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MINIREVIEW

Light Therapy and Psychiatry (42380A)

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Circadian (24-hr) rhythms are driven by an endogenous pacemaker. In constant conditions free of external time cues (Zeitgebers), the pacemaker and its driven rhythms "free run" at an intrinsic period close to, but not precisely, 24 hr (1). Twenty-four hour precision is accomplished mainly by entrainment, or synchronization, to the 24-hr light–dark cycle through daily phase shifts (a shift to either an earlier or a later time of the day) that result from exposure to light (2–4).

These phase shifts vary in magnitude and direction according to when the light exposure occurs, a relationship that can be described by a phase response curve (PRC). The basic features of a PRC are that phase delays (shifts to a later time) occur in response to light exposure during the first part of the subjective night and that phase advances (shifts to an earlier time) occur in response to light exposure during the second part of the subjective night. (In constant dark conditions, subjective night refers to the sleep phase of diurnal animals and the activity phase of nocturnal animals.) During the subjective day, light exposure has relatively little effect. Generally, the middle of the night is when phase shifts are of the greatest magnitude and when there is an inflection point in the PRC that separates delay responses from advance responses.

In nature, only moonlight illuminates the high-amplitude portions of the PRC that occur in the middle of the night. Entrainment to the 24-hr day is thus provided by exposure to sunlight at dawn and at dusk, resulting in a phase advance and a phase delay, respectively, each day. These phase shifts compensate for each other and their net effect must also compensate for the pacemaker's intrinsic (free-running) period. For example, as is generally the case in humans (5), if the pacemaker's intrinsic period is approximately 25 hr, then it must advance its phase by 1 hr each day or else drift later and later.

Seasonal biological rhythms are cued to day length, or the photoperiod, although they also depend to some extent on the circadian timing system (1). The pineal gland exerts its effects on seasonal rhythms through hormonally transducing the length of the day by producing melatonin (5-methoxy-*N*-acetyltryptamine) during the night (6). Thus, melatonin production begins after dusk and ends before dawn (7, 8). Like other circadian rhythms, the melatonin production rhythm free runs in constant darkness (9). It also has well-defined "on" and "off" periods that alternate like an hourglass at approximately 12-hr intervals. The endogenous circadian pacemaker for melatonin production is located in the suprachiasmatic nucleus (SCN) of the hypothalamus (10–12), which is thought to be the pacemaker for most circadian rhythms (13, 14). The SCN sends a circadian signal through a well-defined neural pathway that terminates in the peripheral sympathetic innervation of the pineal (15, 16).

Photic information is conveyed to the SCN via the retinohypothalamic tract extending from the retina to the hypothalamus (17). Exposure to light entrains the circadian rhythm of melatonin production [in a manner that can be described by a PRC (18)]. Light also has a second effect on melatonin production, whereby acute exposure during the night suppresses melatonin production (19). Darkness during the day does not stimulate melatonin production because after the SCN has stopped melatonin production in the morning, it remains turned off for the rest of the day.

The entrainment and suppressant effects of light combine to produce seasonal changes in the pattern of melatonin production. One school of thought (20) minimizes the role of the suppressant effect of light in nature, postulating two separate (though coupled) endogenous circadian pacemakers—one that controls the onset of night-time melatonin pro-

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duction which is cued mainly to dusk and one that controls the offset which is cued mainly to dawn. Another school of thought emphasizes a role for the suppressant effect of light during long photoperiods and assumes that both the onset and the offset of melatonin production can be controlled by a single pacemaker (21, 22).

Until recently, there was uniform agreement among chronobiologists and pineal physiologists that light played at best a minor role in regulating human biological rhythms and melatonin physiology (5, 23, 24). It was thought that humans as a species were uniquely lacking in chronobiological responses to light. This conclusion was based on a number of studies in which light exposure repeatedly failed to suppress night-time melatonin production in humans or to entrain human circadian rhythms (5, 24–30).

Reversal of this thinking occurred after it was demonstrated that bright light of 2500 lux could suppress night-time melatonin production in humans (31). Apparently, previous studies used light of insufficient intensity for humans (although of adequate intensity for almost all other species). Once an intensity threshold is exceeded, the brighter the light, the greater the suppression (31). These findings had at least three significant implications: (i) humans have circadian and seasonal rhythms that respond to sunlight (which is generally 20 to 200 times brighter than indoor light), (ii) ordinary indoor light is not bright enough to interfere with the response to sunlight, and (iii) bright artificial light can be used experimentally, and perhaps therapeutically, to manipulate these rhythms. Accordingly, it was then shown that bright light could increase the range of entrainment of the human temperature and activity–rest circadian rhythms (32).

