



CLINICAL REVIEW

Evolving applications of light therapy[☆]

Michael Terman

Department of Psychiatry, Columbia University, New York State Psychiatric Institute, 1051 Riverside Drive, Unit 50, New York, NY 10032, USA

KEYWORDS

Light therapy;
Depression;
Bipolar disorder;
Sleep;
Circadian rhythms;
Evidence-based
medicine;
Seasonal affective
disorder;
Attention deficit hy-
peractivity disorder;
Dementia;
Parkinson's disease;
Bulimia nervosa

Summary The psychiatric intervention, light therapy, grew from an intensive 25-year research focus on seasonal affective disorder (SAD). Dosing and timing strategies have been honed to optimize the antidepressant effect, and efficacy relative to placebo has provided the evidence base for widespread implementation. A persistent question has been whether the model system for SAD has wider utility for psychiatric disturbance, even beyond depression. The circadian phase-shifting capacity of timed light exposure is universal, and chronobiological factors are at play across the disease spectrum. Recent promising initiatives extend to light treatment for nonseasonal major depressive disorder and bipolar depression, including drug- and electroconvulsive therapy-resistant cases. With light therapy, patients with antepartum depression may find an alternative to medication during pregnancy. Cognitive improvement under light therapy has been noted in adult attention deficit hyperactivity disorder. Motor function in Parkinson's disease has improved in parallel with the antidepressant effect of light therapy. The rest-activity disturbance of elderly dementia has been partially allayed under light therapy. In a new initiative, three major chronotherapeutic inventions—light therapy, sleep deprivation (wake therapy) and sleep time displacement (sleep phase advance therapy) are being combined to snap hospitalized patients out of deep depression and maintain long-term improvement.

© 2007 Elsevier Ltd. All rights reserved.

I have been asked to review the Future, a nice challenge. The focus of course must be on “preliminary data,” a term that merits some critical comment.

Conventional clinical trials of light therapy are difficult if not impossible to achieve. There is the placebo control bugaboo—one cannot literally

blind a light treatment study, and naysayers will always be able to dismiss the results of otherwise-controlled studies. Light therapy evolved from biologically oriented thinking. The original control groups were not, strictly speaking, placebos. Rather, they were active experimental manipulations within or between subjects, such as the time of day of light administration (the circadian phase-shifting variable) and the dosing trade-off between light intensity and exposure duration. Even though such studies inform mechanisms of action, some meta-analysts see in them no evidence of specific

[☆]Dedicated to Anna Wirz-Justice in recognition of her contributions to the field made during her career at the Psychiatric University Clinics Basel.

E-mail address: mt12@columbia.edu

antidepressant activity. To conclude that such studies are not “evidence-based” is no gift to science or to patients, and it downgrades the research initiative.

Selection of studies for meta-analyses can be heavily biased, despite the formalistic listings of “high-quality” inclusion criteria. I have been asked on occasion to comment on meta-analyses in progress. In one case, my challenge of inclusion criteria (which had led to negative conclusions for antidepressant efficacy) effectively terminated the project rather than recasting the analyses in a more comprehensive manner. The study director told me, “I know nothing about psychiatric rating scales.” An obvious problem is that evidence-based meta-analysis is, by its nature, outdated when a research field such as ours is active. Clinical thinking and judgment are often years ahead of evidence-based post-hoc compilations. In an underfunded field such as light therapy, meta-analyses are often based on very few studies, and one or two additional trials (completed but not included) might easily reverse conclusions. Periodic updates—as by the Cochrane Collaboration—are salutary, but they are still victims of inertia.

Even when investigators forgo mechanistic studies in favor of placebo-controlled yes–no designs, their efforts can be stymied by the mismatch between evidence-based criteria and clinical understanding. For example, inclusion in a meta-analysis by a national health standards agency required a placebo control. In the same country, researchers were prohibited by their ethics committee to use a placebo given that the efficacy of light therapy “is already well established.” The meta-analysis could therefore only include studies from other countries.

