

# Morning vs Evening Light Treatment of Patients With Winter Depression

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**Background:** According to the phase-shift hypothesis for winter depression, morning light (which causes a circadian phase advance) should be more antidepressant than evening light (which causes a delay). Although no studies have shown evening light to be more antidepressant than morning light, investigations have shown either no difference or morning light to be superior. The present study assesses these light-exposure schedules in both crossover and parallel-group comparisons.

**Methods:** Fifty-one patients and 49 matched controls were studied for 6 weeks. After a prebaseline assessment and a light/dark and sleep/wake adaptation baseline week, subjects were exposed to bright light at either 6 to 8 AM or 7 to 9 PM for 2 weeks. After a week of withdrawal from light treatment, they were crossed over to the other light schedule. Dim-light melatonin onsets

were obtained 7 times during the study to assess circadian phase position.

**Results:** Morning light phase-advanced the dim-light melatonin onset and was more antidepressant than evening light, which phase-delayed it. These findings were statistically significant for both crossover and parallel-group comparisons. Dim-light melatonin onsets were generally delayed in the patients compared with the controls.

**Conclusions:** These results should help establish the importance of circadian (morning or evening) time of light exposure in the treatment of winter depression. We recommend that bright-light exposure be scheduled immediately on awakening in the treatment of most patients with seasonal affective disorder.

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**T**HE DISCOVERY that human melatonin production can be suppressed by bright light<sup>1</sup> led to the initial test of bright light in treating winter depression.<sup>2,3</sup> Subsequently, Rosenthal and coworkers<sup>4</sup> coined the term *seasonal affective disorder* (SAD) for this disorder, described its clinical features, and conducted the first controlled investigation in which comparatively dim light was used as a placebo control. A form of recurrent depression marked by an annual onset from midautumn to early winter, SAD may affect more than 10 million Americans.<sup>5</sup> Its prevalence is greatest in females, and it is often accompanied by atypical symptoms of fatigue, hypersomnia, carbohydrate craving, and weight gain.

Among the first hypotheses for SAD<sup>6,7</sup> is the phase-shift hypothesis (PSH),<sup>8-10</sup> which postulates that bright light is antidepressant in patients with SAD at least in part by causing a circadian phase *advance*. It is well established that bright-light exposure in the morning causes a

phase advance and in the evening causes a phase *delay*.<sup>8,9,11-18</sup> Critical to the PSH is that bright-light exposure should be more antidepressant when it is scheduled in the morning than when it is scheduled in the evening, because most patients with SAD are expected to have phase-delayed circadian rhythms when depressed in the winter. However, some clinicians recommend exposure at other times of the day, particularly if morning is not convenient.<sup>19</sup> Therefore, for both practical and theoretical reasons, it is important to know if circadian time of exposure affects light's antidepressant efficacy.

**See also pages 861, 863, 875, and 883**

There are no investigations that demonstrate evening light (EL) to be more antidepressant than morning light (ML). Studies are divided between those that show ML to be superior and those that show no difference (see the "Comment"

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## SUBJECTS AND METHODS

### SUBJECTS

After approval by the institutional review board at Oregon Health Sciences University, Portland, the study was conducted each January and February during 4 winters (1989-1992) in Portland, (45°N latitude). Subjects were recruited through advertisements in area newspapers, television interviews, and referrals from health professionals. About 1900 patients were sent a Seasonal Pattern Assessment Questionnaire,<sup>20</sup> a 21-item Beck Depression Inventory,<sup>21</sup> and a health and sleep screening questionnaire that inquired about medical and psychiatric history. More than 80 potential subjects were interviewed.

To be admitted into the study, all patients had to (1) meet *DSM-III-R* criteria<sup>22</sup> for moderate to severe major depressive disorder (without psychotic episodes) or bipolar disorder (depressed or not otherwise specified) with a winter-type seasonal pattern; (2) score 20 or higher on the Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version (SIGH-SAD)<sup>23</sup> with a Hamilton Depression scale<sup>24</sup> score of 10 or more and an atypical score of 5 or more<sup>25</sup>; (3) report that a depression developed during the fall or winter and remitted the following spring for at least the 2 preceding years; (4) be in good physical health; (5) not be suicidal; (6) not have used psychotropic medications for the previous 4 weeks or other medications that interfere with endogenous melatonin production; and (7) not have other psychiatric or medical illnesses. Control subjects did not have notable medical or psychiatric problems (including seasonal fluctuations in mood, sleep, appetite, and energy) and were taking no medications that could interfere with mood or endogenous melatonin production.

