

Light Therapy for Seasonal and Nonseasonal Depression: Efficacy, Protocol, Safety, and Side Effects

By Michael Terman, PhD, and Jiuan Su Terman, PhD

Needs Assessment

Light therapy can provide a potent alternative or adjunct to antidepressant drug treatment. Recent successes in light treatment of major depression with or without seasonal pattern underscore the need for clinicians to familiarize themselves with the methodology for inpatient and outpatient applications.

Learning Objectives

At the end of this activity, the participant should be able to:

- Identify established and investigational applications of light therapy beyond that for seasonal affective disorder, including augmentation of drug treatment.
- Identify the physical properties of light that underlie the antidepressant effect.
- Identify dosing parameters for individualizing the treatment regimen.
- Determine the optimum timing of light exposure based on the patient's chronotype (or circadian rhythm phase).
- Recognize side effects of light exposure and their control by dosing manipulations.

Target Audience

Psychiatrists, psychologists, and primary care physicians

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To Receive Credit for This Activity

Read this article, and the two CME-designated accompanying articles, reflect on the information presented, and then complete the CME quiz found on pages 672 and 673. To obtain credits, you should score 70% or better. Termination date: August 31, 2007. The estimated time to complete this activity is 3 hours.

ABSTRACT

Bright light therapy for seasonal affective disorder (SAD) has been investigated and applied for over 20 years. Physicians and clinicians are increasingly confident that bright light therapy is a potent, specifically active, nonpharmaceutical treatment modality. Indeed, the domain of light treatment is moving beyond SAD, to nonseasonal depression (unipolar and bipolar), seasonal flare-ups of bulimia nervosa, circadian sleep phase disorders, and more. Light therapy is simple to deliver to outpatients and inpatients

alike, although the optimum dosing of light and treatment time of day requires individual adjustment. The side-effect profile is favorable in comparison with medications, although the clinician must remain vigilant about emergent hypomania and autonomic hyperactivation, especially during the first few days of treatment. Importantly, light therapy provides a compatible adjunct to antidepressant medication, which can result in accelerated improvement and fewer residual symptoms.

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INTRODUCTION

Exposure of the eyes to light of appropriate intensity and duration, at an appropriate time of day, can have marked effects on the affective and physical symptoms of depressive illness and the timing and duration of sleep. The most extensive clinical trials have focused on winter depression, or seasonal affective disorder (SAD). Here, we review and evaluate the application of light therapy for SAD and subsyndromal SAD. Beyond SAD, we consider light therapy for other major depressive disorders (MDDs): nonseasonal (recurrent, chronic), premenstrual, antepartum, postpartum, depression associated with bulimia nervosa (BN), and seasonal manifestations of adult attention-deficit disorder (ADD). We present studies using bright light therapy as an adjunct to antidepressant medication, wake therapy (sleep deprivation), or both in a novel set of protocols designed to accelerate and sustain the treatment response and prevent relapse. We describe the critical features of light delivery systems, timing and dose optimization, ocular safety factors and potential adverse effects. Finally, we describe a set of promising though less-investigated nonpharmaceutical interventions for SAD, including dawn simulation, negative air ionization, physical exercise, and cognitive-behavioral therapy (CBT).

BRIGHT LIGHT THERAPY FOR SEASONAL AFFECTIVE DISORDER

Since the 1984 seminal report by Rosenthal and colleagues,¹ which defined the syndrome of SAD and presented the first controlled trial of bright light therapy, treatment studies have focused on parameters that influence response, including exposure schedule, duration, intensity, and wavelength spectrum. The original regimen used 2,500-lux fluorescent illumination presented in 3-hour morning and evening sessions. In an impressive systematic development, many research groups jumped on board with variations on the protocol that quickly produced a set of trenchant comparisons and controls. A cross-center analysis of 332 patients in 25 studies² summarized the results for: dual daily sessions at 2,500 lux for 2 hours; single morning, midday, and evening sessions; brief sessions (30 minutes); and lower light intensity (5–400 lux in a variety of spectral composition). One week of morning treatment produced a significantly higher remission rate (53%) than evening (38%), or midday (32%) treatment. Dual daily sessions provided no benefit over morning alone. Bright light treatment at all three times of day was more effective than under the dim

light controls, though only morning (or morning plus evening) light was superior to the brief light control. Two subsequent studies^{3,4} increased light intensity to 10,000 lux in 30–40-minute sessions, with remission rates of ~75%, which matched the most successful 2,500-lux, 2-hour studies.² At these shorter durations, both dim light (400 lux) and lower-level bright light (3,000 lux) were significantly less effective.

A drawback of early studies was small sample sizes that lacked the statistical power to demonstrate consistent time-of-day effects. This led to controversy about the importance of the particular daily treatment schedule. Furthermore, skeptics argued that any use of a light stimulus (dim, brief, or evening) voided its validity as a placebo control, leaving open the question of specific therapeutic efficacy. If timing were irrelevant,^{5–9} the mechanism of light therapy, it was proposed, might lie in a simple photon counting process. However, other early studies^{3,10–12} showed morning light to be superior to evening light. In the latter situation, the mechanism could lie in circadian system receptivity to light, which might reflect diurnal variation in retinal photoreceptor sensitivity¹³ or the phase-shifting response of the internal circadian clock,¹⁰ processes that might not be mutually independent. Internal clock phase is revealed by the timing of pineal melatonin production that occurs earlier after morning light exposure and later after exposure in the evening and throughout most of the night.^{10,11,14} In such a case, the antidepressant response to light would occur in conjunction with phase-advance resetting of the internal clock to morning light.

In 1998, these problems were addressed in a set of three large clinical trials^{15–17} summarized in Table 1. Eastman and colleagues¹⁶ administered light in the morning or evening, and an inert placebo (inactive negative ion generator) to parallel groups. Although all groups showed progressive improvement over 4 weeks, patients administered morning light were most likely to show remissions exceeding the placebo rate. Lewy and colleagues¹⁶ conducted a crossover study of morning and evening light. Although there was no placebo control, morning light was more effective than evening light. Terman and colleagues¹⁷ performed both crossover and balanced parallel-group comparisons, which included nonphotic control groups that received negative air ions at a low or high concentration. Morning light produced a higher remission rate than evening light and the putative placebo, low-density ions. However, the response to evening light also exceeded that for low-density

ions. Indeed, in the trials by Lewy and colleagues¹⁶ and Terman and colleagues,¹⁷ a minority of patients responded preferentially to evening light. The thrust of these clinical trials¹⁵⁻¹⁷ leads to the recommendation that patients with SAD initially be given morning light shortly after awakening. The dose of 10,000 lux for 30 minutes^{3,17} appears to be most efficient. Although lower intensities also can be effective, they require substantially longer exposure durations.^{15,16} In order to accommodate such morning treatment, most patients would have to awaken far earlier than at baseline, which could be infeasible for daily use in the long run.