Bright light therapy for seasonal affective disorder (SAD)

This pioneering research field, now 25 years old, has undergone three sets of challenges: (a) conceptual affront to mainline antidepressant pharmacotherapy; (b) difficulty honing convincing placebo controls; and (c) lacking industry support for major clinical trials, small sample sizes with inherent outcome variability. Nonetheless, perseverance has finally produced consensus even in meta-analytic terms. An American Psychiatric Association (APA) work group of psychopharmacologists was able to glean 8 of 45 potential studies for consideration.¹ Sample sizes varied widely (7–85) but the designs were randomized with

“acceptable” placebo controls including low-intensity light and an inert or low-output negative air ionizer. The work group concluded that there was a “significant reduction in depression symptom severity following bright light therapy.... In other words, when the ‘noise’ from unreliable studies is removed, the effects of light therapy are comparable to those found in many antidepressant pharmacotherapy trials” (p. 660).

Had studies with biologically active controls been included, the results would have been even more convincing. In reviewing a trio of the largest studies, Wirz-Justice⁵ integrated the two types of evidence: “Light is as effective as drugs, perhaps more so.... In spite of the differences in design [of these 3 studies], some important correspondences emerge with respect to remission rates. The 2 placebo-controlled trials^{2,3}... have nearly identical results: both morning and evening light are better than placebo, and morning light is superior to evening light. The third study⁴ also demonstrates a morning light superiority [without a placebo control].... These comparisons of therapeutic outcome are based on very stringent criteria for remission, not just response, within a rather short time (2–4 weeks). Such stringent criteria, when applied to a 5-week multicenter trial of fluoxetine in patients with SAD, did not differentiate between drug (33%, $n = 36$) and placebo (28%, $n = 32$). Fourteen patients with SAD treated with light for 5 weeks tended to remit more (50%, $n = 20$) than those treated with fluoxetine (25%, $n = 20$; $P = 0.10$).⁶”

The timing of light relative to endogenous melatonin onset—a basic circadian rhythm concept—is a further refinement that homes in on one of the antidepressant mechanisms of light therapy and provides a means to optimize clinical response. Within the favored morning interval, light administered 7.5–9.5 h after evening melatonin onset produces twice the remission rate (approximately 80% vs. 40%) of light presented 9.5–11 h after melatonin onset.⁷ Concurrently, the phase advance to earlier light exposure is larger than that to later light exposure. Clinically, this information is useless unless one knows the patient’s circadian rhythm phase, since melatonin onsets can vary between patients by as much as 6 h. A practical solution is found in the Horne-Östberg Morningness–Eveningness Questionnaire (MEQ) score,⁸ which measures diurnal preference for activities and correlates strongly with melatonin onset.⁹ Based on the score, the clinician can approximately infer melatonin onset and guide the patient toward the optimum timing of morning light. Yet these refinements cannot be considered evidence-based.

Dawn simulation therapy for SAD

Dawn simulation presents a slow, incremental light signal in the bedroom at the end of the sleep interval, with maximum intensity two orders of magnitude lower than in post-awakening bright light therapy (e.g., 300 lux vs. 10,000 lux).¹⁰ Until recently, all the controlled studies were from David Avery's group in Seattle. Nonetheless, they have been meta-analyzed. (How can this be done for one center, when meta-analysis is meant to derive a conclusion across centers?) Dawn simulation showed efficacy relative to dimmer or briefer signals, enough to impress the APA work group.¹ An additional, later study from my group rounds out the analysis.¹¹ Here, the proportion of subjects with depression rating scale improvement of 50% or more was 0.62 for dawn simulation, 0.63 for bright light therapy and 0.17 for the low-output negative air ionizer placebo. The proportion of subjects with depression rating scale improvement of 50% or more was 0.86 when termination of the dawn signal (simulated sunrise time) was scheduled 8–9 h after melatonin onset—according to the metric of circadian time—and 0.47 for later sunrises (Terman JS & Terman M, in preparation). Since dawn simulation appears to match post-awakening bright light in efficacy, it may become the next-generation light therapy given its convenient use while the patient sleeps. This might undermine various industry press releases and publications¹² asserting patients prefer a drug for SAD because of the daily “burden” of light therapy sessions.