A total of 56 patients and 52 controls participated. Two patients did not complete the study, 3 were found to have other psychiatric problems after beginning the study, and 2 had immeasurable melatonin levels (which are excluded from any dim-light melatonin onset [DLMO] analyses). Three controls did not complete the study. Controls and patients were matched by age and sex as closely as possible. Informed consent was obtained from all participants.

### LIGHT TREATMENT

The light fixtures contained two 40-W cool-white fluorescent tubes (Hughes Lighting Technologies, Lake Hopatcong, NJ). To determine the distance to obtain 2500 lux, intensities were measured for each light fixture using a light meter with a photometric sensor. Subjects were

instructed to sit 45° to the light with their eyes at midfixtural level and to gaze across it once or twice a minute, rather than stare directly at it.

A prebaseline assessment was followed by a baseline week, 2 weeks of a first in-home light treatment period (I-1 and I-2), a withdrawal week, and 2 weeks of a second light treatment period (II-1 and II-2). Subjects were assigned to receive either ML first (6 to 8 AM; MLF group) or EL first (7 to 9 PM; ELF group), balanced for age, sex, and prebaseline SIGH-SAD rating. Before the study, subjects were asked whether they thought ML or EL would be more antidepressant, equally antidepressant, or make no difference; they could also answer “don’t know.” During the study, subjects were asked to avoid unscheduled bright-light exposure (such as in the supermarket) from 6 PM to 8 AM and not to travel outside the time zone. Subjects were also asked to maintain a 10 PM to 6 AM sleep schedule and to complete a written daily sleep and mood diary. For most subjects, sleep diary data were also obtained for 2 weeks before entry into the study. Morning wake-up times were verified each day by having subjects call the laboratory and leave a voice-mail message.

### MELATONIN

Subjects were admitted to the Clinical Research Center at Oregon Health Sciences University for a prebaseline visit followed by 6 weekly visits for assessment of the DLMO (a very reliable marker of circadian phase position<sup>26</sup>) and behavioral (29-item SIGH-SAD) ratings by 2 independent blind raters (including, at times, N.L.C., M.L.B., and J.M.L.J.). Subjects also completed a Beck Depression Inventory each week. Under dim light (<50 lux), blood samples (3-5 mL) were drawn every 30 minutes from 6 to 11 PM (sometimes later). (Dim light is necessary in sighted people to avoid the acute suppressant effect of light on melatonin<sup>1</sup>; we currently recommend light intensities of <30 lux for the DLMO.) Samples were immediately centrifuged, and plasma was separated and frozen for later analysis. Melatonin was assayed by means of a modification of the highly sensitive and specific gas chromatographic–negative chemical ionization mass spectrometric method.<sup>27</sup> The DLMO was defined as the first interpolated point above 10 pg/mL that continued to rise.

### STATISTICS

For continuous data, repeated-measures analyses of variance (ANOVAs) were performed, followed by group or paired *t* tests, where appropriate. For categorical data,  $\chi^2$  and Fisher exact tests were used. Unless otherwise stated, results described as statistically significant refer to  $P \leq .05$  on a 2-tailed test.

