Background: We investigated a possible mechanism of action for the antidepressant response to light—phase advances of the circadian clock—by measuring the onset of melatonin secretion before and after light treatment in the morning or evening.

Methods: Plasma melatonin was sampled in 42 patients with seasonal affective disorder, in the evening or overnight while depressed and after 10 to 14 days of light therapy (10,000 lux for 30 minutes) when symptoms were reassessed.

Results: Morning light produced phase advances of the melatonin rhythm, while evening light produced delays, the magnitude depending on the interval between melatonin onset and light exposure, or circadian time (morning, 7.5 to 11 hours; evening, 1.5 to 3 hours). Delays were larger the later the evening light (r = 0.40), while advances were larger the earlier the morning light (r = 0.50). Although depression ratings were similar with light at either time of day, response to morning light increased with the size of phase advances up to 2.7 hours (r = 0.44) regardless of baseline phase position, while there was no such correlation for evening light. In an expanded sample (N = 80) with the sleep midpoint used as a reference anchor for circadian time, early morning light exposure was superior to late morning and to evening exposure.

Conclusion: The antidepressant effect of light is potentiated by early-morning administration in circadian time, optimally about 8.5 hours after melatonin onset or 2.5 hours after the sleep midpoint.

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SUBJECTS AND METHODS

SUBJECTS

Participants included 42 research volunteers aged 21 to 56 years (mean ± SD, 39.2 ± 9.3 years), with 29 women (69%) and 13 men (31%). Intake evaluations were based on the Structured Clinical Interview for DSM-III-R,19 administered by trained research staff. Diagnoses—all with seasonal pattern, winter type—were major depressive disorder, recurrent (code 296.3) in 29 subjects (69%), and bipolar disorder not otherwise specified (code 296.7) in 13 (31%). Candidates with comorbid Axis I disorders or recent history of a suicide attempt were excluded. Subjects were part of a larger group that underwent clinical trials of light therapy but were also available for evening or overnight laboratory sessions during which blood was sampled for melatonin concentration. An expanded analysis (N=80) included 38 additional subjects from the complete group who provided sleep logs but not melatonin data.

PROCEDURE

Details of treatment have been previously described.8 Within a crossover design, 21 subjects first received morning light and then evening light (M1E2), and 21 received treatment in the opposite order (E1M2). Transitions were immediate, without withdrawals. After a minimum 2-week baseline interval that verified a current depressive episode, subjects received 10 to 14 days of treatment in both periods, 30 minutes per day. Subjects were instructed to maintain consistent bedtimes and wake-up times throughout the study, according to their habitual schedule. They used the lights at home either soon after awakening (6:32 AM ± 56 minutes) or approximately 2 hours before bedtime (9:30 PM ± 64 minutes). The lighting device provided 10000 lux, 2700K fluorescent illumination through a 28.61-cm diffusing screen. Raters who were blinded to the treatment administered the 29-item Structured Interview Guide for the Hamilton Depression Rating Scale—Seasonal Affective Disorder Version (SIGH-SAD)21 at baseline and after both treatment periods, on the same days melatonin was sampled. Melatonin was sampled at 30-minute intervals in 2 protocols. Nine subjects underwent 15-hour overnight sessions beginning approximately 4 hours before their habitual sleep onset. Eight of these subjects completed 3 assessments, at baseline and after both treatment periods, while the ninth declined reassessment after baseline. Thirty-three subjects underwent 5-hour evening sessions after they returned home. Nineteen of these subjects completed all 3 assessments; 2 subjects whose baseline sessions were aborted for technical reasons completed only posttreatment assessments; and 12 subjects were scheduled for and completed only baseline and first-period assessments. Given these variations, we used the maximum available sample size for each analysis.

Blood samples (4 mL) were obtained while subjects were seated or resting in bed, using an indwelling venous catheter in the forearm. Ambient illumination was 1 to 5 lux provided by a 1.50-watt shaded incandescent reading lamp. Subjects commenced dim light exposure at least 1 hour before the first sample was collected. Illumination remained constant across the sampling sessions except during sleep when the light was extinguished.