Bright light therapy for nonseasonal depression

Studies of light therapy for nonseasonal depression have a history at least as long as studies of SAD, but on the whole the results have been less clear-cut.¹³ The APA work group found, within its selection, positive evidence for efficacy except when light therapy and medication were combined.¹ Studies completed by the time of publication clearly would have reversed that conclusion.^{14–16} The adjunctive use of light with medication is potent. The strategy has been recommended by the Committee on Chronotherapeutics of the International Society for Affective Disorders¹⁷ and in an international response¹⁸ to a review of new antidepressants that overlooked light therapy, published in *Science*.¹⁸

A difficulty with most nonseasonal studies has been their inability to confront the early hypothesis that light therapy is specifically tuned to patients

with SAD as a countermeasure to long winter nights. Seasonality lies on a continuous dimension from noticeable (but not disturbing) to mildly, moderately and severely disturbing.¹⁹ SAD falls into the latter category, with major depressive episodes restricted to winter. In a far larger number of cases, recurrent or chronic depressions are exacerbated in winter but can occur at any time of year. Such patients provide moderate global seasonality scores²⁰ in comparison to higher scores for SAD. Thus, patients with nonseasonal depressions can still show seasonality, which might be the key to their response to light therapy. Subsequent to an inconclusive meta-analysis of light therapy for nonseasonal depression,¹³ we sought to clarify this issue with a patient sample in which depression was chronic (at least 2 years, but most often far longer) and without any seasonal modulation.²¹ Under morning light therapy, the proportion of subjects with depression rating scale improvement of 50% or more was 0.60 vs. 0.10 for the low-output negative air ionizer placebo. We can begin to surmise that light therapy for seasonal and nonseasonal depression is equally effective.

Why might this equivalence be? Are patients with nonseasonal depression light deprived at any time of year? Perhaps they are—spending most of their time indoors, often in bed with shades drawn, “escaping the world.” What ensues? Exacerbation of circadian rhythm phase delay, given the absence of the critical early morning light signal that synchronizes the internal clock to local time. Such delay may be depressogenic regardless of the season.

The mood in psychiatric practice is gradually changing, at least among the younger generation. Psychiatric residents and medical students are asking for and beginning to receive training in light therapy and chronobiology. One resident recently reported that he now routinely prescribes light therapy for any depressed patient who expresses hesitation about antidepressant medication. The growing concern about medication side effects would seem to augur well for our alternative.

Back to the future

As we move beyond “definitive” randomized, controlled trials we arrive at the *terra incognita* of small, underpowered, controlled trials; open trials; systematic case series; and one-of-a-kind clinical observations, some with internal controls (dose–response, discontinuation and resumption). Here is where the action lies. Given the clear-cut

results of light therapy for SAD, clinicians can view this new evidence more confidently than was possible when light therapy was novel. Since new applications are proliferating, there is no way they will pass the evidence-based filter for many years, if ever. Yet some of these data oblige clinical application now.

Refractory unipolar depression

Treatment-resistant depression remains prevalent and vexing. In the present context, our objective was to see if light therapy is effective—by itself or as an adjuvant—in patients who have been unresponsive to conventional drug treatment, electroconvulsive therapy (ECT), or both. The opportunity arises out of desperation, as when a suicidal hospitalized patient does not improve. Having heard about light therapy, the attending psychiatrist says, “Why not try it?” The chronotherapist (M.T.) evaluates the sleep pattern without objective measurement, obtains an MEQ chronotype score if the patient can manage the questionnaire, and immediately begins a course of light therapy under nursing supervision. The nurses maintain a daily log of session start and stop times, and note any difficulties such as side effects or the patient’s refusal to comply.

Light therapy is not introduced as an alternative, but always as an add-on to treatments (antidepressants, mood stabilizers, antipsychotics and ECT) that have not yielded adequate, if any improvement. In some cases, hypnotic medication is discontinued, tapered or rescheduled when the chronotherapist suspects masking (induction) of the sleep episode out of phase with the circadian clock. The chronotherapist may also request that patients not be awakened for testing of vital signs before their normal wake-up time. In my clinical experience, early awakening followed by a “second sleep” is itself depressogenic.

In one exploratory effort (collaboration Stewart et al., M.D.²²), treatment-resistant patients were first given tranylcypromine—they had not previously received monoamine oxidase inhibitors (MAOIs)—building to the highest tolerable dose (≤ 120 mg). About 40% of these patients responded. After finding little or no improvement, four patients began morning 10,000 lux light therapy. Timing of treatment was determined on the basis of their MEQ scores. The initial duration of light exposure was 30 min, and was adjusted upward individually if there was no response within 2 weeks, or downward if there were side effects (headache, early awakening). Patients also

maintained sleep logs and daily mood and energy ratings, and were evaluated weekly on the Hamilton Depression Rating Scale. Here are the case summaries.