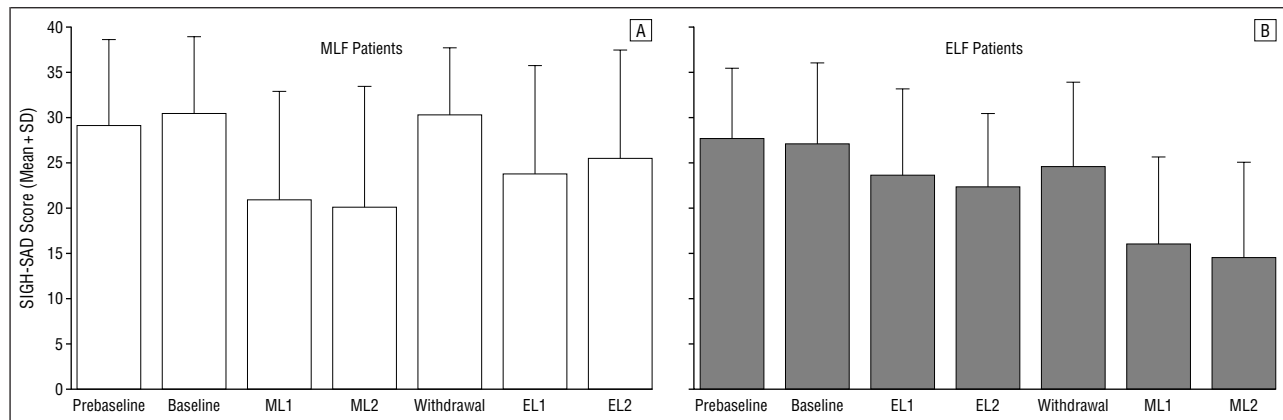
section). This may be similar to the pharmacological literature, in which antidepressant medication has been shown to be superior or equal, but rarely inferior, to placebo.

Morning light has been found to be more antidepressant primarily in crossover studies, whereas most parallel-group studies have failed to demonstrate a statistically significant benefit of ML. The following investigation studied a large number of patients, so as to have sufficient power to assess ML vs EL in both parallel (first

treatment period) and crossover comparisons. We hypothesized that ML would be more antidepressant than EL.

## RESULTS

Fifty-one patients with SAD (45 women) and 49 controls (40 women) completed the study. There was minimal minority representation. Complete DLMO sets were



**Figure 1.** Patient behavioral ratings on the Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version (SIGH-SAD) for patients who received morning light first (MLF) and evening light first (ELF). ML1 and ML2 indicate weeks 1 and 2, respectively, of morning light treatment; EL1 and EL2, weeks 1 and 2, respectively, of evening light treatment.

**Table 1. Decrease in SIGH-SAD Scores After EL and ML\***

	ML	EL
MLF patients (n = 27)	10.35 ± 10.71	4.98 ± 10.42
	$t_{26} = 1.68, P = .11$	
ELF patients (n = 24)	10.08 ± 9.13	4.75 ± 9.13
	$t_{23} = 1.90, P = .07$	
Total	10.23 ± 9.90	4.87 ± 10.71
	$t_{50} = 2.52, P = .02$	

\*Data are presented as mean ± SD, compared with baseline or withdrawal weeks. Abbreviations are explained in the legend to Figure 1.

obtained for all of the controls and 49 of the patients. The mean ± SD age of the patients was 40.2 ± 8.9 years (range, 25-61 years), while that of the controls was 38.3 ± 11.1 years (range, 22-68 years). Twenty-seven patients and 24 controls received MLF, and 24 patients and 25 controls received ELF.

### SIGH-SAD RATINGS

The SIGH-SAD scores throughout the study by treatment group are shown in **Figure 1**. A repeated-measures ANOVA was performed on the patient 29-item SIGH-SAD scores, with order of treatment (MLF or ELF) as the grouping variable and treatment as the repeated measure (baseline, withdrawal, ML, and EL). The first week of light treatment was not included in any analyses. A main effect was found for treatment ( $F_3 = 23.14, P < .001$ ) and for order of treatment ( $F_1 = 4.53, P = .04$ ). The interaction was not significant.

Previous crossover studies have reported an order effect, in which EL is more effective when administered as a novel treatment than when it follows treatment with ML.<sup>25</sup> In our data, there is the suggestion of such an effect, in that ML ratings were not significantly lower than EL ratings in the first treatment period but were so in the second treatment period ( $t_{49} = 3.44, P = .001$ ). However, posttreatment ratings did not significantly differ between the 2 treatment periods. Furthermore, with-

drawal week ratings were not different from baseline week ratings, which indicates that no carryover resulted from light treatment. Change scores were calculated by subtracting posttreatment ratings from those of the appropriate baseline or withdrawal week. When change scores were combined for the first and second treatment periods (**Table 1**), the decrease in ratings after ML was twice that of EL.