Blood was centrifuged and plasma was separated and frozen for further analysis. The plasma was subjected to a direct radioimmunoassay based on an antisemum obtained from the University of Surrey, Guildford, England. The assay was cross-validated against gas chromatography/mass spectrometry in collaboration with A. J. Lewy, MD, PhD (Oregon Health Sciences University, Portland). The comparison yielded a high correlation (r=0.95; slope, 1.02; intercept, 5.7 pg/mL), and we achieved a lower detectable limit of 2.5 pg/mL. In 8 consecutive analytical runs with 3 quality control levels (22, 33, and 93 pg/mL), the within- and between-run relative SD percentages were 10.4 and 14.6, 12.9 and 11.8, and 3.9 and 4.5, respectively.

STATISTICAL ANALYSIS

Rating scale scores were analyzed as raw data and in terms of the percentage change from baseline. Univariate and multivariate analyses of variance and covariance were used to detect group and group × period interactions and the influence of baseline regressors. Linear regression, including forward stepwise multiple regression (F to enter, 4.0; to remove, 3.996) and the correlation coefficient, r, were used to measure the relationship between continuous variables. Group means were compared by t tests and categorical differences by the χ² test. For all statistical tests, an α level of .05 (2-tailed) served as the criterion for significant differences.

To test a set of correlations between melatonin phase anchor points across baseline, morning light, and evening light samples in overnight sessions, the significance of the observed value was determined by reference to a random probability distribution of correlations for all 8 permutations of subject pairing, keeping conditions matched.

ing light, and evening light conditions (grand mean ± SD, 853 ± 588 pg 30 min/mL; F12,1=1.92, P=.18), though there were significant interindividual differences (F12,142=54.22, P=.001). The secretion patterns were similar in shape (Figure 1). Melatonin levels began to rise between 8 PM and 10 PM, reaching maximum concentration between 1 AM and 4 AM, and returning to daytime levels between 8:30 AM and 10 AM. However, the curves were displaced from each other such that morning light phase advanced the cycle and evening phase delayed it relative to baseline (condition × time: F46,308=4.45, P<.001). Phase determinations were based on 2 discrete markers: (1) the dim light melatonin onset (DLMO) at a 10 pg/mL threshold, and (2) the time of melatonin synthesis offset (SynOff) estimated by the last high-amplitude data point preceding the steep early morning decline.22 The correlation between DLMO and SynOff was high (r=0.64, n=23, P=.02 by randomization test; data were excluded in 1 case with an atypical secretion pattern). The 2 measures indicated similar bidirectional phase shifts (DLMO vs SynOff for morning light, 1.51 ± 0.87 hours vs 1.25 ± 2.27 hours; for evening light, −1.34 ± 0.65 hours vs −1.9 ± 1.15 hours). We attribute the greater variability of the SynOff shifts to determinations based on visual inspection.22 Because most subjects in the study underwent only 5-hour sampling in the evening, the DLMO was used as the phase marker in further analyses.
Figure 1. Mean plasma melatonin concentration measured under dim light conditions (1-5 lux, with darkness during sleep) at 30-minute intervals in overnight sessions at baseline and after 10 to 14 days of treatment with morning or evening light, presented in crossovers. The 3 underlying curves for each of 8 subjects were normalized to compensate for varying amplitude by weighting each data point by the grand mean area under the curve.

**Figure 2** shows correlations, all significant, between the baseline DLMO and sleep onset, offset, and derived midpoints. The sleep midpoint, which shows the highest correlation ($r=0.66$, $n=41$, $P<.001$) and slope of unity, can be used to predict an individual's DLMO with an SE of ±0.79 hours and maximum error across all data points of ±1.57 hours. Thus, with blood drawn at 30-minute intervals to determine the onset of melatonin secretion, a sampling interval of 4.5 hours centered 6 hours before the sleep midpoint would be expected to capture the DLMO with at least 1 adjacent subthreshold (<10 pg/mL) and suprathreshold (>10 pg/mL) value.