Variations in the wavelength spectrum of light have received relatively little study. Although the earliest studies² used full-spectrum fluorescent lamps—with more blue and ultraviolet (UV) A energy than conventional cool- and soft-white broad-spectrum fluorescent lamps—these were soon found unnecessary.¹⁸⁻²⁰ Finer distinctions between lamp types have focused on the action of narrow wavelength bands. A comparison of efficacy of non-overlapping green and red fluorescent illumination equated for quantum emission²¹ found minimal response to red, while green produced a response similar to that of broad-spectrum white light. A related comparison²² found white light better than both red and blue. These studies left open the question of whether the white-light response is primarily determined by its green component. Recent attention has focused on the blue region, which actively suppresses melatonin production²³ and elicits circadian rhythm phase shifts.^{24,25} In a comparison of blue light with red light of lower intensity (designed as a placebo control), the antidepressant response to blue was superior, similar to that seen for white light in other studies.²⁶ Whether there is a therapeutic advantage to narrow-band green or blue over white illumination requires further study, particularly regarding their tolerability and adverse effects.

In a 2005 meta-analysis of randomized, controlled trials of light therapy,²⁷ the American Psychiatric Association Committee on Research in Psychiatric Treatments found the results “[suggestive] that bright light treatment [and dawn simulation for SAD and bright light for nonseasonal depression] are efficacious, with effect sizes equivalent to those in most antidepressant pharmacotherapy trials.” Accordingly, light therapy has been directly compared with fluoxetine in a 5-week trial,²⁸ one group receiving 2 hours/day of 3,000-lux light in addition to a placebo pill, while the other group received

fluoxetine 20 mg plus dim light (100 lux). Both groups showed equivalent major improvement. In a refined 8-week multicenter replication,²⁹ the results were similar. However, neither trial included a double-placebo control (dim light plus placebo pill).

A recent field trial of primary care patients³⁰ underscores how much the benefit over placebo may depend on more structured research trials. Patients were randomized into 10,000-lux white or 500-lux red light for 30–60 minutes/day treatment at any time of day until 1900 hours for 4 weeks. Improvement was assessed only by self-ratings. Remission rates for the two groups—around 30%—did not differ, although 75% of the patients given bright light achieved $\geq 50\%$ reduction in depression rating scale scores versus $\sim 50\%$ of the patients given red ($P=0.11$); by our computation, the effect size (0.36) is small. On this basis, Wileman and colleagues³⁰ hesitated to recommend bright light therapy for open treatment. Another

TABLE 1. SUMMARY OF REMISSION RATES*

| | Remission Rate (%/N) | | |
|------------------------------------|-------------------------|------------------|--|
| | Morning Light | Evening Light | Placebo (Negative-Ion Generator) |
| Terman et al^{17†} | | | |
| First treatment | 54 (25/46) | 33 (13/39) | 11 (2/19) |
| Crossover | 60 (28/47) | 30 (14/47) | ND |
| Eastman et al^{15‡} | | | |
| First treatment | 55 (18/33) | 28 (9/32) | 16 (5/31) |
| Lewy et al^{16§} | | | |
| First treatment | 22 (6/27) | 4 (1/24) | ND |
| Crossover | 27 (14/51) | 4 (2/51) | ND |

*Defined as improvement of $\geq 50\%$ in the score on the Structured Interview Guide for the Hamilton Depression Rating Scale—Seasonal Affective Disorder Version and posttreatment score of ≤ 8 ; recalculated from original data sets.

† Six-year study; 10,000 lux for 0.5 hours, 2 weeks.

‡ Six-year study; 6,000 lux for 1.5 hours, 4 weeks.

§ Four-year study; 2,500 lux for 2 hours, 2 weeks

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ND=not done.

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factor that compromises treatment efficacy is the presence of certain comorbid disorders. Although not yet extensively investigated, two of these have been identified: Axis I anxiety disorders³¹ and Axis II personality disorders.³² In one case of comorbid SAD and schizoaffective disorder,³³ however, depressive symptoms remitted under light therapy, although disordered thought persisted.

BRIGHT LIGHT THERAPY FOR OTHER CONDITIONS

Subsyndromal Seasonal Affective Disorder and the Healthy, Nonseasonal Population

The phenomenology of subsyndromal SAD, or winter doldrums, is similar to that of SAD, except that patients do not meet MDD criteria. However, the presence and severity of atypical neurovegetative symptoms, including food cravings and difficulty awakening, can be similar to those in SAD, as can fatigability (leading to characterization as a seasonal anergic syndrome).^{34,35} Since subsyndromal SAD has far higher prevalence than SAD itself,³⁶ if light therapy were also effective it would provide an important additional application. Clinical trials have indeed demonstrated significant improvement.³⁷⁻³⁹ Optimum light scheduling and dose appear to be similar for subsyndromal SAD and SAD,³⁸ although one study of office workers⁴⁰ found flexible scheduling in mid-morning or mid-afternoon to be equally (but not necessarily maximally) effective. Importantly, the lower severity of depressed mood in subsyndromal SAD does not imply that a lower dose of light will be sufficient to relieve symptoms.

Early studies^{37,41,42} reported that bright light treatment did not benefit non-depressed, healthy individuals without history of seasonal difficulties. A recent study,⁴³ however, found improved mood and vitality over 1 month using 1 hour of bright light exposure daily. The effect appears to be enhanced by combining the light exposure with physical exercise. Winter exercise in the presence of bright light (2,500–4,000 lux) was more effective than under ordinary room light (~500 lux) in improving mood, functioning, and general well-being.^{44,45} This regimen benefited individuals whether or not they exhibited subsyndromal SAD. Interestingly, atypical neurovegetative symptoms improved only in those who exercised under bright light, not dim light.

Nonseasonal Major Depressive Disorder

Beyond its established application for SAD, light therapy for nonseasonal depression appears

both safe and effective. Kripke⁴⁶ compared several controlled trials in terms of the relative benefit of light versus various placebo controls. In as little as 1 week, the results fell within the range of classic antidepressant drug studies of 4–16 weeks. For example, one study of nonseasonal MDD⁴⁷ gave 7 days of light therapy to 27 inpatients and obtained a benefit of 24% over dim light. However, morning or evening exposures showed no difference nor did phase shifts of the body temperature cycle relate to clinical improvement. Using a ceiling-light installation at 3,000–4,000 lux, a 10-day open-label trial with 28 unmedicated hospitalized patients⁴⁸ resulted in depression rating scale improvement >50% in 17 cases. A blinded trial of 29 inpatients with nonseasonal recurrent MDD⁴⁹ found 64.1% improvement in rating scale scores after 3 weeks of morning light treatment (5,000 lux, 2 hours; n=9), which was not significantly different from groups receiving imipramine 150 mg/day or the combination of light with imipramine. Goel and colleagues⁵⁰ gave 5 weeks morning bright light therapy (10,000 lux, 1 hour) to outpatients with chronic MDD of ≥2 years who achieved a remission rate of 50%; a control group given low-density negative air ionization showed only minor improvement. A recent Cochrane meta-analysis⁵¹ confirms the therapeutic use of bright light boxes (but not other light exposure methods) for nonseasonal depression.