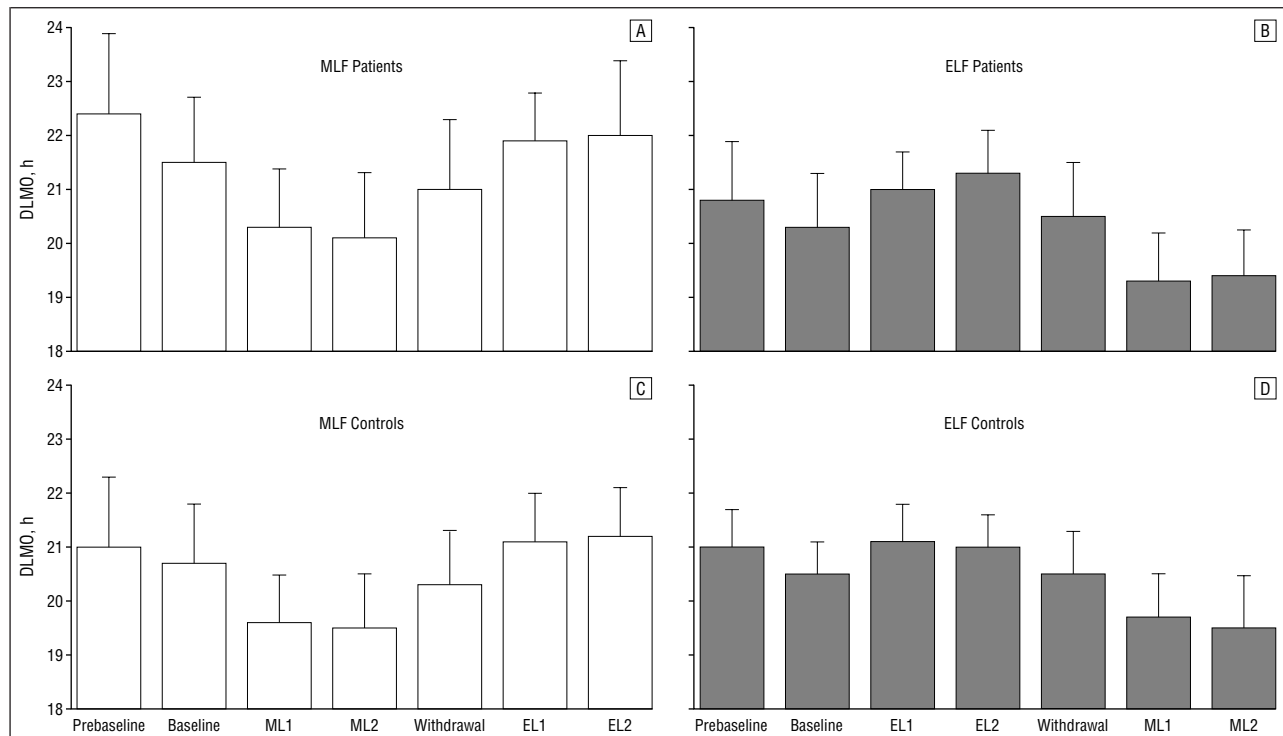
Combining SIGH-SAD scores of both MLF and ELF groups, ML ratings (17.45 ± 12.2) were 37% lower ( $t_{50} = 7.38, P < .001$ ) than the appropriate pretreatment ratings (27.68 ± 9.17), and EL ratings (23.95 ± 10.39) were 17% lower ( $t_{50} = 3.58, P < .001$ ) than the appropriate pretreatment ratings (28.82 ± 8.18). The ML ratings were 27% lower than EL ratings ( $t_{50} = 3.26, P = .002$ ).

