon signed rank tests were used for the paired data from the expectation questionnaire, and Spearman’s correlations were used for correlational analysis. All data analyses were conducted using the SPSS for Windows software package (SPSS, Inc., 1994).

3. Results

Fourteen patients entered and completed the study. The mean age (± S.D.) was 38.7 ± 4.1 years (range 32–45 years). The mean menstrual cycle length (± S.D.) was 28.5 ± 2.2 days (range 25–32 days), and the mean duration of symptoms (± S.D.) was 9.5 ± 4.7 days (range 4–14 days). Four patients (29%) had past histories of major depressive disorder, but none met criteria for major depressive episode during the course of this study. The Global Seasonality Score (GSS), as derived from the SPAQ, had a mean (± S.D.) of 11.4 ± 4.2. The 6-month protocol was initiated during the months of February (two patients), March (three patients), April (three patients), May
(three patients), August (two patients) and October (one patient). Seven patients were treated in the dim red light condition during the summer months of June, July, and August, compared to eight patients treated in the bright white light condition during those months.

Table 1 summarizes data from the 2-month baseline period. As expected, scores were significantly higher during the symptomatic luteal phase compared to the follicular phase (all $P < 0.002$). There were no significant differences between the two baseline cycles within either menstrual phase. The expectation questionnaire scores were not significantly different between red light and white light (Wilcoxon signed ranks test, $z = 0.94$, $P > 0.34$, ns), showing that the study deception was effective in balancing expectations of response between the two treatment conditions.

Table 2 summarizes the results of each outcome measure for each treatment condition. There were statistically significant overall differences between the three conditions (baseline, dim light, bright light) in all the outcome measures. For each measure, patients improved during both active and placebo treatment conditions, but post hoc paired comparisons showed that only the active bright white light condition was found to be significantly better than the baseline condition. No significant differences were found between the dim red light condition and baseline, nor between the two light conditions. There was no significant effect of order of treatment, i.e. when the bright white light condition was presented first or second (Mann Whitney $U = 19.5$, $P > 0.50$, ns).

In the Clinical Global Impression-Improvement scores, patients were rated by the blinded clinicians as Much Improved or Very Much Improved in 25 of the 28 cycles (89%) during bright white light treatment, compared to 18 of 28 cycles (65%) during the dim red light treatment (McNemar’s $\chi^2 = 3.69$, d.f. = 1, $P < 0.03$). At the conclusion of the study, 10 patients (71%) preferred the white light, three patients (21%) preferred the red light, and one patient (7%) had no preference. The light treatments were well tolerated by the patients, with no serious adverse events reported. Seasonality, as measured by the GSS, did not correlate with improvement during the bright white light condition (Spearman’s $\rho = -0.09$, $P > 0.75$, ns); neither did the expectation of benefits score (Spearman’s $\rho = -0.25$, $P > 0.35$, ns).

4. Discussion

This study found that women with LLPDD significantly improved during treatment with

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td>Outcome measures during the two-menstrual-cycle baseline ($n = 14$)*</td>
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<tr>
<td></td>
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<tr>
<td>29-item Hamilton Depression Rating Scale (SIGH-SAD)</td>
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<tr>
<td>Beck Depression Inventory (BDI)</td>
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<tr>
<td>Premenstrual Tension Scale (PMTS)</td>
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<td>Clinical Global Impression–Severity (CGI–S)</td>
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*All comparisons of luteal vs. follicular scores within each cycle are significantly different, $P < 0.002$. There are no significant differences between Cycle 1 and Cycle 2 on any scores.
Table 2
Outcome measures vs. light condition (n = 14)

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Baseline</th>
<th>Dim red light</th>
<th>Bright white light</th>
<th>x²</th>
<th>P</th>
<th>Contrasts¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D.</td>
<td>Mean</td>
<td>S.D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29-item Hamilton Depression Rating Scale (SIGH–SAD)</td>
<td>20.8</td>
<td>13.5</td>
<td>8.4</td>
<td>10.3</td>
<td>9.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Beck Depression Inventory (BDI)</td>
<td>32.0</td>
<td>19.1</td>
<td>18.0</td>
<td>14.3</td>
<td>15.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Premenstrual Tension Scale (PMTS)</td>
<td>22.1</td>
<td>10.0</td>
<td>11.4</td>
<td>10.9</td>
<td>8.6</td>
<td>0.008</td>
</tr>
<tr>
<td>Clinical Global Impression–Severity (CGI–S)</td>
<td>2.6</td>
<td>1.6</td>
<td>0.78</td>
<td>1.4</td>
<td>0.78</td>
<td>0.009</td>
</tr>
</tbody>
</table>

¹Means represent the difference between scores at luteal and mid-follicular phase assessments in each menstrual cycle, summed over two cycles.
²Friedman's two-way ANOVA, d.f. = 2.
³Pairwise comparisons using Nemenyi's Tests.