**PHASE SHIFTS TO MORNING AND EVENING LIGHT**

Twenty-seven subjects provided DLMO estimates at baseline and in both legs of the morning-evening crossover. Baseline DLMOs were nearly identical across groups (M1E2, 21:36±1:12 hours; E1M2, 21:30±1:06 hours). The magnitude of phase shift in either direction depended on the treatment sequence (**Figure 3**). Phase advances were larger when morning treatment followed evening treatment than following baseline (1.31±0.84 hours vs 0.74±0.77 hours), while phase delays were larger when evening treatment followed morning treatment than baseline (−1.25±0.78 hours vs −0.71±0.59 hours vs 0.74±0.77 hours), while phase delays were larger when evening treatment followed morning treatment than following baseline (1.31±0.84 hours vs 0.74±0.77 hours vs 1.01±0.79 hours and maximum error across all data points of ±1.57 hours). Thus, with blood drawn at 30-minute intervals to determine the onset of melatonin secretion, a sampling interval of 4.5 hours centered 6 hours before the sleep midpoint would be expected to capture the DLMO with at least 1 adjacent subthreshold (<10 pg/mL) and suprathreshold (>10 pg/mL) value.

36 of 40 subjects) beyond which there was unsystematic scatter. In general, phase delays increased the later the evening CT ($r=−0.40$, $n=36$, $P=.01$) while phase advances decreased the later the morning CT ($r=−0.50$, $n=23$, $P=.008$) with greatest advances occurring approximately 8-hours post-DLMO (**Figure 4**). There was no significant effect when the same data were plotted against the clock time of light exposure rather than CT (evening, $r=−0.17$; morning, $r=−0.19$).

**RELATION BETWEEN CIRCADIAN PHASE AND TREATMENT RESPONSE TO LIGHT**

The study included 3 classes of dependent variables that might be interrelated: melatonin phase shifts and changes in the timing of sleep (onset, midpoint, offset, and duration) and in depression ratings. When morning and evening light treatment were compared in a multivariate analysis of variance, there was a significant overall effect ($Wilks Λ=0.33, F_{5,31}=21.12, P<.001$). Posttreatment DLMOs showed a large, significant morning-
evening contrast (Table). Although sleep onset showed no significant change, wake-up was approximately 30 minutes earlier with a commensurate advance in the midpoint and reduction in duration. By contrast, the percentage change in depression ratings did not differ (morning, 58.8%±29.2%; evening, 57.9%±28.8%). Although the morning light effect accounts for only 19.4% of the variance, the regression line indicates a 2-fold change in response, from approximately 40% to 80% between the smallest and largest phase shifts.

There was no significant correlation between (1) baseline DLMO and severity of depression (SIGH-SAD score); (2) baseline DLMO and percentage change in SIGH-SAD score after first-period treatment with morning or evening light; and (3) posttreatment DLMO and SIGH-SAD change. Thus, we were able to rule out circadian phase position—in contrast with phase shifts—as a factor determining treatment response.

We sought corroboration of the morning light phase shift effect in a larger sample that received parallel group, first-period treatment in the main clinical trial. Remission rate under morning light (24 [58.5%] of 41) was nearly twice that under evening light (12 [30.8%] of 39; χ² = 6.23, P = .02). Given the absence of melatonin data in roughly half of this group, we derived the CT of light administration from the baseline sleep midpoint (Figure 2). Under morning light there was a significant correlation between CT and the percentage change in SIGH-SAD score (r = −0.38, P = .01) that was absent under evening light (r = −0.03). When the morning group was split according to the median CT (earlier or later than 9.53 hours after the estimated DLMO), the early CT group showed a large, significant advantage (SIGH-SAD percentage change, 75.6%±16.4% vs 52.5%±29.8%, P = .004; remission, 16 [80.0%] of 20 vs 8 [38.1%] of 21, χ² = 7.41, P = .007). When compared with the response to evening light (percentage change, 54.1%±30.1%; remission, 12 [30.1%] of 39), early-morning CT also showed distinct superiority (percentage change, P = .002; remission, χ² = 12.85, P < .001), while late-morning CT and evening light were not significantly different.
PHASE SHIFTS OF SLEEP-WAKE VS MELATONIN RHYTHMS