Light therapy for elderly patients deserves separate mention. Although its use to alleviate disruptive and cognitive symptoms of senile dementia has been extensively investigated, a review of the effect on sleep and behavior⁵² found the results inconclusive, with further confirmation in another Cochrane review⁵³ that also considered effects on mood. Few light therapy studies have focused on geriatric depression, per se. A small crossover study (N=10) in institutionalized patients without MDD⁵⁴ but with moderate-to-high Geriatric Depression Scale scores tested morning bright versus dim light (10,000 lux versus 300 lux, 30 minutes, 5 days), and obtained significant mood improvement under the active condition. In Taiwan, a trial of hospitalized patients with MDD (N=30)⁵⁵ found alleviation of depressive symptoms after 5 days of morning light treatment (5000 lux, 50 minutes) in comparison with an untreated control group. However, the largest such trial (N=80, 5 weeks)⁵⁶ found no significant benefit of bright light (10,000 lux, 1 hour; morning, midday, or evening) over a 10-lux dim red control. This raises doubt about the general util-

ity of bright light therapy for geriatric depression, even though there was a trend toward greater improvement with morning exposure.

Premenstrual Dysphoric Disorder

In an early 1-month investigation of light therapy during the luteal phase,⁵⁷ patients with premenstrual dysphoric disorder (PMDD) showed improved mood under evening but not morning treatment (2,500 lux, 2 hours). A subsequent crossover study,⁵⁸ however, showed no difference between morning and evening exposure. Bright and dim light had similar effects. By contrast, a 2-month study by Lam and colleagues,⁵⁹ using evening bright light (10,000 lux, 30 minutes), found significant improvement relative to a dim light control, with alleviation of both mood and physical symptoms. It is not yet clear whether seasonality of PMDD or comorbid SAD increases the likelihood of positive response to light. Although seasonality was not an inclusion criterion in the 2-month study, the average score on a seasonality scale was more than twice that for the general population. Although larger controlled trials are needed and the relative advantage of morning light awaits investigation, the method used by Lam and colleagues⁵⁹ is a viable option for the open treatment of PMDD and milder premenstrual syndrome, especially for women who have not responded to medication.

Antepartum and Postpartum Major Depressive Disorder

Both open-label⁶⁰ and controlled⁶¹ studies have successfully employed light therapy for MDD during pregnancy, which offers a safe somatic treatment alternative to antidepressants whether or not the woman has a history of seasonality. Both efficacy and side effects have been shown to be dose-dependent.⁶¹ For example, a nonresponder to 5 weeks of 7,000 lux, 60-minute light therapy upon awakening showed full remission when session duration was increased to 75 minutes. A responder who developed irritable hypomania under the same initial treatment conditions became depressed when duration was reduced to 45 minutes, but responded without hypomania when duration was increased to 50 minutes. Although larger-scale, definitive trials are needed, morning light therapy is a viable option for treatment of antepartum depression.

Although two cases of successful light therapy (10,000 lux, 30 minutes between 0700–0900 hours, 4 weeks) for postpartum depression⁶² have been described, a subsequent controlled trial⁶³ using a

500-lux placebo failed to show bright light superiority. Five hundred lux may have been too bright to demonstrate a difference.

Bulimia Nervosa

Early studies^{64,65} indicated that winter seasonal mood changes are prevalent in patients with BN. Indeed, comorbid SAD and BN describes a distinct patient population with winter worsening of binge eating and purging.⁶⁶ In a 2-week crossover study, Lam and colleagues⁶⁷ showed a marked superiority of morning bright light therapy (10,000 lux, 30 minutes) over a dim light control in improving mood and controlling bulimic symptoms. Furthermore, a 4-week open-treatment study of patients with comorbid SAD and BN⁶⁸ yielded average reductions of 46% in binge eating and 36% in purging, along with a 56% reduction in depression scale scores. In a parallel group study of morning light therapy during the winter months, Braun and colleagues⁶⁹ also obtained greater reductions in bingeing and purging under bright (10,000 lux, 30 minutes) compared with dim (50 lux) light. Interestingly, the patients did not have comorbid SAD. However, another controlled study of BN patients, most with comorbid MDD,⁷⁰ found improved mood after 7 days of evening bright light therapy (2,500 lux versus 500 lux control) but no change in bingeing, regardless of whether patients met criteria for SAD. Morning light exposure may be essential for treatment of BN symptoms. There have been several positive case reports^{71,72} on the use of light therapy to assist with weight reduction and control obesity, but controlled trials are still needed.

Adult Attention-Deficit Disorder

Early morning light therapy (10,000 lux, 30 minutes, 3 weeks) in a heterogeneous group of ADD patients (seasonal, nonseasonal; depressed, not depressed) has produced significant reduction in ADD symptoms independent of mood improvement.⁷³ The most responsive subgroup showed high seasonality of ADD regardless of seasonal mood variation. As with SAD, morning light also reduced eveningness ratings on the Horne-Östberg Morningness-Eveningness Questionnaire (MEQ), which reflects circadian rhythm phase advances.

MANAGEMENT OF LIGHT TREATMENT

Timing of Light Therapy Sessions

Although a circadian rhythm phase advance often accompanies the antidepressant response to early morning light exposure, advances also occur in par-

tial responders and nonresponders and, thus, might be an epiphenomenon. One needs to show that the size of phase advance correlates with the magnitude of improvement. Thus far, this has been demonstrated by only Terman and colleagues.¹⁴ In a protocol with 10,000-lux treatment for 30 minutes on habitual awakening, the magnitude of antidepressant response was negatively correlated with the interval between evening melatonin onset and morning treatment time ($r=-0.38$, $P=.01$). We emphasize that this correlation accounts for only 14% of the variance, which indicates that the circadian timing of morning light, while significant, is not the exclusive factor influencing response above-and-beyond placebo effects. Nonetheless, as shown in Figure 1, light therapy given ~7.5–9.5 hours after melatonin onset yields twice the remission rate (80% versus 38%) of light given 9.5–11.0 hours after melatonin onset. Clock time of morning light administration provides only a rough guideline, since baseline melatonin onset spans a 5–6 hour range from ~1900–0100 hours across the patient population.

To maximize the likelihood of a treatment response, the clinician may therefore initiate morning light no later than 8.5 hours after a patient's melatonin onset. Unfortunately, such diagnos-

tic information is not readily available. A future solution may lie in the use of a salivary melatonin assay⁷⁴ with home sampling, and rapid turnaround by a commercial laboratory. An approximate solution, however, lies in the relation between melatonin onset and the MEQ^{75,76} score, which for SAD patients are strongly associated ($r=0.80$, $N=71$, $P<.001$).⁷⁷ Thus, one can schedule morning light at individually specified circadian times by inferring the time of melatonin onset from the MEQ, a strategy that facilitates circadian rhythm phase advances as well as the antidepressant response.