Bright white light when compared to baseline. A putative placebo condition, dim red light, produced an improvement in symptoms, but this improvement was not statistically significant compared to baseline. Clinical improvement was noted in both mood symptoms, as measured by the SIGH–SAD and BDI, and in physical symptoms as measured by the PMTS. The pre-treatment expectation ratings for the two conditions were similar, suggesting that the effects of the active bright light were not due simply to expectations of benefit. These results, however, should be considered preliminary because of the small sample size, and because no statistically significant differences were found in the post hoc direct comparisons between the two light treatment conditions. This may have been due to a Type II error, however, because the bright white light condition consistently produced greater improvement than the dim red light, and the majority of women preferred the active bright light condition at study completion. Most light therapy studies in SAD have shown superiority of higher intensity light compared to light <500-lx intensity (Terman et al., 1989; Tam et al., 1995), but some studies have shown significant clinical responses even to 300-lx light (Grota et al., 1989). It is thus possible that the 500-lx light condition may be characterized as an ‘active’ placebo. Additionally, studies in SAD have shown that morning light exposure is superior to evening light exposure (Terman et al., 1989, 1998; Tam et al., 1995; Eastman et al., 1998; Lewy et al., 1998). Since we used only evening timing of light treatment, we are unable to address whether a similar effect is seen in patients with LLPDD.

Previous studies of light therapy in LLPDD had equivocal results. Parry et al. (1987) reported a pilot study involving a patient with seasonal LLPDD who improved with evening bright light treatment during winter. In a second study, six women with well-diagnosed LLPDD were treated in a two-menstrual-cycle crossover trial of morning vs. evening bright light treatment (Parry et al., 1989). The light treatment used 2500-lx full-spectrum fluorescent light boxes for 2 h/day for 1 week during the symptomatic luteal phase. Subjective and objective ratings of depression improved significantly from baseline after treatment with evening light, but not after treatment with morning light. There were no significant differences between morning and evening light. Because it was unclear whether morning light could be considered an appropriate placebo, the investigators conducted an extended crossover study in 19 patients with LLPDD, comparing one men-
strual cycle of treatment each with morning bright light, evening bright light, and a putative placebo condition, evening dim light (Parry et al., 1993). The bright light conditions used 2500 lx white light and the dim light condition used 10 lx red light. All three conditions resulted in significant improvement with no significant differences between any of the light treatments, so a placebo response to the bright light conditions could not be ruled out.

Both of the latter studies used crossover designs with treatment given for only a single menstrual cycle. Shorter treatment periods may account in part for the high placebo response rates in LLPDD (Rubinow and Schmidt, 1995). Using treatment over two menstrual cycles, we were able to show some statistical differences between the active light treatment and the placebo light treatment, but further studies of light therapy in LLPDD should incorporate longer treatment periods and larger sample sizes to prevent Type II errors. Parry has also noted that patients with LLPDD who continued using bright light therapy have maintained clinical improvement over a 12–18-month follow-up (Parry, 1998).

The mechanism of action of light therapy in LLPDD is unknown. Some investigators have suggested that LLPDD is associated with disturbances in circadian rhythms. Evidence for this hypothesis includes studies showing that patients with LLPDD, compared to normal comparison subjects, have reduced duration of nocturnal melatonin secretion and phase-advance of melatonin offset (Parry et al., 1990), phase-delayed melatonin onset time and reduced melatonin amplitude in the luteal phase compared to the follicular phase (Parry et al., 1997), and phase-advance of TSH rhythms (Parry et al., 1996). Light therapy may act by correcting abnormal circadian rhythms in a manner similar to that hypothesized in SAD (Lewy et al., 1988).

Other studies indicate dysregulation of serotonergic function in LLPDD (Taylor et al., 1984; Rapkin et al., 1987; Halbreich and Tworek, 1993; Menkes et al., 1994; Su et al., 1997). Light therapy may correct some of the serotonergic abnormalities found in SAD (Yatham et al., 1997). A rapid tryptophan depletion technique causes a relapse in depressive symptoms in patients with SAD who are in remission following light therapy (Lam et al., 1996; Neumeister et al., 1997, 1998), thereby indicating that the therapeutic effects of bright light may be mediated through the serotonergic system. Hence, it is possible that bright light also acts through serotonergic mechanisms in LLPDD.

Given the common serotonergic findings between LLPDD and SAD, it is interesting that over one-third of women with LLPDD seen in a PMS clinic experience significant seasonal worsening of their symptoms (Maskall et al., 1997). LLPDD shares similar symptomatology with SAD, including atypical vegetative symptoms such as hypersomnia, hyperphagia with carbohydrate craving and weight gain. The patients with LLPDD were not selected for seasonality of symptoms in this study, but the overall seasonality of the group was high, as indicated by a mean GSS score of 11.4, compared to the general population mean GSS score of 5.3 (Kasper et al., 1989). The number of patients studied during the summer months was balanced between the two light conditions, suggesting that spontaneous summer improvement is not likely to explain the superiority of the bright white light condition. It is still possible that seasonal LLPDD patients will be more likely to respond to light therapy during the more symptomatic winter months. In our small sample, however, there was no clear indication that individual seasonality, as measured by the GSS score, affected the clinical response to light therapy.

In summary, we found that evening bright light therapy significantly improved mood and physical symptoms of LLPDD. Further research will be needed to confirm these findings, to determine the role of light therapy in the clinical treatment of LLPDD, and to elucidate the mechanism of action of light therapy in LLPDD.

Acknowledgements

Preliminary results of this study were presented at the 150th Annual Meeting of the American Psychiatric Association, San Diego, CA, May, 1997, and at the 9th Annual Meeting of the
Society for Light Treatment and Biological Rhythms, Vancouver, Canada, June 1997. This research was funded, in part, by grants from the Medical Research Council of Canada (to RWL and APZ).

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