The antidepressant effect of morning light might be attributed to the DLMO phase advance or accompanying sleep changes. We performed forward stepwise multiple regressions for SIGH-SAD percentage change separately for morning and evening light, which included all the sleep measures and DLMO change. Under morning light the DLMO phase advance was the only measure retained in the model (F1,20=6.09, P=.02). Notably, wake-up time was excluded. Under evening light, none of the variables was retained in the model. We conclude that sleep changes did not affect clinical response.

An elaboration of the phase shift hypothesis attributes improvement to changes in the phase angle difference (PAD) between sleep and other circadian rhythms (eg, of melatonin), rather than to the circadian phase shift alone. In pretreatment to posttreatment comparisons, the interval between melatonin and sleep onset increased by 0.90±0.81 hours under morning light (P<.001), placing the DLMO 2.45±1.25 hours before sleep. By contrast, under evening light the interval decreased by −0.90±0.75 hours (P<.001), placing the DLMO 1.22±1.21 hours before sleep. The SIGH-SAD percentage change was significantly correlated with the change in PAD (ΔPAD) under morning light (r=0.42, n=28, P=.03), which mirrors the correlation with DLMO change alone (r=0.44, Figure 5). Under evening light, improvement was not significantly correlated with the ΔPAD (r=−0.20, n=40, P=.22). Furthermore, ΔPADs computed against the sleep midpoint and wake-up time showed no relationship with clinical improvement under either morning or evening light.

This study demonstrates that morning and evening light exposure at 10000 lux, 30 minutes per day produces phase shifts of the melatonin rhythm consistent with human phase response curves (PRCs) and other morning-evening comparisons. Two laboratory PRC paradigms have presented light pulses across the circadian cycle under free-running conditions (5000 lux, 3-hour exposure on a single day or 3 consecutive days) or constant routines (10000 lux, 3 days). By contrast, we generated discrete delay and advance portions of the PRC at the edges of the subjective night, which represented the cumulative effect of 10 to 14 daily 30-minute light exposures in subjects who maintained habitual sleep-wake cycles and entrainment in their normal living environment. Delays up to 2.80 hours occurred after evening light exposure, and advances up to 2.65 hours occurred after morning light exposure, depending on the CT of exposure relative to the pretreatment DLMO. When PRCs are measured throughout the night—a procedure incompatible with habitual sleep—there is a crossover between delays and advances before the time subjects normally awaken, around the nocturnal core body temperature minimum, which closely matches the Syn-Off. In our situation we predict that light presentation earlier than 7.5 hours post-DLMO would yield smaller phase advances and lower antidepressant efficacy, with a crossover to phase delays corresponding to the SynOff in our overnight samples, 7.17±1.25 hours post-DLMO. Direct measurement of the crossover point would require that subjects awaken at earlier CT than in this study, or possibly receive illumination while asleep.

Although it was initially hypothesized that patients with winter depression would show delayed circadian rhythms relative to normal control subjects, results have been equivocal, both positive and negative. Our study lacked a normal control comparison, yet we found that following morning light, patients who were relatively phase delayed at baseline did not show greater improvement in depression scores. Three other studies also found no relationship between baseline circadian phase and clinical improvement.

Our protocol did not impose a standard clock time for sleep (or for light exposure) as in earlier studies, but rather allowed individual subjects to follow their habitual sleep schedule. A corollary of the phase shift hypothesis is that the crucial determinant of antidepressant efficacy is the ΔPAD between sleep and other circadian rhythms (eg, melatonin). Indeed, the key may lie in the phase relation between sleep and the circadian rhythm of mood, which recently has been demonstrated in patients and healthy subjects using rating scales. Since sleep onset did not change after light treatment in our study, the ΔPAD resulted simply from the DLMO phase shift. A related study found that morning light produced a smaller phase advance of sleep than of the melatonin rhythm, but overall the ΔPAD was minimal despite a therapeutic response. While the ΔPAD in our study was significantly correlated with the therapeutic response under morning light, response did not vary with the PAD itself (2.45±1.26 hours; range, −0.35 to 4.25 hours). Thus, although treatment succeeded in expanding the PAD, we cannot identify an optimum posttreatment interval associated with euthymia.