A list of recommended light exposure times, derived from the regression of the MEQ score on melatonin onset, is shown in Table 2. An online, automated version of the questionnaire returns the recommended treatment time to the respondent,⁷⁸ and patients can complete this exercise and print out results in preparation for the psychiatric consultation session. Sessions should begin within 10 minutes of scheduled wake-up time. In most cases, treatment will begin earlier than the baseline wake-up time (which is also highly correlated with melatonin onset and the MEQ score), but this depends on the patient's habitual sleep duration. For example, a short sleeper, whose bedtime is at midnight and who awakens at 0600 hours, would start treatment on habitual awakening. In contrast, a longer sleeper, with onset at 2330 hours and awakening at 0730 hours, would need to wake up 1 hour earlier, at 0630 hours. For every 30 minutes of sleep beyond 6 hours, waking up for light treatment is 15 minutes earlier than habitual awakening at baseline—a maximum of 1.5 hours earlier if sleep duration extends to 9 hours. The MEQ algorithm should be considered a “best guess” strategy to determine the initial timing of light exposure, with a potential need for clinical adjustment.

Response Assessment

SAD is not alone in high representation of atypical neurovegetative symptoms above and beyond the classic symptoms of depressed mood. Indeed, in a recent comparison study of patients with SAD or nonseasonal depression, the proportion meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for atypical features was nearly equivalent (65% and 64%, respectively).⁷⁹ Thus, evaluation of the response to light therapy needs to encompass a broader range of symptoms than tallied on the Hamilton Depression Scale (HAM-D),⁸⁰ which was tailored for melancholia. The presence of atypical symptoms predicts the response to light

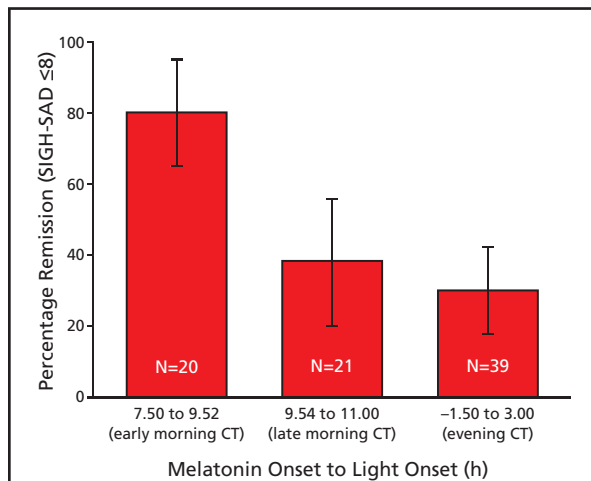


FIGURE 1. Remission rate (percentage of subjects±95% CI) to 10,000-lux, 30-minute light exposure in patients with winter remission, anchored to the CT of the treatment session*

* Zero-hour circadian time is specified by the onset of melatonin production at 10 pg/mL, as determined by radioimmunoassay of plasma samples taken at 30-minute intervals throughout the evening under dim room-light conditions <5 lux.¹⁴

SIGH-SAD=Structured Interview for the Hamilton Depression Rating Scale-Seasonal Affective Disorder Version; CT=circadian time; h=hours.

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therapy for SAD.⁸¹⁻⁸³ Such a predictive relationship has yet to be evaluated for nonseasonal depression.

In an effort to generate systematic comparisons of clinical trials, the *Structured Interview for the HAM-D-Seasonal Affective Disorder Version (SIGH-SAD)*⁸⁴ has been widely applied. The instrument tallies 21 items of the HAM-D, seven additional items from a preexisting supplementary atypical symptom scale,⁸⁵ an additional atypical symptom prominent in SAD (afternoon or evening slump), and two unscored exploratory items (difficulty awakening⁸⁷ and temperature discomfort⁸⁸). In 2003, this instrument was revised for use in depression studies regardless of seasonality (*SIGH-ADS*),⁸⁹ with the sleep items recast to minimize the problem of exaggerated ratings based on patients' subjective impressions. Depending on symptom frequency and severity, the interview can take between 10 and 30 minutes, which may place limitations on its usefulness in clinical practice. A reliable⁹⁰ self-rating version (*SIGH-SAD-SR*)⁹¹ is available, however, which patients can complete at home to assist the clinician in tracking progress and managing adjustments of the light therapy regimen. This instrument can also be used as a quality-control check on *SIGH-SAD* and *SIGH-ADS* interviewer ratings¹⁷ and independently in outpatient trials.^{29,44,92,93}

Compliance and Monitoring

Light therapy is typically self-administered at home on a schedule recommended by the clinician. Administration at outpatient clinics is not practical for early-morning timing. To the extent that timing is important to maximize the therapeutic effect, compliance is a sine qua non. When commencing treatment, therefore, it is helpful to ask the patient to call every few days or to fax log records of sleep, treatment times, and mood ratings;⁹⁴ this will assist the clinician in managing timing and dose adjustments.

In contrast with structured research studies, the motivation and compliance of patients in open treatment can be problematic. Despite an agreement to awaken for light treatment at a specific hour, patients may ignore the alarm, considering additional sleep to be the priority of the moment, and may delay or skip treatment. Patients frequently attempt to test whether improvement can be achieved without rigid compliance, and they may quit if managed too rigidly. Indeed, the behavioral investment in a maintenance regimen of light treatment is considerable, far exceeding that of pharmacotherapy.

For hypersomnia patients who are unable to awaken when instructed, light exposure initially can be scheduled at the time of habitual awakening and then edged earlier across days toward the target interval. Some patients compensate for earlier wake-up times with earlier bedtimes or napping, but others are comfortable with less sleep as the antidepressant effect sets in. Clinical experience suggests that most such patients could not sustain the earlier awakening without the use of light.

Variations in the sleep pattern, if they occur, may provide important information for guiding the course of treatment. Online adjustment in scheduling, although labor intensive for the clinician, often succeeds. Our strategy has been to encourage adherence to a recommended light exposure schedule, but to consider the obtained sleep pattern as a dependent measure that often reflects changes in mood state, sleep need, and circadian rhythm phase.

TABLE 2. TIMING OF MORNING LIGHT THERAPY* BASED ON MORNINGNESS-EVENINGNESS SCORE⁸⁶

| MEQ Score | Start Time (hours) |
|-----------|--------------------|
| 16–18 | 0845 |
| 19–22 | 0830 |
| 23–26 | 0815 |
| 27–30 | 0800 |
| 31–34 | 0745 |
| 35–38 | 0730 |
| 39–41 | 0715 |
| 42–45 | 0700 |
| 46–49 | 0645 |
| 50–53 | 0630 |
| 54–57 | 0615 |
| 58–61 | 0600 |
| 62–65 | 0545 |
| 66–68 | 0530 |
| 69–72 | 0515 |
| 73–76 | 0500 |
| 77–80 | 0445 |
| 81–84 | 0430 |
| 85–86 | 0415 |

*Start of 10,000-lux, 30-minute session, ~8.5 hours after estimated melatonin onset.

