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Antidepressant and Circadian Phase–Shifting Effects of Light

ALFRED J. LEWY,* ROBERT L. SACK, L. STEPHEN MILLER, TANA M. HOBAN

Bright light can suppress nighttime melatonin production in humans, but ordinary indoor light does not have this effect. This finding suggested that bright light may have other chronobiologic effects in humans as well. Eight patients who regularly became depressed in the winter (as day length shortens) significantly improved after 1 week of exposure to bright light in the morning (but not after 1 week of bright light in the evening). The antidepressant response to morning light was accompanied by an advance (shift to an earlier time) in the onset of nighttime melatonin production. These results suggest that timing may be critical for the antidepressant effects of bright light.

WE SHOWED EARLIER (*1*) THAT bright (2500 lux) light is necessary for suppression of nighttime melatonin production in humans, whereas other animals respond to light of ordinary intensity (*2*). This suggested that humans could have biological rhythms cued to natural daylight that would remain unperturbed by the use of ordinary indoor light (*3*) and that bright light could be used to manipulate these rhythms. We first tested this idea during the winter of 1980 when we successfully treated a patient with recurrent winter depression by exposing him for several days to light at an intensity of 2000 lux from 0600 to 0900 and from 1600 to 1900 (*4*). Since then, many such patients have been similarly treated (*5, 6*).

Subsequent studies showed that dim light is not effective in treating this disorder (*5, 6*). However, there is disagreement about whether the time of exposure to light is important. Some investigators have concluded that only duration and brightness are important (*7–9*), whereas we have held that time of exposure to light is also critical (*10–12*).

We hypothesized (*10–12*) that the antidepressant effect of bright light depends on shifting the phase (timing) of circadian (24-hour) rhythms. The effect of bright light would vary according to a phase response curve (PRC) similar to those described for other animals (*13, 14*); light in the morning would advance circadian rhythms (shift them to an earlier time) and light in the evening would delay them (shift them to a later time) (*15*). We further hypothesized that the circadian rhythms of most patients with winter depression are abnormally phase-delayed and that most of these patients should preferentially respond to morning light which would provide a corrective phase advance (*11, 12*). We now present data from a study designed to test these hypotheses.

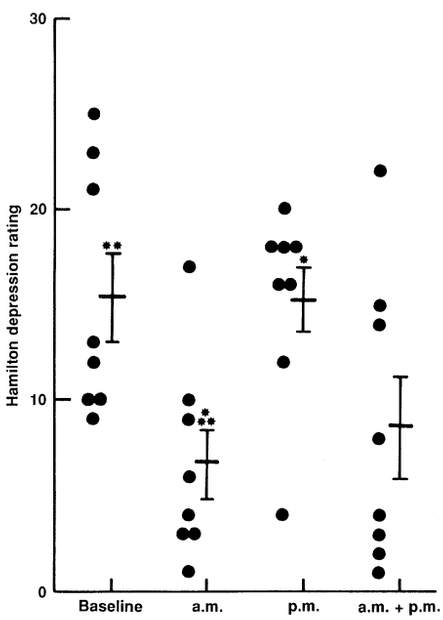

Fig. 1. Individual and average 21-item Hamilton depression ratings (±SEM) for eight patients with winter depression for each of the 4 weeks of the study. An analysis of variance for repeated measures indicated a significant ($P = 0.026$) difference between treatments. Only the paired t tests comparing the week of morning (a.m.) light and the baseline week (**$P = 0.004$) and comparing the week of a.m. light and the week of evening (p.m.) light (*$P = 0.045$) were significant. Average depression ratings (±SEM) for the seven normal control subjects were 3.0 ± 0.9 at baseline, 2.4 ± 0.3 (a.m. light), 6.1 ± 1.6 (p.m. light), and 4.3 ± 0.9 (a.m. + p.m. light).

During a 4-week protocol, seven normal control subjects and eight patients with winter depression (*16*) stayed indoors between 1700 and 0800 shielded from bright light and slept only between 2200 and 0600. The first week was a baseline week. During the second week, subjects were randomly assigned to morning bright light exposure (0600 to 0800) or to evening bright light exposure (2000 to 2200), and during the third week these assignments were reversed (*17*). During the fourth week, all subjects were exposed to bright light both in the morning and in the evening. Under continuous dim light (*15*), blood was sampled for melatonin every 30 minutes between 1800 and 2300 on the first (prebaseline) day of the study and on the last day of each week and was subsequently assayed for melatonin by the gas chromatographic–negative chemical ionization mass spectrometry (GC-MS) technique of Lewy and Markey (*18*). Subjects were rated with the 21-item Hamilton depression scale (HAM-D) (*19*) on the evening of each blood drawing by a psychiatrist (R.L.S.) who was not aware of the treatment conditions assigned for weeks 2 to 4. Patients were told that an antidepressant response could potentially occur on any of the 4 weeks of the study, depending on the individual.