Further exploration of the suppressant effects of light in humans has provided preliminary evidence suggesting that most bright white light sources should be effective, because the peak wavelengths for melatonin suppression appear to be around 509 nm (33). Presumably, the same action spectrum holds for other chronobiologic effects of light in humans.

Before it became clear to psychiatrists that bright light could be used to treat chronobiologic abnormalities, chronobiologic studies exclusively used paradigms of sleep deprivation (34–36) and shifted sleep schedules (37–39). Depressed patients whose circadian rhythms were thought to be abnormally advanced with respect to sleep were treated by sleep deprivation (34–36) or by advancing their sleep schedules (37). Patients with delayed sleep phase syndrome were treated by sequentially delaying sleep each day until the desired sleep schedule was reached (38, 39). Although effective in some patients, these treatments were unwieldy and did not specifically take into account the fact that shifting sleep also shifted the perceived light–dark cycle.

On the other hand, bright light therapy is rapidly becoming the treatment of choice for chronobiologic abnormalities because it is easy to administer and has few side effects. Bright light therapy has been most extensively applied to the syndrome of "winter depression," first described around the turn of the century (40–43). In winter, these patients complain of fatigue, hypersomnia, overeating and feelings of sadness; in the spring, these symptoms typically remit spontaneously. Subsequent to the original study in 1980 (44), over a hundred patients with winter depression (or seasonal affective disorder, as it is sometimes called) have been treated with bright light.

The first study (44) of light treatment involved the use of bright light exposure from 6 to 9 AM and from 4 to 7 PM. The strategy was to extend the day length so that it was equal to the photoperiod of the time of year when the patient's depression typically remitted. The two periods of light exposure were analogous to the pulses of light used in animal studies that are sufficient to define the day length and to cue seasonal rhythms. The following winter (1981) nine more patients were studied, crossed over between bright and dim light exposure 3 hr before dawn and 3 hr after dusk (45). Bright light exposure caused a statistically significant reduction in depression ratings, whereas dim light (the placebo control) had little effect.

Researchers most experienced in studying winter depression agree that this disorder is effectively treated by exposure to bright light; they also agree that symmetrically lengthening the day (extending the photoperiod) is not critical for the antidepressant effect. Research

groups differ, however, as to whether or not they think that bright light works through (i) suppression of melatonin production (46), (ii) photon counting (i.e., exposure to a critical number of photons) (47–51) or (iii) shifting circadian phase position (21, 22, 52–56).

To test the suppression of melatonin production hypothesis, melatonin was administered in the morning and evening to winter depressive patients who were concurrently responding to bright light scheduled at these times (46). Melatonin administration brought back some, but not all, of the depressive symptoms. At first these results were interpreted as support for a partial role for melatonin (46). However, the following winter administration of atenolol, a β-adrenergic blocker that can reduce night-time melatonin production, failed to significantly lower depression ratings (50), thus causing the melatonin suppression hypothesis to be rejected by the same investigators who originally proposed it.

These studies remain inconclusive, particularly since atenolol was not administered in the morning. Apparently, atenolol was administered in the evening because of a pilot study in which evening bright light was noted to have an antidepressant effect (57). Further support for this finding came from a study that compared 5 or 6 hr of bright vs dim light in the evening, suggesting that the bright light was more effective (48). (However, analysis of the raw data included in this report reveals no significant difference between the depression ratings at the end of the week of bright evening light and those at the end of the week of dim evening light.)

Nevertheless, these findings were interpreted to mean that morning light was not critical (47, 48, 57). The photon counting hypothesis was then proposed, which states that it is the duration of the bright light exposure and not its timing that is critical for its antidepressant effect in winter depression (48–50). This hypothesis seems to have also evolved from two other studies (47, 51). One study (47) done single-blind on six patients in Alaska found that 2 hr of bright light exposure in the morning only or evening only were as effective as 1 hr of exposure both morning and evening. The other study (51) involved seven winter depressive patients who were crossed over between a long and a short photoperiod. The long photoperiod consisted of bright light from 7:30 to 10:30 AM and from 8 to 11 PM. For the short photoperiod, bright light was scheduled from 9 AM to noon and from 2 to 5 PM. Both photoperiods were equally antidepressive. The investigators concluded that duration, not timing of bright light exposure was critical, hence the photon counting hypothesis. The photon counting hypothesis has led these investigators to wonder if perhaps the skin, and not the eyes, mediated the antidepressant effects of bright light in winter depression (51).