MEQ=Horne-Östberg Morningness-Eveningness Questionnaire.

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Treatment Start-Up, Maintenance and Discontinuation

The patient's initial trial of light therapy will almost always occur in winter after the depression has become severe. If the treatment is effective, one needs to decide when to resume it in subsequent years—proactively, while the patient still feels well early in the season, or only after symptoms recur. Either method will work but both solutions have negative aspects. If treatment is proactive, there is a chance it will be unnecessary because the patient is “skipping” a winter. Such skipping may explain why, in a comparison of treatment begun before or after symptom onset, the proactive group showed fewer symptoms throughout the winter.⁹⁵ Indeed, the regularity of winter recurrence has been questioned,⁹⁶⁻¹⁰⁰ and it is common in clinical trials that patients who fulfill retrospective diagnostic criteria for SAD do not necessarily become depressed during the year of the study. On the other hand, one wants to avoid the suffering of relapse. A solution is to coach the patient to detect reliable precursors of winter relapse, such as difficulty waking, daytime fatigue, and carbohydrate craving,⁹⁹⁻¹⁰¹ and begin treatment only once they occur.



FIGURE 2. Bright light therapy set-up for 10,000-lux illumination*

* Apparatus details: downward-tilted, smoothly-diffusing, ultra-violet-absorbing, 32 x 41-cm polycarbonate screen; high-frequency-ballasted soft-white fluorescent lamps at 4,000 Kelvin color temperature. Photo, courtesy Center for Environmental Therapeutics (<http://www.cet.org>).

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Even in summer, some patients with SAD will slump and even become briefly depressed during weeks of cloudy or rainy weather when outdoor illumination is reduced. Resuming light therapy during these periods is salutary.

The question of how long to continue light therapy each year is not simple. One early study¹⁰² found that many patients remained well after only brief treatment prior to full symptom onset. However, in an independent replication,⁹³ all patients experienced relapse within 3 weeks, most within 1 week. Patients need to learn how consistently to take the treatment (whether daily is necessary), when they can safely discontinue it for the season, and whether light intensity or duration should be tapered before discontinuation. The need for consistency varies individually; some patients slump after skipping a single day, while others can maintain good mood for ≥ 1 week. Once a patient has responded in an initial trial, it makes sense to explore the response to skipping days or weeks. New York data⁹³ indicate that regardless of the month of seasonal relapse, which might occur any time between September and January, most patients show spontaneous remission in early May. Experienced patients prefer to continue treatment through April. At that point, treatment can be discontinued abruptly (tapering is unnecessary), and in rare cases when the patient slumps it can be resumed for several weeks more.

The light treatment protocol for nonseasonal depression depends on the individual's episode course, which may not be known. Often, the treatment is begun adjunctively only after an adequate medication trial has shown only poor or partial improvement. In adding light, the clinician needs to consider two potentially interactive factors, drug dose adjustment, and photosensitization. If there is an improvement with light, it may be possible to decrease drug dose, even to discontinuation. If the patient must continue with one or more drugs that photosensitize in the visible range (see the “Ocular Safety” and “Side Effects” sections), light dose, drug dose, or both may need to be reduced, and routine ophthalmology check-ups instituted. Patients with chronic depression may need to maintain the treatment indefinitely, irrespective of the season. Those with winter seasonal exacerbation, lacking summer remission, may not require year-round treatment if the benefit is specific to the “SAD overlay”—in which case light therapy can be scheduled as if it were for SAD. Patients with discrete, recurrent nonseasonal patterns will need to test whether discontinuation causes slumping or relapse, and resume treatment accordingly.

Such withdrawal probes should be held off until symptom remission under daily treatment has been maintained for at least 1 month.

Therapeutic Lighting Apparatus

Many of the early research studies used a standard 61 × 122-cm fluorescent ceiling unit, with a plastic prismatic diffusion screen, placed vertically on a table ~90 cm from the user, providing ~2,500 lux illuminance at the eyes. Smaller, more lightweight units are now commercially available; however, their specific design features have most often not been clinically tested. Factors include lamp type (output and spectrum), filter, ballast frequency (for fluorescent lamps), size and positioning of radiating surface, heat emission, and so on. One clinically tested model (Figure 2) illustrates second-generation apparatus modifications, including smaller size, portability, raised and downward-tilted placement of the radiating surface, a smooth polycarbonate diffusion screen with nearly complete UV filtering, and high-output white fluorescent lamps (non-glaring 4,000 Kelvin color temperature) driven by high-frequency solid-state ballasts that eliminate flicker. At a 30–33 cm distance from the screen, the combination of elements in this configuration yields a maximum illuminance of ~10,000 lux, which has become the standard treatment dose.¹⁰³ With the direction of gaze downward toward the table surface, such a configuration provides illumination suitable for reading, and despite illuminance far higher than in normal home lighting, is generally well tolerated. As apparatus becomes smaller, however, the field of illumination narrows, and even small changes in head position can substantially reduce the intensity of light that reaches the eyes. This problem is a liability of recently marketed miniature lighting devices.

A major complication in comparing light boxes and studies is the problematic specification of lux, the dosing variable. Lux meters vary widely both in their sensitivity across the visible spectrum and the size of the illuminated field they transduce. Some manufacturers grossly overestimate lux levels using narrowly focused sensors that measure output only from the center of the radiating source, while the eye sees the entire screen surface and darker surround. Furthermore, lamps vary idiosyncratically in spectral distribution; since photoreceptors are differentially sensitive to discrete wavelength bands, lux level cannot be directly compared. An alternative measure of intensity is the irradiance, or power (in $\mu\text{w}/\text{cm}^2$) received from a light source

irrespective of retinal spectral sensitivity. Lux and power are linearly related only when the spectral composition of the light is held constant. Thus, two lamps providing equivalent lux will differ in power output, and vice versa.

Although simple in design, home construction of light boxes is discouraged because of the danger of excessive irradiation; some amateur assemblers have experienced corneal and eyelid burns. Because the critical design features have not been specified or regulated by federal authorities or the profession, clinicians should seek documentation by the manufacturer of the safety and effectiveness of any apparatus under consideration.

Claims for the specific efficacy of any particular lamp type or spectral distribution, although common, are unsubstantiated. Unfortunately, systems are marketed that provide excessive visual glare, exposure to naked bulbs, direct intense illumination from below the eyes (“ski slope” effect), and intentionally augmented UV radiation. Both the clinician and patient must be vigilant in the selection of an apparatus. Suggested criteria are listed on the Suppliers page of the nonprofit Center for Environmental Therapeutics Web site.¹⁰⁴ Clinicians should contact light box suppliers about trial offers or return policies, in order to ascertain the efficacy of a patient’s home treatment before final purchase.