Based on the present melatonin data, one would conclude that a phase advance is neither necessary nor sufficient for the therapeutic effect because the remission rates for morning light and evening light were not significantly different. Other studies have also sought a correspondence between phase shifts and clinical response and were unable to distinguish responders from nonresponders on this basis. However, all of these studies have been limited by the sample size used to assess the antidepressant effect, which has inherently high variance. Notably, 3 larger studies one including the present subjects have demonstrated morning light superiority.

The increased power of larger samples seems necessary to overshadow the nonspecific benefits of evening light exposure. When we expanded the parallel groups’ sample in the present study, for example, morning light superiority was clearly located to an early CT exposure interval that would serve to magnify phase advances. In the present crossover groups (M1E2 and E1M2), we expected to find greater antidepressant response in M2 than...
M1, since M2 phase shifts were larger. However, although the remission rate was twice as high in M2 (6 [60%] of 10 vs 5 [29.4%] of 17), the small sample size prevented detection of a significant difference ($\chi^2 = 2.44, P = .12$). Rather than recommending that patients initially be given a phase delay by evening light to magnify the phase advance to morning light, an implication of the parallel group analysis is that the antidepressant effect of M1 can be directly enhanced by light exposure at earlier CT. For long sleepers this would require waking up for light therapy before habitual rise time.

A novel finding of our study is the correlation between the magnitude of phase advances to morning light and improvement in depression ratings. Such results confirm the hypothesis of Lewy and Sack and colleagues, who also showed that improvement under evening light is coincident with a group mean phase advance of the DLMO, although they did not find a correlation between size of the advance and antidepressant response across individuals. The results do not confirm our earlier hypothesis that light would be efficacious unless it induces a phase delay. Patients with large phase delays to evening light were no more depressed than those with smaller delays or those with small advances to morning light.

A signal detection analysis of morning vs evening light response showed maximum group contrasts at criteria of 70% to 100% improvement in SIGH-SAD score, or a final score between 0 and 8. In the present study, such strong response is associated with phase advances to morning light of approximately 1.5 to 2.5 hours, obtained at DLMO-to-light intervals of 7.5 to 9.0 hours. If the response to evening light were no more than a placebo effect, as has been proposed, the specificity of morning light could be attributed to phase advances of at least 1.5 hours.

The early-CT advantage of morning light exposure seems to be key to the specific efficacy of this treatment modality. This interpretation is strengthened by the fact that subjects had no knowledge of their DLMOs or the CT of light exposure, yet responded in a phase-shift dependent manner. Further research is needed to determine whether evening light (or morning light at late CT) exerts an antidepressant effect beyond that of placebo. The most convincing analysis used an inert nonphotonic control (a dummy negative ionizer) with response rates and expectation ratings no different from those under evening light. In a related trial, response rate was higher for evening light than for low-density ionization, but expectations also were higher. Other studies supporting evening light efficacy have lacked adequate placebo controls, with conclusions mainly based on nonsignificant differences from morning or midday light treatment.

In conclusion, we recommend that for maximum advantage, light therapy of 10 000 lux for 30 minutes should be scheduled in circadian rather than clock time, about 8.5 hours after the baseline DLMO. A DLMO phase diagnostic is not yet readily available in clinical practice. However, the DLMO can be inferred within an acceptable margin of error from the self-reported sleep midpoint (Figure 2). This algorithm does not apply to people who sleep “out of phase” with their circadian clock, such as shift workers, but is confined to stable sleepers with 6 to 9 hours duration, onset between 10:00 PM and 1:00 AM, and waking between 5:30 AM and 9:00 AM. By consulting a derived table, the clinician can select an appropriate treatment time which then can be adjusted depending on the patient’s initial response.

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