Remission criteria (≥50% decrease in 29-item SIGH-SAD ratings to a posttreatment score of ≤14, a Hamilton Depression scale score of ≤7 with an atypical score of ≤7, or a Hamilton Depression scale score ≤2 with an atypical score ≤10)<sup>25</sup> indicated that 19 (37%) of the 51 patients responded after ML, while only 3 (6%) did after EL. Two of these patients also met criteria after ML, leaving only 1 who responded exclusively to EL. These findings were statistically significant ( $\chi^2 = 20.65, P < .001$ ).

For the first treatment period (the parallel-group comparison), change scores (Table 1) in the MLF group were more than twice those of the ELF group (10.35 ± 10.71 vs 4.75 ± 9.13;  $t_{40} = 1.99, P = .05$ ); percentage change scores from baseline were 36% for ML compared with 8% for EL ( $t_{40} = 2.09, P = .04$ ). Of the 27 patients in the first treatment period, 8 (30%) responded after ML, while only 1 did after EL ( $\chi^2 = 6.88, P = .008$ ). In the MLF group, withdrawal week ratings were significantly ( $t_{26} = 5.40, P < .001$ ) greater than ML ratings, indicating that these patients relapsed, whereas patients in the ELF group did not significantly worsen during the withdrawal week. Beck Depression Inventory scores were generally consistent with the above findings.

### MELATONIN ANALYSIS

A repeated-measures ANOVA was performed on patients' and controls' DLMOs with treatment as the repeated



**Figure 2.** Dim-light melatonin onset (DLMO) times (and SDs) for patients and controls who received morning light first (MLF) and evening light first (ELF). Other abbreviations are explained in the legend to Figure 1.

measure. As mentioned above, the first week of treatment in both treatment periods was excluded in the statistical analyses. Main effects were found for treatment week ( $F_3 = 191.53$ ,  $P < .001$ ) and for group (ie, patients were delayed compared with controls) ( $F_1 = 5.04$ ,  $P = .03$ ). The interaction was not significant. Next, a repeated-measures ANOVA was performed with order of treatment as the grouping variable and week of treatment as the repeated measure. For patients, there was a main effect for order of treatment ( $F_1 = 9.09$ ,  $P = .004$ ) and for treatment week ( $F_3 = 105.02$ ,  $P < .001$ ). The interaction was also significant ( $F_3 = 3.93$ ,  $P = .009$ ). For controls, a main effect was not found for order of treatment but was found for treatment week ( $F_3 = 96.34$ ,  $P < .001$ ). The interaction was not significant.

Patients were delayed compared with controls at all weeks of the study ( $F_1 = 4.59$ ,  $P = .03$ ) (**Figure 2**). This was mainly because of the MLF patient group. **Table 2** shows the mean DLMO times at prebaseline, as well as for the baseline and withdrawal weeks.

Both patients ( $t_{48} = 6.41$ ,  $P < .001$ ) and controls ( $t_{48} = 6.98$ ,  $P < .001$ ) advanced after the baseline week (Figure 2), probably because of natural light exposure earlier in the morning. Relative to baseline and withdrawal weeks, the advance response to ML and the delay response to EL, respectively, were statistically significant for both patients ( $t_{48} = 9.23$ ,  $P < .001$  and  $t_{48} = 6.88$ ,  $P < .001$ ) and controls ( $t_{48} = 9.53$ ,  $P < .001$  and  $t_{48} = 5.99$ ,  $P < .001$ ). Withdrawal week DLMOs came back to their baseline times for both patients and controls.

### SLEEP MEASURES

These will be reported on more extensively in another publication, as well as analyses of more esoteric vari-

**Table 2. Pretreatment DLMO Times for Patients and Controls\***

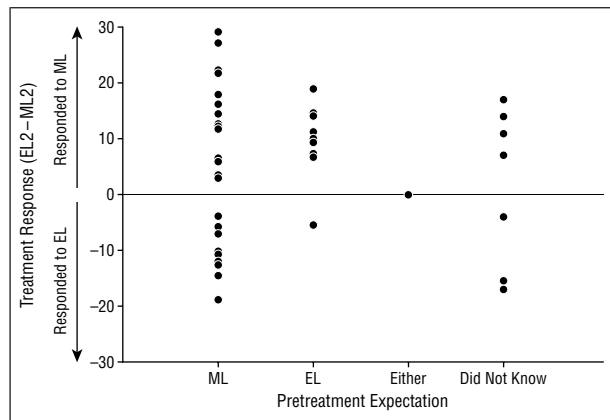
	Controls	Patients
Prebaseline	21:05 ± 0:59	21:37 ± 1:33
Baseline	20:35 ± 0:54	20:57 ± 1:16
Withdrawal	20:24 ± 0:51	20:50 ± 1:05
	$t_{96} = 2.08$ , $P = .04$ $t_{96} = 1.60$ , $P = .11$ $t_{96} = 2.16$ , $P = .03$	