In an alternate configuration, head-mounted ambulatory lighting units (in a visor configuration) have been developed for increased convenience of use. However, despite a set of multicenter trials for SAD,¹⁰⁵⁻¹⁰⁷ bright light exposure with this device has shown no advantage over dim light exposure, and convincing demonstrations of clinical efficacy are still needed.¹⁰⁸ One promising visor study¹⁰⁹ has demonstrated circadian phase shifting, and pending design enhancements may yet show clinical utility.

Ocular Safety

Ophthalmologic evaluations of unmedicated patients with normal oculo-retinal status¹¹⁰ have shown no obvious acute light-induced pathology or long-term sequelae. Although the intensity of bright light treatment falls well within the low outdoor daylight range, the exposure conditions differ from those outdoors and prolonged use entails far greater cumulative light exposure than is normally experienced by urban dwellers and workers.^{111,112} Potentially damaging wavelengths above the UV range extend into the visible range up to 500 nm (blue light),^{113,114} and one conservative proposal¹¹⁵ advocates screening out such low-wavelength

light altogether. On the other hand, recent data²⁶ indicate that the discrete blue wavelength range >450 nm is therapeutically active, and may be an essential component of broad-spectrum white light. Alarming, one already sees manufacturers promoting blue-light devices without considering that the interaction of blue with longer wavelengths in the white-light spectrum may be important both for efficacy and safety. At present, we recommend maintaining broad-spectrum white illumination, but filtering out wavelengths <450 nm—the blue light hazard is magnified in that range. At the opposite end of the spectrum, ocular exposure to infrared illumination, which comprises ~90% of the output of incandescent lamps, poses a risk of damage to the lens and cornea (as does UV) as well as the retina and pigment epithelium.¹¹⁶ Thus, despite having been marketed for bright light therapy, incandescent lamps are contraindicated.

Light box diffusion filters vary widely in short-wavelength transmission (for examples, see Remé and colleagues¹¹⁷). Transmission curves should be demanded of manufacturers and compared with published standards. Normal age-related clouding of the lens and ocular media, not to mention cataract formation, serve to exacerbate glare, which can make exposure to both blue and white light quite uncomfortable.¹¹⁷ Furthermore, both UV and blue light can interact with photosensitizing medications to promote or accelerate retinal pathology, whether acute or slow and cumulative. Even with complete UV screening, photosensitization in visible range has been noted for several psychiatric drugs (imipramine, phenothiazine, lithium), supplements (hypericum, melatonin), and other medicines (porphyrin, 8-methoxypsoralen, chloroquine, hydrocholorothiazide, tetracycline).¹¹⁶ In one reported case,¹¹⁸ a patient received combination treatment with clomipramine, an anticholinergic tricyclic antidepressant, and full-spectrum fluorescent light. After 5 days, there was reduced visual acuity, contrast sensitivity and foveal sensitivity, and central scotomas and lesions, fortunately with only minor residual aftereffects in contrast sensitivity and scotoma 1 year after discontinuation. Filtered wrap-around goggles have been developed to eliminate transmission of short-wavelength blue light while maximizing exposure >500 nm, reducing glare, enhancing visual acuity and brightness, and minimizing the risk of drug photosensitization.¹¹⁹

Although there are no definite contraindications for bright light treatment other than for the retinopathies, research studies have routinely excluded

patients with glaucoma and cataract. Some such patients have used light therapy effectively in open treatment; this should be done, however, only with ophthalmologic monitoring. A simple eye checkup is advised for all new patients, for which a structured examination chart has been designed.¹²⁰ The examination has occasionally revealed preexisting ocular conditions that should be distinguished from potential consequences of bright light treatment.

Side Effects

Adverse events associated with light therapy can be attributed in part to the parameters of light exposure, including dose (intensity and exposure duration), timing, spectral content, and method of exposure (diffuse, focused, direct, indirect, and angle of incidence relative to the eyes). Importantly, the emergence of sleep disturbances provides an important information toward adjustment of treatment timing: if evening light is scheduled too late, one often sees initial insomnia and hyperactivation. If morning light is timed too early, one often sees premature awakening with the inability to resume sleep.

The earliest clinical trials of 2,500-lux light therapy^{1,121} noted infrequent side effects of hypomania, irritability, headache, and nausea. Such symptoms often subside after several days of treatment. If persistent, they can be reduced or eliminated with dose decreases. Rarely have patients discontinued treatment due to side effects. While headache is usually responsive to dose reduction, we have been unable to relieve the symptom this way in two cases, one of which required discontinuation. Similarly, there is another report¹²² of one of 36 patients dropping out due to headache during a 7-day trial. Studies with portable head-mounted units containing incandescent bulbs with illuminance of 60–3,500 lux have also noted side effects of headache, eyestrain, and feeling “wired,” but the symptoms were not dose-dependent.¹²³ A 42-item side-effect inventory was administered to 30 patients with SAD after treatment with unfiltered full-spectrum fluorescent light at 2,500 lux for 2 hours/day.¹²⁴ Other than for one case of hypomania, there were no clinically significant side effects. Patients given evening light (the timing relative to bedtime was unspecified) reported initial insomnia. Mild visual complaints included blurred vision, eyestrain, and photophobia. Another study with daily assessment of side effects across 5 days of light therapy (10,000 lux, 30 minutes)¹²⁵ reported headaches and eye strain, glare, seeing spots, blurring,

and irritation as common symptoms that subsided from 34% frequency on day 1 to <10% on day 5.

Two cases of induced manic episodes¹²⁶ have been reported in drug refractory nonseasonal unipolar depressives beginning after 4–5 days of light treatment. A few cases of light-induced agitation and hypomania have been noted, also in patients with nonseasonal depression.¹²⁷ A patient with seasonally recurrent brief depressions developed rapid mood swings after light overexposure (far exceeding 30 minutes/day at 10,000 lux),¹²⁸ and a unipolar SAD patient with similar exposure experienced an initial manic episode¹²⁹; both patients required discontinuation and medication. We had one bipolar patient with SAD who became manic after the use of lights and was administered lithium as an effective countermeasure¹³⁰; others who have used mood stabilizers have responded to light therapy without mania.^{131,132} However, there is a need for continued caution. In an ongoing trial, some depressed patients with bipolar disorder have developed not only hypomania, but also mixed states during morning light therapy, even though they were taking an antimanic agent. Symptoms abated with dose and timing adjustments (K. Wisner, written communication, 2004). In rapid-cycling bipolar disorder, early-morning exposure appears riskier than midday exposure, while midday exposure is tolerated well, with positive effect.¹³³

Suicide attempt or ideation has been reported in three patients after 4 days (in 2 cases) or 14 days of 5,000 lux, 2 hours of early-evening light treatment.¹³⁴ Another patient with SAD committed suicide after 5 days of 10,000 lux, 30 minutes morning light treatment.¹³⁵ Since light therapy generally has been regarded as having mild side effects, the particular circumstances of these patients warrants close examination. Lam and colleagues¹³⁶ performed a retrospective analysis of 191 SAD cases treated in an open-clinic setting with morning light (2,500 lux, 2 hours or 10,000 lux, 30 minutes). There was significant improvement in HAM-D suicide ratings, with 45% of patients showing score reductions and 3% showing slight worsening. The authors suggested that the incidents described in the case reports^{134,135} might be attributable to spontaneous worsening of depression under ineffective treatment, especially as a complication of treatment initiation. Indeed, the first three cases were all severe depressions of 5–10 weeks duration, two of the cases with suicidal thoughts that preceded light therapy. One of these patients had experienced relapse 3 days after discontinuing light therapy; the suicide attempt occurred on day 4, when the treatment

was reintroduced. Then hospitalized, light therapy was continued successfully and the patient was discharged. The fourth patient¹³⁵ had been diagnosed with bipolar disorder-depressed, with suicidal ideation before starting light therapy.

