

## SHORT COMMUNICATION

### THERAPEUTIC MECHANISM IN SEASONAL AFFECTIVE DISORDER: DO FLUOXETINE AND LIGHT OPERATE THROUGH ADVANCING CIRCADIAN PHASE?

Greg Murray,<sup>1</sup> Erin E. Michalak,<sup>2</sup> Anthony J. Levitt,<sup>3</sup> Robert D. Levitan,<sup>3</sup> Murray W. Enns,<sup>4</sup> Rachel Morehouse,<sup>5</sup> and Raymond W. Lam<sup>2</sup>

<sup>1</sup>*Faculty of Life and Social Sciences, Swinburne University of Technology, Melbourne, Victoria, Australia*

<sup>2</sup>*Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada*

<sup>3</sup>*Department of Psychiatry, University of Toronto, Toronto, ON, Canada*

<sup>4</sup>*Department of Psychiatry, University of Manitoba, Winnipeg, MB, Canada*

<sup>5</sup>*Department of Psychiatry, Dalhousie University, Saint John, NB, Canada*

In the context of Lewy's phase delay hypothesis, the present study tested whether effective treatment of winter Seasonal Affective Disorder (SAD) is mediated by advancing of circadian phase. Following a baseline week, 78 outpatients with SAD were randomized into 8 weeks of treatment with either fluoxetine and placebo light treatment or light treatment and placebo pill. Depression levels were measured on the Ham<sub>17+7</sub> and the BDI-II, and circadian phase was estimated on the basis of daily sleep logs and self-reported morningness-eveningness. Among the 61 outpatients with complete data, both treatments were associated with significant antidepressant effect and phase advance. However, pre- and post-treatment comparisons found that the degree of symptom change did not correlate with the degree of phase change associated with treatment. The study therefore provides no evidence that circadian phase advance mediates the therapeutic mechanism in patients with SAD. Findings are discussed in terms of the limitations of the circadian measures employed.

**Keywords** Seasonal Affective Disorder, Phase-Shift Hypothesis, Light Treatment, Fluoxetine, Circadian

## INTRODUCTION

Lewy's phase-shift hypothesis (PSH) (Lewy et al., 1989) is the most prominent chronobiological model of Seasonal Affective Disorder (SAD)

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Address correspondence to Greg Murray, Faculty of Life and Social Sciences, Swinburne University of Technology, PO Box 218, John St., Hawthorn 3122, Melbourne, Victoria, Australia. E-mail: gwm@swin.edu.au

(Rosenthal et al., 1984). The PSH proposes that winter depressive episodes in SAD are caused by a phase delay of circadian rhythms, and that morning bright light should be therapeutic because it corrects the abnormal delay by phase advancing the endogenous oscillator. As predicted by the PSH, studies of light treatment for SAD have tended to find that (i) morning light treatment is associated with a phase advance, and (ii) morning light treatment is effective (Lewy et al., 1998; Sack et al., 1990). However, these two conclusions alone do not demonstrate that changes in circadian phase mediate light therapy for patients with SAD; a critical remaining test is the correlation between treatment-related phase changes and therapeutic effect.

The present study sought to address this question, and extend it to investigation of the pharmacotherapy of SAD. Antidepressant medication is a second effective treatment for SAD (see Lam et al., 1995; Moscovitch et al., 2004), and it is appropriate to consider whether the predictions of the PSH are also confirmed with this intervention. Two hypotheses were therefore tested. First, it was predicted that effective treatment with either morning light or fluoxetine would be associated with advances in circadian phase relative to clock time. Second, it was predicted that the degree of circadian phase advance would correlate significantly with the degree of change in depression. Circadian phase was measured indirectly, through sleep timing estimates derived from daily sleep logs and self-reports of morningness-eveningness. Both these measures have been shown to have moderate to large correlations with physiological measures of circadian phase (Baehr et al., 2000; Martin and Eastman, 2002; Terman et al., 2001).