\*DLMO indicates dim-light melatonin onset, in clock time (hours:minutes).

ables (eg, phase-angle differences). In the patients, EL sleep onset was 31 minutes later than with ML ( $t_{44} = 6.51$ ,  $P < .001$ ), and ML sleep offset was 19 minutes earlier than with EL ( $t_{44} = 4.23$ ,  $P < .001$ ). Total sleep time after EL was not different from that after ML.

### PATIENT EXPECTATIONS

At the beginning of the study, we were able to obtain expectation ratings in 44 of the patients. Most patients (26 [59%]) thought that ML would be more antidepressant than EL (**Figure 3**). However, there was no relationship between this expectation and actual response ( $\chi^2 = 2.32$ , Fisher exact  $P = .22$ ); while 16 of 26 patients who expected ML to be more antidepressant did better with ML, only 1 of 9 patients who thought that EL would be more antidepressant did better with EL.



**Figure 3.** Results of the expectation questionnaire. Patients were asked, "Which would you think would be more effective in the treatment of winter depression, light early in the day or late in the day, or that it would make no difference (if you absolutely have no idea and cannot give a best guess, check 'don't know')?" ML indicates morning light, and EL, evening light. Treatment response was determined by the score on the Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version<sup>23</sup> after the second week of ML (ML2) subtracted from that after the second week of EL (EL2).

### COMMENT

This study clearly shows that ML is at least twice as antidepressant as EL in the treatment of SAD. An order or carryover effect has been raised<sup>25,28-31</sup> as a potential confounder in crossover studies, but it does not appear to be a problem in the present study.

Most,<sup>9,32,33</sup> but not all,<sup>34</sup> investigations that demonstrated ML superiority were crossover studies, whereas most previous investigations that found no difference between ML and EL were of the parallel-group type.<sup>31,35-37</sup> When present, the order effect was the following: the antidepressant superiority of ML over EL was greater in the second treatment period than in the first treatment period. In the present study, we found only a slight order effect, which was not the same as reported by others, and there was no evidence of a carryover effect. Perhaps this was because of the withdrawal week between treatment periods. It should also be mentioned that there was no significant interaction between treatment and order of treatment on the ANOVA.

In any event, ML was more antidepressant than EL when each treatment period was analyzed separately, including the first treatment (parallel-group) comparison. Furthermore, ML was more antidepressant than EL in the entire (crossover) data set. Together with 2 other recent, large-sample, parallel-group investigations,<sup>37,38</sup> the present study will, we hope, help end whatever doubts remain about ML's antidepressant superiority.

Our expectation data are probably open to different interpretations. Half of the patients expected ML to be more efficacious than EL, whereas only 9 expected EL to be more efficacious. On the other hand, these expectations did not correctly predict the response to light treatment. Only slightly more than half of the patients who responded best to ML predicted this accurately, and in the case of EL, the antidepressant response actually went in the opposite direction from that expected (Figure 3).

In this and in 1 of our previous studies,<sup>33</sup> EL ratings were lower than those at baseline. Why does EL not make patients more depressed than at baseline? One explanation might be that EL's placebo component is greater than its depressant (phase-delay) component, so that its net effect is somewhat efficacious. The same placebo component is presumably present in ML, but in this case the 2 effects are additive, perhaps limited by an overall ceiling.