There have been several additional case reports¹³⁷⁻¹⁴¹ of adverse emergent events or exacerbation of preexisting conditions. In two cases,^{137,138} hot flashes followed initiation of light therapy, although there has also been one report of successful light treatment of hot flashes in a perimenopausal patient with SAD.¹³⁹ In another case, the patient reported first-time occurrence of menometrorrhagia during first month of otherwise successful light therapy.¹⁴⁰ The bleeding recurred on a later trial, and light therapy was discontinued. We have had two patients report transient, mild uterine bleeding immediately after starting light therapy at midcycle; however, it did not recur the following month, and the menstrual cycles were undisturbed (M. Terman, PhD, J.S. Terman, PhD, unpublished data, 1984–1987). In an unusual case,¹⁴¹ a patient with a history of trigeminal neuralgic syndrome, currently in remission, experienced repeated flare-ups during 10,000-lux light therapy sessions, but not at lower intensity.

Apart from avoiding the obvious interaction of photosensitizing medications with light exposure in the UV and far-blue spectral range, it should be noted that the use of light therapy to augment antidepressant drug treatment could promote emergent symptoms that are not seen without the combination. In a study of 42 patients with nonseasonal MDD,¹⁴² light therapy (5,000 lux, 2 hours, early evening) added to trimipramine 200 mg/day increased sedation, restlessness, sleep disturbances, and vertigo, with decreased appetite. There is a report¹⁴³ of two patients using serotonergic drugs (fluoxetine 20 mg/day, sertraline 150 mg/day) who showed emergent symptoms suggestive of the serotonin syndrome 3–5 days after beginning light therapy (10,000 lux, 30 minutes), with diarrhea, nausea, hyperthermia, agitation, and disorientation.

The side-effect profile for patients using a downward-tilted fluorescent light box protected by a smooth diffusion screen (Figure 2), with 30–minutes daily exposures at 10,000 lux, is of particular interest because this method has had widespread application. A study of 83 patients with SAD¹³⁰ who were evaluated for 88 potential side effects¹⁴⁴ identified a small number of emergent symptoms at a frequency of 6% to 16%, including nausea, headache, jumpiness/jitteriness, and eye irritation. These results must be weighed against the improvement of far larger numbers patients who showed similar symptoms at

baseline but became asymptomatic after light treatment; all symptoms, except nausea, showed greater improvement than exacerbation. Mild nausea, interestingly, was characteristic primarily of light responders. This pattern of results forces attention to the risk-benefit ratio. Furthermore, symptom emergence might reflect the natural course of the depressive episode in nonresponders to light rather than a specific response to light exposure.

BRIGHT LIGHT THERAPY AS AN ADJUNCT TO ANTIDEPRESSANT MEDICATION, WAKE THERAPY, OR BOTH

Early studies¹⁴⁵ demonstrated the utility of bright light augmentation of antidepressant treatment in drug nonresponders with nonseasonal MDD, and improved antidepressant response relative to placebo in patients with SAD, when initiating treatment with 10 days of light therapy.¹⁴⁶ In a novel treatment approach for rapid-cycling bipolar disorder, 3 months of bright light therapy at midday (added to a stable medication regimen) improved mood ratings compared with morning or evening light, whereas there was a risk of hypomanic overresponse to morning light.¹³³ In a study with adolescent-onset bipolar disorder,¹⁴⁷ 1 week of morning and evening light therapy (10,000 lux, 45–60 minutes) added to the medication regimen significantly reduced breakthrough depressive symptoms.

Several investigators^{148–152} have combined light with drugs and found accelerated improvement relative to drugs alone, and the method has already seen widespread use with European inpatients.¹⁴⁹ A Canadian study¹⁵⁰ demonstrated the benefit of morning bright light therapy (10,000 lux, 30 minutes) in hospitalized, medicated unipolar or bipolar patients, with less improvement at 2,500 lux. In a large Danish study of patients with SAD (N=282),¹⁵¹ responders to 1 week of light therapy (5,000 lux, 2 hours, administered in the clinic) maintained their rapid improvement for 15 weeks with addition of citalopram 40–60 mg/day versus placebo. The same research group proceeded to large outpatient trial for patients with nonseasonal depression (N=102) by combining sertraline 50 mg/day with morning light treatment (10,000 lux, 60 minutes versus 50 lux, 30 minutes).¹⁵² Both remission rate and speed of improvement were greater under the active light condition.

In an expanded protocol conducted in Germany, patients with nonseasonal depression received light therapy, medications and a single session of late-night sleep deprivation¹⁵³ (“wake therapy”) at the start of treatment, with marked improvement in 1 day and benefit over a dim light control within 1 week.¹⁵⁴

In Italy,¹⁵⁵ this model has been extended for general inpatient use, following treatment studies of nonseasonal MDD (in conjunction with citalopram 40 mg/day) and bipolar disorder (in conjunction with unspecified doses of lithium)¹⁵⁶ that showed large benefits attributable to morning light therapy.

Combined light and wake therapy can feasibly be self-administered at home. One controlled study¹⁵⁷ yielded a remission rate of 43% in a group for whom standard antidepressants and psychotherapy had been inadequate. The recent successful completion of large-scale trials in Europe¹⁵⁸ strongly supports the implementation of adjunctive light and wake therapy for treatment of nonseasonal MDD, with the prospect of reduced duration of hospitalization. The protocol also holds promise for patients with SAD, who show the same first-day boost of wake therapy.¹⁵⁹

NEWER EXPLORATORY NONPHARMACEUTICAL TREATMENTS FOR SEASONAL AFFECTIVE DISORDER

Although bright light therapy can be considered the treatment of choice for SAD, with rapid improvement and generally mild side effects,¹³¹ there remains a significant number of nonresponders and partial responders. Some treatment failures undoubtedly result from nonoptimum dosing and timing (Figure 1). Yet, with typical remission rates around 50% and significant partial improvement around 66%,² the field has been motivated to search for alternate effective nonpharmaceutical interventions. It is also important to ascertain the effectiveness of antidepressant medications for SAD,¹⁶⁰ as exemplified by the randomized trials of fluoxetine 20 mg/day versus bright light,^{28,29} discussed above, or bupropion versus placebo.¹⁶¹ Below, we review a set of recently investigated nonpharmaceutical interventions that may be useful as adjuncts or alternatives to bright light therapy and medication.