## MATERIALS AND METHODS

### Design

Data were collected from CAN-SAD, a multicenter, double-blind, randomized, parallel-design study comparing the effectiveness of light and fluoxetine in the treatment of SAD (for more details of methods see Lam et al., in press). The protocol provided data at baseline and across 8 treatment weeks, with participants randomized into two treatment groups: active light and placebo drug or active drug and placebo light.

### Sample

Inclusion criteria for the study were: 1) outpatients aged 18 to 65 years, and 2) presence of major depressive episodes with a seasonal (winter) pattern. In addition, participants were required to score 20 or higher on the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967), 17-item version, or 14 or higher on the Ham<sub>17</sub> if the 24-item version

score was 23 or higher. The study was reviewed and approved by local Institutional Review Boards and met the ethical standards set forth by the Journal for biological rhythm research (Touitou et al., 2004).

## Materials

Clinician-rated depression was measured on the Structured Interview Guide for the HDRS, SAD version (SIGH-SAD, Williams et al., 1988), specifically the Ham<sub>17</sub> plus 7-item atypical addendum score (Ham<sub>17+7</sub>). Self-report of depression was measured on the Beck Depression Inventory II (BDI-II) (Beck et al., 1996), a widely used and validated tool.

Shifts towards morningness on the Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) (Horne and Östberg, 1976) are commonly interpreted as indicating a phase advance (*e.g.*, Murray et al., 2003). The MEQ was completed at baseline and at treatment week 8. Self-reported sleep and wake times were recorded on a daily sleep log, with the study hypotheses being tested on 7-day average measures calculated at baseline and at treatment week 8.

## Procedures

The active treatment condition was a full-spectrum fluorescent light box emitting 10,000 lux light. The control treatment consisted of the same light box fitted with neutral density gel filters emitting 100 lux. Participants sat under the light box for 30 min upon awakening, between a fixed time window of 07:00 to 08:00 h. The medications were administered as a once-a-day (morning) treatment regimen. Each capsule contained either fluoxetine (20 mg) or placebo.

## RESULTS

Of the 96 participants entered into the study (66.7% female, 33.3% male), 18 were excluded from analyses because inspection of sleep logs suggested deviation from the imposed sleep schedule. Of the remaining 78 participants, complete data were obtained from 61 (light:  $n = 29$ , fluoxetine:  $n = 32$ ). Treatment was associated with large effect size decreases in depression, as assessed by baseline *vs.* treatment week 8 comparisons of the Ham<sub>17+7</sub> (partial  $\eta^2 = 0.84$ ,  $p < 0.001$ ) and BDI-II scores (partial  $\eta^2 = 0.69$ ,  $p < 0.001$ ). For the present purposes, it is important to note that treatment group did not have a significant interaction with the time effect in either measure of depression ( $F[1,67] = 0.21$  and  $F[1,65] = 0.07$  for Ham<sub>17+7</sub> and BDI-II, respectively). As predicted, treatment was associated with significant phase advances relative to clock time as measured in MEQ scores and sleep onset data (Table 1, upper panel). In contrast,

**TABLE 1** Comparison of Baseline and Final Treatment Week Distributions of Four Measures of Circadian Phase

Group	Baseline		Treatment week 8	
	Mean	SD	Mean	SD
Whole sample				
MEQ	50.03	10.57	54.37	9.49***
Sleep onset (h)	23:33	00:55	23:17	00:46**
Wake (h)	07:02	01:59	07:09	00:55
Mid-sleep (h)	03:17	01:09	03:13	00:41
Light group				
MEQ	50.42	9.35	54.39	8.29**
Sleep onset (h)	23:33	00:57	23:17	00:45*
Wake (h)	07:17	01:44	07:15	00:46
Mid-sleep (h)	03:25	01:04	03:16	00:37
Fluoxetine group				
MEQ	49.65	11.75	54.35	10.66***
Sleep onset (h)	23:32	00:54	23:16	00:47*
Wake (h)	06:50	02:11	07:04	01:02
Mid-sleep (h)	03:11	01:14	03:10	00:45

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ . Sleep variables are presented in military time. SD = Standard deviation.

wake and mid-sleep times did not change significantly with treatment. This pattern of findings recurred when the light group (Table 1, middle panel) and fluoxetine group (lower panel) were analyzed separately.