At baseline, HAM-D ratings for the patients (Fig. 1) averaged 15.4 ± 2.3, which is considered to be a moderate degree of depression (*19*). After a week of morning light, ratings were significantly lower [6.6 ± 1.8 ($P = 0.004$)] and not significantly different from those of the control subjects. Ratings after a week of evening light (15.2 ± 1.8) were not significantly different from those of the baseline week but were significantly greater than those after a week of morning light ($P = 0.045$). Depression ratings after the week of both morning and evening light (8.6 ± 2.7) were not significantly different from those of any of the preceding 3 weeks.

Average onset times of melatonin secretion for both subject groups are shown in Fig. 2. Prebaseline and baseline melatonin onset times of the patients were significantly delayed compared to those of the normal controls ($P = 0.02$ and 0.05, respectively). Morning light exposure advanced the time of onset of melatonin secretion and evening light delayed it (*20*). The combination of morning and evening light caused the melatonin onset times to shift to intermediate

Sleep and Mood Disorders, Laboratory, Departments of Psychiatry, Ophthalmology, and Pharmacology, Oregon Health Sciences University, Portland, OR 97201.

*To whom correspondence should be addressed.

phase positions. Exposure of the patients to morning light (which was most effective in reducing depression ratings) advanced their melatonin onset times to a phase position similar to that of the normal controls. Melatonin onsets of patients appeared to advance relatively more in response to morning light exposure in comparison to normal controls and appeared to show relatively less delay in response to evening light.

For both patients and normal controls, morning light advanced the melatonin onset times, evening light delayed them, and the combination caused melatonin onset times to shift to intermediate phase positions as if the morning and evening exposures were counteracting each other when scheduled together. Morning light was also more effective than evening light in reducing depression ratings. The combination of light exposure both morning and evening seemed to have an antidepressant effect intermediate between that of morning light alone and evening light alone, again as if they were counteracting each other.

The most compelling explanation for these results is that the antidepressant effect of bright light in the treatment of winter depression is at least in part related to advancing the phase of the melatonin onset and, by implication, other circadian rhythms as well. By inference, these patients should have circadian rhythms that are abnormally phase-delayed. In fact, prebaseline and baseline times of melatonin onset for the patients were significantly delayed compared to onset times for the group of normal control subjects.

The phase-advancing effect of morning light was maximized by beginning the exposure to bright light immediately upon awakening, and the phase-delaying effect of evening light was maximized by ending the exposure to bright light just before sleep (*21*) while minimizing any interference with sleep. In the initial studies (*4, 5*), subjects were not exposed to evening bright light as late as in the present study. Consequently, the earlier studies did not use optimal exposure schedules to test whether or not the phase-shifting effect of light exposure was critical for its antidepressant effect. In other studies (*6, 7*) that showed a (moderate) antidepressant response to evening bright light exposure, sleep time was not specifically held constant nor were patients required to avoid bright light at dawn (*22*), as in the present study; thus, patients in these earlier studies could have been exposed to bright light at both times (a moderately effective treatment consistent with the results of the present study).

The times of melatonin onset in the patients appeared to advance relatively more in response to morning light and delay relatively less in response to evening light than in the normal control subjects, suggesting either a difference in PRC shape (*14*) or phase-delayed PRC's in the patients. Either possibility is compatible with abnormally phase-delayed circadian rhythms in the patients and suggests (*14*) that their average intrinsic (free-running) periods would be greater than that reported for normal individuals (25.0 ± 0.5) (*23*).

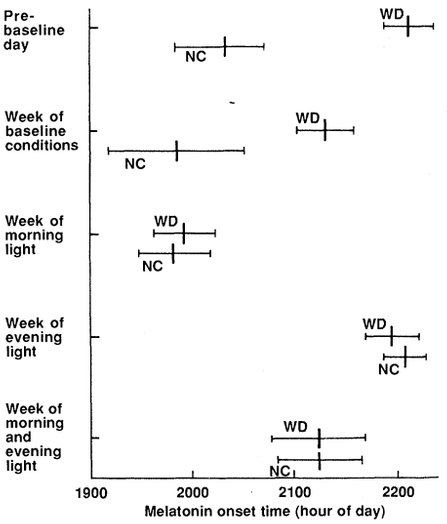

Fig. 2. Average melatonin onset times (±SEM) for normal controls (NC) and patients with winter depression (WD) (n = 6 to 8, except n = 4 for the prebaseline melatonin values). An analysis of variance for repeated measures indicated a significant difference between treatments for both patients (P = 0.001) and normal controls (P = 0.009). Significant paired t tests for the patients were baseline versus a.m. (P = 0.001), baseline versus p.m. (P = 0.012), and a.m. versus p.m. (P = 0.001). Significant paired t tests for the normal controls were baseline versus a.m. + p.m. (P = 0.039), a.m. versus p.m. (P = 0.004), and a.m. versus a.m. + p.m. (P = 0.003). Melatonin onset times of the patients were delayed compared to those of the normal controls at both prebaseline (P = 0.02) and baseline (P = 0.05) (Student's t test).