Indeed, lack of a placebo control in the present study calls into question our finding that EL ratings were significantly lower than baseline ratings. To date, 1 study has shown EL to be more effective than a credible placebo control<sup>38</sup> and 1 study has not.<sup>39</sup> If EL is eventually shown to be an effective antidepressant compared with a credible placebo control, then it would be reasonable to conclude that light has more than 1 mechanism of action for its antidepressant efficacy, such as an "energizing effect."<sup>40</sup> However, as long as ML is shown to be more antidepressant than EL, the PSH will remain a viable explanation for 1 of light's antidepressant effects.

Lack of a credible placebo control seriously confounds interpretation of studies that found no difference in antidepressant efficacy between ML and EL (these studies are reviewed elsewhere<sup>31,40</sup>). For example, in a large-sample investigation in which ML and EL were found to be equally antidepressant when administered in parallel to separate groups of patients,<sup>31</sup> raters were presumably blind only as to time of light exposure. Thus, in this study raters could have enabled a bias that time of light exposure is not important by rating all patients as improved whenever they were exposed to light.

Of some concern in the present investigation is that the patients do not appear to be as phase-delayed as in previous studies. Two of 3 assessments showed patients to be phase-delayed compared with controls, whereas 1 would have barely achieved statistical significance on a 1-tailed test (Table 2). There were also small changes in sleep times, which cannot be ruled out as influencing depression ratings in this study.

However, if ML were more antidepressant merely because it helped patients adapt better to the earlier sleep schedule, we should have found more of a benefit of ML than EL in the first treatment period than in the second treatment period (such was not the case). Similarly, patients should have worsened during their adaptation to the earlier sleep schedule of the first baseline week, and these ratings should have been higher than those of the withdrawal week; on the contrary, ratings during the 3 nontreatment weeks were virtually identical. Furthermore, 2 other recent large-sample studies in which sleep was stabilized according to habitual schedules found ML to be superior to EL.<sup>38,39</sup>

A more detailed analysis of the rather complicated interactions between the DLMO, sleep times, behavioral ratings, and other variables will be the subject of another report. However, preliminary analyses do not disclose anything that would change the major findings of the present study.

Phase delays have been reported in patients with winter depression compared with controls in some studies,<sup>9,33,41</sup> but not in others,<sup>42</sup> and no study has reported a

phase advance. However, an ipsative phase delay (ie, a delay in patients when depressed in the winter compared with when they are euthymic in the summer)<sup>10</sup> has not always been found.<sup>43,44</sup> Nevertheless, a phase advance consistently accompanies patients who do well with ML, and a phase delay accompanies their relative worsening when switched to EL.<sup>9,33</sup>

Although the finding that ML is more antidepressant than EL supports the PSH, other hypotheses are not excluded, for example, the circadian phase instability hypothesis, which in many respects is similar to the PSH.<sup>45</sup> Serotonin may mediate some of these changes.<sup>46</sup> There is little evidence for the circadian amplitude hypothesis.<sup>47</sup>

The simplest alternative explanation of our behavioral results is that people may be more sensitive to light in the morning.<sup>7</sup> This hypothesis is also not mutually exclusive with the more specific PSH, and we do not think that the reported increase in sensitivity in the morning<sup>48</sup> would be sufficient to explain why, after responding to ML, patients would experience a relative relapse with EL, particularly since bright-light exposure should rapidly cause desensitization. Such an increase in ML vs EL sensitivity would have to be more than 4-fold (after a remission has been achieved with 2 hours of 2500-lux ML, the response can be maintained after reduction to 30 minutes of exposure<sup>49</sup>), which does not seem to be the case.<sup>48</sup>

In summary, the present study adds to the body of literature that attests to ML's antidepressant superiority in the treatment of most patients with SAD (the exceptional patient with SAD with marked early-morning awakening might theoretically benefit from late-evening bright-light exposure). These findings are based on both parallel and crossover comparisons. Our behavioral results and, to a lesser extent, our circadian phase data continue to be consistent with, but do not conclusively prove, the PSH for SAD, which awaits more documentation of phase delays and/or antidepressant responses to another phase-advancing agent, such as melatonin administered in the afternoon.<sup>50,51</sup> It would then be very interesting to understand how such small differences in circadian phase could trigger such important clinical changes. Even if proved, the PSH may explain only 1 mechanism of action for light's antidepressant effect.

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