Pearson correlations were used to test the predicted association between degree of symptom change and degree of phase change across the 8 weeks of treatment. Whether measured in terms of the Ham<sub>17+7</sub> or BDI-II change, none of the correlations approached significance. The bivariate correlations between change in Ham<sub>17+7</sub> and change in circadian phase, as measured in MEQ, sleep onset, wake time, and mid-sleep, were 0.03, -0.20, 0.18, and 0.11, respectively. The coefficients generated by the corresponding analyses using the BDI-II measure were -0.09, -0.15, 0.09, and 0.03. For completeness, these analyses were then conducted for the two treatment groups separately. After Bonferroni adjustment for multiple tests, no evidence of an association between phase advance and depression improvement was found in either group.

## DISCUSSION

Among a group of 61 SAD outpatients diagnosed with moderate-to-severe depression, both fluoxetine and light interventions produced the expected substantial improvement in depression symptoms across an 8-week treatment protocol, providing the opportunity to test two deductions

from Lewy's PSH. As expected, treatment was accompanied by significant phase advance in two measures known to relate to the phase of the circadian oscillator, namely, MEQ score and time of sleep onset. This finding is consistent with a range of studies demonstrating a phase-advancing property of morning light in the treatment of SAD (*e.g.*, Lewy et al., 1998). The failure to find phase-advance effects with treatment in the remaining two measures (wake time and sleep mid-point) is most likely due to the fixed wake window required by the experimental protocol.

A novel finding here is that evidence for the phase-advancing effects of morning light was mirrored in the fluoxetine treatment group. Although historically linked to investigations of the phase-shifting properties of light, the PSH concerns pathogenesis and might be expected to generalize to treatments other than light (Lewy, 2002). The present data suggest that the phase shifting effects of fluoxetine and light in SAD treatment are comparable, although the lack of a double placebo condition (see below) cautions against over interpretation of this finding.

Correlational analyses provided no support for the central hypothesis that the degree of therapeutic effect is associated with the degree of phase advance achieved. This result is consistent with the bulk of previous studies providing data on circadian correlates of light treatment (Eastman et al., 1993; Thalen et al., 1995; Thompson et al., 1997; Wirz-Justice et al., 1995, but not Terman et al., 2001). The weight of evidence across studies therefore suggests that circadian phase change relative to clock time is not part of the therapeutic mechanism of light treatment for SAD, and the present study suggests that this inference also generalizes to fluoxetine treatment. [Lewy has recently clarified the PSH to propose that light treatment operates not by advancing circadian phase per se, but by normalizing the phase angle between sleep and circadian rhythms (Lewy et al., 2003). Analyses of our data from this perspective will be presented separately.]

The most significant limitation of the present study was reliance on self-reported sleep-wake times and MEQ scores as measures of circadian phase. Not only are these indirect measures of the circadian signal, but the use of sleep parameters (most particularly wake time, as noted above) was compromised by the experimental regimen of fixed early wake time. The role of Type II error in the findings therefore cannot be ruled out. A second limitation was the absence of double-placebo and double-active conditions in the design. It is possible, for example, that behavioral aspects of the light placebo affected circadian function by regularising zeitgeber information at a critical time of day (Sachs et al., 2003). Nonetheless, within its limitations, the present study aligns with the majority of previous research in suggesting that, although effective intervention for SAD might coincide with phase advance of circadian rhythms, these circadian changes do not correlate with, and are therefore unlikely to mediate, therapeutic effects.

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