Although many of these patients have difficulty arising in the morning, their sleep does not seem to be as delayed as in delayed sleep phase insomnia (*24*) in which all circadian rhythms—including sleep—are presumably delayed to the same extent. Because sleep time was held constant in the present study, the advance of one or more endogenous circadian rhythms as a result of morning light exposure reduced a phase angle between these circadian rhythms and sleep (or a sleep-dependent process) (*25, 26*).

Although the present study suggests that the mechanism for the antidepressant effects of bright light is related to a phase advance in circadian rhythms presumably correcting a pathogenic phase delay, we cannot rule out the possibility that another biological or psychological component might be required for winter depression to develop. Nor can we rule out that these patients might respond to another type of treatment. Nonetheless, the present study draws attention to a psychiatric disorder that appears to be effectively treated by a biological intervention consistent with the change in natural photoperiod that accompanies its seasonal pattern of recurrence. The present study, however, further suggests that the chronobiologic abnormality of these patients may be related more to their circadian rhythms than to seasonal rhythms (*27*). These findings suggest some approaches for assessing and treating other hypothesized circadian rhythm disturbances, such as certain other types of sleep and mood disorders (*10–12, 28*), shift work difficulties, and jet lag (*29*).

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one or two endogenous circadian pacemakers govern the evening rise and morning fall in melatonin levels is controversial [H. Illnerova and J. Vanecek, *J. Comp. Physiol.* **145**, 539 (1982)]. If the former is the case, the melatonin onset time reflects the phase of the melatonin circadian pacemaker; in the latter case, the onset would mainly be reflecting the phase of the evening circadian pacemaker for melatonin production.

16. Patients were recruited through a newspaper ad in the fall of 1984. They were admitted into the study if they met Research Diagnostic Criteria (RDC) [J. P. Feighner *et al.*, *Arch. Gen. Psychiatry* **26**, 57 (1972)] for a major depression that developed during the fall or winter and remitted the following spring or summer (for at least the last two consecutive years) and had not used psychotropic drugs for at least 2 weeks prior to admission into the study. Control subjects were also screened with the RDC. There was no significant age difference between the two groups. Approximately one-fourth of the subjects in each group was male. In addition, six individuals with winter depression were studied as inpatients on the Clinical Research Center under a related, but different, set of lighting schedules (they were exposed to an additional 15 minutes of light from 0800 to 0815 and from 1645 to 1700 for the entire protocol). Consequently, the results from this group could not be combined with those of the outpatients, even though they were similar.
17. Subjects were instructed to sit at a 45° angle 2.5 to 3 feet in front of a fixture containing eight 40-watt, 4-foot fluorescent lamps and to scan their eyes across the fixture every few minutes. Subjects were randomly assigned to either Vita-Lite (Duro-Test) or cool white (General Electric) lamps for the entire study. Light intensities were approximately 2500 lux for both types of lamps. There were no significantly different effects on any dependent variables; consequently, data from both types of lamps could be combined.
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19. The standard Hamilton scale [M. Hamilton, *J. Neurol. Neurosurg. Psychiatry* **26**, 56 (1960); *Psychiatr. Neurol. Neurochir.* **72**, 201 (1969)] actually underestimates the severity of depression in winter depressive patients, because it includes hyposomnia and weight loss in the ratings; winter depressive patients tend to have hypersomnia and to gain weight when symptomatic.
20. The timing of the melatonin onset was not a result of difference in amplitude, as assessed by overnight collections of urine analyzed for 6-hydroxymelatonin, the major metabolite of melatonin, by the GC-MS technique [M. Tetsuo, S. P. Markey, R. W. Colburn, I. J. Kopin, *Anal. Biochem.* **110**, 208 (1981)].
21. Exposure to bright light in the middle of the day has less of a phase-shifting effect in animals (*13, 14*), although the precise boundaries of this "dead zone" are not known for either normal controls or patients.
22. In one of these studies (*7*), depression ratings fell significantly more under bright evening light than under dim evening light compared to baseline. However, depression ratings under bright evening light were not significantly different from those under dim evening light. These and other light treatment studies are reviewed more comprehensively elsewhere [A. J. Lewy and R. L. Sack, *Proc. Soc. Exp. Biol. Med.* **183**, 11 (1986)].
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25. The previously proposed "phase advance hypothesis for affective disorders" [M. Papousek, *Fortschr. Neurol. Psychiatr. Ihrer Grenzgeb.* **43**, 381 (1975); D. F. Kripke, D. J. Mullaney, M. L. Atkinson, S. Wolf, *Biol. Psychiatry* **13**, 335 (1978); T. A. Wehr, A. Wirz-Justice, F. K. Goodwin, W. Duncan, J. C. Gillin, *Science* **206**, 710 (1979)] states that affective disorders result from an internal phase angle disturbance in which the sleep pacemaker is not as advanced as the temperature pacemaker [whether or not these overt circadian rhythms represent different endogenous pacemakers (*26*), advancing sleep appeared to be transiently effective in ameliorating depressive symptoms in some of these patients]. Just as in these patients sleep was presumably not as phase-shifted (advanced) as their other circadian rhythms, we (*11*) proposed that sleep is not as phase-shifted (delayed) as the other circadian rhythms in the winter depressive patients of the present study. Thus, we think affective symptoms may result from an internal phase angle disturbance of either type. Accordingly, we (*11, 12*) have proposed that patients (who are thought to have a chronobiologic component to their sleep or mood disorder) be "phase typed" on an individual basis: phase-advanced patients should preferentially respond to evening bright light exposure and phase-delayed patients should preferentially respond to morning bright light (holding sleep time constant after it normalizes).
26. With regard to the mathematical models of the human circadian system, our findings appear to be more supportive of the one-oscillator model proposed by S. Daan, D. G. M. Beersma, A. A. Borbely [*Am. J. Physiol.* **246**, R161 (1984)] and C. I. Eastman [in *Mathematical Models of the Circadian Sleep-Wake Cycle*, M. C. Moore-Ede and C. A. Czeisler, Eds. (Raven, New York, 1984), pp. 81–103] than the two-oscillator model proposed by R. A. Wever (*23*) as modified by R. E. Kronauer, C. A. Czeisler, S. F. Pilato, M. C. Moore-Ede, and E. D. Weitzman [*Am. J. Physiol.* **242**, R3 (1982)].
27. If our hypotheses are correct, patients become depressed in the winter because of the later dawn [humans who generally have an intrinsic period greater than 24 hours (*23*) should cue more to dawn than to dusk (*14*)].
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Wind Speed and Mortality Rate of a Marine Fish, the Northern Anchovy (*Engraulis mordax*)