A major problem with interpreting these results as evidence against the importance of timing is that day length is only one way in which the timing of the light could be important. Light might also be working by shifting circadian phase position—the phase shift hypothesis.

Several years ago, we proposed a PRC for humans (58) with features similar to those for other animals (1–4, 18) and found that advancing dusk advances the timing of human melatonin production and delaying dawn delays it (21, 22, 52). Subsequently we were also able to delay the onset of night-time melatonin production with bright light exposure in the evening and to advance it by exposure to bright light in the morning (53). Thus, as would be expected if humans had PRCs similar to those of other animals, bright light exposure in the evening delays circadian phase position and bright light exposure in the morning advances it.

Applying these findings to the study of winter depression, the Hamilton depression ratings of a group of eight winter depressive patients significantly fell after a week of morning (6–8 AM) bright light exposure (during which patients avoided bright light in the evening) but not after a week of evening (8–10 PM) bright light (during which exposure to bright light in the morning was avoided) (56). The response to morning plus evening bright light was intermediate between the response to morning bright light exposure alone and evening bright light alone, as if the evening light was counteracting the effect of the morning light. The preferential response to morning light strongly suggests that its mechanism of action is related to advancing the phase of the circadian rhythms in these patients.

The melatonin onsets were compared between the patient group and a group of seven age- and sex-matched healthy control subjects. Even after a week of controlled conditions (in which sleep was permitted only between 10:00 PM and 6:00 AM and bright light was avoided between 5:00 PM and 8:00 AM), the time of the onset in melatonin production occurred significantly later in the patients than in the healthy control subjects. Normalization of the time of melatonin onset occurred after the week of the morning bright light treatment, which also normalized depression ratings. Furthermore, when the different light exposures were compared, the decline in depression ratings was significantly correlated with the advance in circadian phase position. Thus, the melatonin data, as well as the behavioral response data, suggest that the morning light's antidepressant efficacy is directly related to correcting an intrinsic phase delay abnormality.

Our study, which supports the importance of timing, can be reconciled with the studies that appear to negate it by hypothesizing that the phase angle between sleep (or a sleep-dependent process) and the other circadian rhythms is pathogenic for depression (53, 59). Specifically, in winter depression, sleep is delayed but not as much as the other circadian rhythms (53). In the studies that appear to negate the importance of timing, interventions just before bedtime, such as light exposure, could have delayed sleep if it were not held constant, thus correcting the phase angle between sleep and the other circadian rhythms, especially if patients were thereby waking up into brighter light. Studies that did not control both sleep time and bright light exposure around twilight (46–50, 57) could thus have made it appear that evening light alone was effective. We therefore think that the preferential response to morning bright light exposure will be replicated in future studies that are properly controlled.

There are only two studies to date in which sleep time and bright light exposure around dawn and dusk were carefully controlled: the long/short photoperiod study (51) and our phase shift study (56). These two studies are also reconcilable: the phase shift hypothesis can explain the results from the long/short photoperiod study because the morning light exposures of the two photoperiods overlapped (7:30 to 10:30 AM for the long photoperiod, 9 AM to noon for the short photoperiod). Thus, if the phase shift hypothesis is correct, one would expect an antidepressant effect from either photoperiod on the basis that both lighting schedules were capable of advancing circadian phase position. The long photoperiod might not have been more effective because its later evening light (8 to 11 PM compared to 2 to 5 PM for the short photoperiod) could have been counteracting the greater phase advance shift from its earlier morning light.

Consequently, we think the phase shift hypothesis is valid for bright light treatment of winter depression. However, further studies need to be done before it is confirmed. As mentioned above, the antidepressant effect of delaying sleep while holding the light–dark cycle constant should be investigated, since this could explain why interventions in the evening might be effective (preliminary evidence from our laboratory suggests that this paradigm may be an effective antidepressant for winter depressives). Recent studies, also from our laboratory, suggest that 2 hr of bright light exposure between 6 and 8 AM cause too much of a phase advance in some winter depressives. For these patients, a shorter duration of morning light, or additional light in the evening, might produce the correct amount of phase advance. If evening light is scheduled too late, many patients will not experience a complete remission when exposed to both morning and evening bright light due to too much phase delay from the evening light (46, 51, 60). If it is not scheduled too late, evening light may improve mood by some sort of an immediate "energizing" effect.