Dawn Simulation

One drawback of bright light therapy is the required daily time commitment,⁹⁹ although with the development of efficient 30-minute regimens this is less an obstacle than it was previously. By contrast, dawn simulation is presented during the last period of the patient’s sleep episode. First described by Terman and colleagues¹⁶² in a case series using programmed naturalistic mimics of a gradual springtime dawn twilight, dawn simulation has been studied with procedural variations in several controlled trials. The basic therapeutic strategy is to set time of the sunrise signal earlier than outdoors in winter. In contrast with

post-awakening bright light therapy, the signal is relatively dim, gradually rising over 90 minutes or longer from about 0.001 lux (“starlight”) to ~300 lux (“sunrise under tree cover”) while the patient sleeps with eyes dark-adapted. As with bright light therapy, there is an antidepressant response and normalization of hypersomnic, phase-delayed and fractionated sleep patterns.^{162,163} Avery and colleagues^{164,165} have tested sigmoidal dawn simulation ramps against a variety of controls, in hypersomnic patients with SAD. One week of 250 lux maximum dawn simulation (1.5–2.0-hour duration) was more effective than a dim signal ramped to 0.2 lux for 30 minutes¹⁶⁴ or a red signal ramped for 1.5 hours to 2 lux.¹⁶⁵ In a major 6-week trial with 95 patients, Avery and colleagues¹⁶⁶ also compared bright light (10,000 lux, 0600–0630 hours), dawn simulation (250 lux maximum, 0430–0600 hours), and a dim red ramp (0.5 lux maximum, 0430–0600 hours). The dawn simulation significantly reduced both difficulty awakening and morning drowsiness.^{87,167} Surprisingly, it produced a higher remission rate than bright light therapy, and bright light therapy was not superior to the dim red control.

Terman and Terman¹⁶⁸ have recently completed a 6-year study comparing bright light (10,000 lux, 30 minutes) upon habitual wake-up time, naturalistic dawn simulation (250 lux maximum, beginning 3.5 hours before habitual wake-up time), and a brief light pulse (250 lux beginning 14.5 minutes before habitual wake-up time, for total dose equivalence of light intensity \times duration with the dawn). The light pulse condition was designed to test whether the dawn waveform per se is specifically active. Two additional groups received high- or low-density negative air ionization while asleep, with timing matched to the dawn signal ≥ 0.001 lux. Low-density ions (Table 1) were included as a placebo control.¹⁷ After 3 weeks of treatment, all three lighting conditions were superior to low-density ions, and they did not differ from each other. Although the brief light pulse appeared successful, it was the only lighting condition to produce symptom exacerbation among nonresponders, and in this respect it failed in comparison to dawn simulation.

The effectiveness of dawn simulation may depend on the presentation of diffuse, broad-field illumination that reaches the sleeper in varying postures. Such efficacy has not been demonstrated for inexpensive, commercialized light “alarm clocks”, which have small, directional fields.

Negative Air Ionization

Negative air ionization presents a new therapeutic treatment modality, still poorly understood. Negative ions are not directly perceptible by sensory transduc-

tion, and indeed the routes of biological reception and nervous system response are still unknown. The air circulation outdoors varies greatly in negative ion content (higher in humid, vegetated environments and at the seashore; lower in urban environments and heated or air conditioned interiors). Ions can be infused into the air with simple electronic devices marketed for air purification; many of these, however, do not produce the levels needed for the present purpose. Prior literature¹⁶⁹ suggests that sustained exposure to negative air ionization has a mood elevating effect, but until the recent completion of our controlled trial for treatment of SAD¹⁷ there were no studies of antidepressant effect. We randomly assigned subjects to a 2-week treatment period with 30-minute ion exposure sessions every morning at low or high ion flow rates (1.7×10^{11} or 4.5×10^{13} ions/second). The reduction in depression rating scale scores was significantly greater at the higher dose, with a large effect size. No emergent side effects were identified.¹⁷⁰ As yet, there have been no dose-response studies. High ion flow rate (eg, 4.5×10^{14} ions/second¹³), as used in our most recent studies,^{50,168} may be needed to override uncontrolled modulating environmental factors such as relative humidity, room size, and the proximity of grounded objects. In our recent dawn simulation study described above, two groups received high- or low-density ionization for 90 minutes before habitual wake-up time, sleeping on a conductive, grounded bed sheet that maximized ion flow to the subject. After 3 weeks of treatment, the therapeutic effect of high-density ions was not significantly different from that to bright light or dawn simulation, but far exceeded improvement under low-density ions.

Recently, the antidepressant effect of high-density negative air ions has also been observed in patients with chronic depression ≥ 2 years in a 5-week randomized, controlled trial⁵⁰; thus, the benefit does not depend on a seasonal pattern.

Physical Exercise and Cognitive-Behavioral Therapy

There are two preliminary studies^{171,172} that suggest benefits of exercise and CBT (with emphasis on winter stresses) for SAD. Daily aerobic exercise for 60 minutes was as effective as bright light therapy (2,500 lux, 1400–1600 hours) for patients with SAD, while those with nonseasonal depression responded selectively to exercise in a 1-week trial.¹⁷¹ Patients with SAD given twice-weekly CBT, daily bright light therapy (10,000 lux, 45 minutes in the morning and evening), or both all showed significant reduction in depressive symptoms.¹⁷² It is interesting to note that a

follow-up visit 1 year later suggested superior lasting benefit of CBT in terms of current symptom severity and remission and relapse rate.

CONCLUSION

The accumulated data on light therapy for SAD²⁷ and nonseasonal depression^{27,51} support its broad application in psychiatric clinical practice, whether or not as monotherapy.^{158,173} Clinicians should consider adjunctive light therapy when the response to antidepressants is delayed or incomplete. At the same time, further research is needed to clarify mechanisms of action that complement circadian rhythm phase shifting to produce the antidepressant effect. The promise of automated treatment delivery during sleep, removing the challenge of behavioral compliance, motivates further investigation of dawn simulation and negative air ionization, separately or in combination.

RESOURCES

MEQ,⁷⁶ interview-based and self-rating depression scales,^{84,89,91} eye examination chart¹²⁰ and sleep log⁹⁴ cited are available in the Clinical Assessment Tools packet and E-files distributed by the Center for Environmental Therapeutics.¹⁰⁴ The Web site also includes online assessments of morningness-eveningness chronotype, depression, and seasonality, with individualized feedback. The Center for Environmental Therapeutics also offers an author-supervised translation review service; the *SIGH-ADS*⁸⁹ is currently available in English and back-translated German versions. The Society for Light Treatment and Biological Rhythms (www.sltr.org) offers a continuing medical education course associated with its annual scientific meeting (next in Quebec City, Canada, July 2006), and hosts a lively listserv for members. **CNS**

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