RANDALL M. PETERMAN* AND MICHAEL J. BRADFORD*

Large variability in recruitment of marine fishes creates challenging management problems. In northern anchovy (*Engraulis mordax*), there is a significant linear relation between larval mortality rate and the frequency of calm, low wind speed periods during the spawning season, possibly because calm winds permit maintenance of concentrated patches of larval food. Neither cannibalism on larvae nor offshore transport contributed significantly to interannual variation in early larval mortality. These results are consistent with the hypothesis that wind-driven turbulent mixing affects variability in survival of young fish larvae. However, abundance of recruits does not necessarily reflect abundance of larvae surviving through this early stage.

INTERANNUAL VARIABILITY IN ABUNdance of a new cohort of young fish (recruitment) is usually large in marine fish species (the coefficient of variation is typically 80%) (*1*). In some species, this variability appears to be heavily influenced by large-scale physical processes, and there are correlations in annual recruitment among diverse marine fishes throughout large areas (*2*). Evidence that wind is a cause of variability in recruitment and in larval fish mortality has been found on three time scales: evolutionary, interannual, and daily. First, many marine fish species with pelagic eggs and larvae spawn in seasons and in locations that on average have favorable wind conditions for survival of offspring (*3*). Second, some species show low recruitment indices in years when there is extensive wind-driven transport of water away from larval nursery areas (*4*). Third, days of high winds associated with storms dissipate concentrated patches of food that are vital to survival of larval fish (*5*).

We tested the mechanism of Lasker's "stable ocean" hypothesis (*5*), which states that "the upper mixed layer of the ocean must be in a stable (nonturbulent) state" to generate sufficient concentration of food to ensure good survival of first-feeding larval fish. We used a wind speed index as a measure of turbulent mixing of the upper ocean and tested whether low wind speeds tend to be associated with low mortality. In addition, we tested the relative importance of offshore transport and cannibalism on larval mortality.

To examine these hypotheses, we used data on the central population of the northern anchovy, *Engraulis mordax*, off the coast of southern California. This is one of the most intensively studied marine fish species; detailed data exist since 1954 on adults, eggs, larvae, and relevant oceanographic variables (*6, 7*). Most spawning occurs from January through April (*8*) and the buoyant eggs hatch into yolk-sac larvae after 3 or 4 days (*9*). The yolk sac is absorbed 1 to 3

Southwest Fisheries Center, National Marine Fisheries Service, La Jolla, CA 92038.

*Present address: Natural Resource Management Program, Simon Fraser University, Burnaby, British Columbia V5A 1S6 Canada.