Compared to winter depression, the efficacy of light therapy for other types of depression is less clear, even though investigations (61, 62) into light therapy of major (melancholic) depression began at the same time as did light therapy of winter depression (44). In contradistinction to winter depression, major (melancholic) depression is often accompanied by early morning awakening and is therefore thought to be associated with phase advanced circadian rhythms (37, 59, 63). One would think that bright light exposure in the evening

would be most effective in these patients (64). However, the first studies of major depression compared bright and dim light exposure only in the morning. The results were statistically significant but weak (61, 62). Subsequent studies on the use of morning bright light for this disorder in which the number of days of exposure was increased did not result in more of an antidepressant effect (63).

Why was morning light administered to these presumably phase advanced patients? A "critical (morning) interval" hypothesis (63) for bright light exposure had been proposed based on a similar theory for sleep deprivation (59). This hypothesis developed from the finding that partial sleep deprivation in the second half of the night is more effective than in the first half of the night in depressed patients (35) whose circadian rhythms were thought to be phase advanced. If these patients were phase advanced, however, morning is precisely the wrong time for bright light exposure, unless morning bright light advances sleep more than the other circadian rhythms (which does not seem to be the case).

In our experience (52, 53, 58), evening is the best time for bright light exposure in these patients; it corrects the circadian rhythm abnormality (that is, it delays sleep in phase advanced patients who have early morning awakening). However, it is not clear in these preliminary studies whether or not bright light has other antidepressant effects in this type of depression. Patients with early morning awakening often have hyposomnia and anorexia. Thus, they appear to be a very different group than the winter depressives who generally have hypersomnia, gain weight and crave carbohydrates in the winter (45).

Future studies may wish to consider winter depressives and major (melancholic) depressives as chronobiologically different. Past studies that grouped them together (66–68) may need to be reconsidered. Heterogeneity may also be present within diagnostic categories, including winter depression, although most of these patients seem to be phase delayed. Different phase types among depressed patients, recognized in the past (69), have in recent years been underemphasized in favor of the phase advance hypothesis for depression (63).

For both groups of patients, the phase shift hypothesis can be used to assess chronobiologic disturbances and to guide the use of bright light therapy. We have therefore proposed that patients first be "phase typed" (phase advanced vs phase delayed) (52, 53). Then the phase disturbance can be corrected by scheduling bright light exposure to shift the circadian rhythms in the appropriate direction. If sleep offset is used to determine phase type, then one would assume that depressed patients with early morning awakening are phase advanced, whereas depressed patients with morning hypersomnia are phase delayed.

Phase typing does not mean that all patients with sleep and mood disorders are either phase delayed or phase advanced. Phase typing is useful only if a chronobiologic disturbance is a component. The more the chronobiologic component is involved, the better should be the clinical response to appropriately timed bright light exposure.

Phase typing and phase shifting may also be useful in the diagnosis and treatment of other disorders. Bright light in the morning appears to be helpful in delayed sleep phase syndrome, whereas bright light in the evening appears to be helpful in advanced sleep phase syndrome (52, 53, 58). The hypothesized PRC for humans has also been used to schedule bright light exposure for amelioration of jet lag (70).

Although melatonin may not necessarily be mediating chronobiologic disorders, it is nonetheless a highly useful marker for circadian phase position and for responses to light. More research on the sources of variance in the melatonin onset needs to be done to determine if it can be used to distinguish abnormally phased individuals from normal. In the not too distant future, however, the melatonin onset may distinguish patients who are phase delayed from those who are phase advanced.

In conclusion, light therapy appears to be the treatment of choice for patients with winter depression. It may also be useful in the treatment of circadian rhythm sleep disorders and for ameliorating jet lag and may possibly be helpful in other types of depression. Research in this area is developing quickly. It is the goal of this paper to review this new field and to tie together as many of these studies as possible

by relying to a great extent on the phase shift hypothesis. More research is needed, of course, before any hypothesis receives general acceptance.

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