Mr. A was 37 years old, separated, with 3 years of melancholic depression, including a suicide attempt within the last year. Earlier, he had shown an unusual seasonal pattern with relapses in March and remissions in late summer. He had undergone prior trials of multiple drug classes, some with thyroid hormone or lithium augmentation, all without response. He was also nonresponsive to multiple unilateral and bilateral ECT. Under tranylcypromine 120 mg, patient showed typical depression- and MAOI-related sleep disturbance, with early, middle and late insomnia. After starting light therapy for 30 min at 07:15 h, the patient experienced headache and early awakening. Duration was reduced to 20 min and then edged up to 25 min. Progress was complicated by several emergency MAOI-induced episodes of heightened blood pressure, controlled by a combination of a calcium channel blocker and beta-blocker. During this period he also reacted badly to a family split-up. However, within 3 months of light therapy his Hamilton score gradually reduced by 53% and his sleep became coalesced, regular (23:30–07:00 h) and satisfying. He was discharged and continued with light + tranylcypromine at home, with a stable, positive response.

Ms. B was 24 years old, single, with a lifetime history of dysthymia and a past history anorexia and social phobia. For the last 6 years, she suffered chronic major depression. She had been nonresponsive to multiple drug trials. However, in one trial she was given a low dose of the MAOI phenelzine with partial response. The dose should have been raised, but this was impossible because manufacturing of the drug had been discontinued at the time. After terminating treatment, she relapsed and attempted suicide. Under tranylcypromine 100 mg, the patient showed early, middle and late insomnia. Light therapy was taken at 07:15 h for 30 min. Sleep promptly coalesced (23:30–07:00 h) and within 3 weeks the patient showed complete remission (Hamilton score = 0) and was discharged. She continued with light + tranylcypromine at home, but was not compliant with light treatment. Several times, whenever she stopped using the light, she would experience relapse within 2 days. On resumption of the light, she would feel improvement within 2 days and complete remission in 4 days.

Ms. C was 41 years old, single, with a lifetime history of dysthymia and four prior major depressive episodes. She experienced intense suicidal

ideation, but there were no attempts. She was unresponsive to multiple drug trials, psychotherapy, psychoanalysis and cognitive behavioral therapy. Under tranylcypromine 60 mg, she experienced initial insomnia and restless sleep. Although her Hamilton score did not change during hospitalization, clinically she had deteriorated. With an MEQ score of 29, she fell into a tail of the distribution as a “definite evening type,” possibly with delayed sleep phase syndrome. Light therapy was begun at 08:00 h for 30 min, and later moved to 07:45 h. Sleep promptly phase advanced to 24:00–07:30 h, and morning awakening became spontaneous, although she maintained an alarm clock backup. She showed gradual improvement to complete remission over 7 weeks (Hamilton score = 3), when she was discharged. She continued with light + tranylcypromine at home, but was not compliant with light treatment. Like Ms. B, she would experience temporary relapses when discontinuing light and quick recovery after resumption.

Ms. D, age 43, married, was more difficult. She was chronically depressed since age 16, with gradual worsening, and met criteria for major depression since age 37. She had a past history of anorexia, panic disorder and agoraphobia. She had attempted suicide and was considered an active suicide risk. She was unresponsive to multiple drug trials and bilateral ECT. Her MEQ score of 76 categorized her as a “definite morning type,” and she would typically sleep from 21:00 to 05:00 h. She had no major sleep complaints, although a baseline sleep log (under tranylcypromine 120 mg) showed brief awakenings in the early morning hours followed by some additional sleep, and—on the night before light therapy began—final awakening at 02:00 h. Light therapy began at 05:30 h for 30 min, later extended to 60 min when there was no improvement. After failure of the morning light trial, she was switched to evening light at 22:00 h in an attempt to counteract her early sleep pattern. She then slept well from 23:00 to 06:00 h, but remained depressed. Nevertheless, she liked the light therapy and was allowed additional afternoon sessions, which gave her increased energy. She took a light box home.

In summary, three of four strongly refractory inpatients have shown positive response to light therapy augmentation of MAOI. Over several years of the tranylcypromine trial, this was the first string of three successive successes. Followed for a year, the three successful patients maintained positive response after hospital discharge. We must wonder, what was the effective agent? The observations that patients did not respond in the hospital to tranylcypromine alone, showed temporary relapse

when they discontinued light therapy, and showed prompt remission after resuming treatment, suggests that the effective agent was light alone. Nonetheless, the patients’ primary providers chose conservatively to maintain the pharmacotherapy on the chance that the global improvement resulted from an interaction with light.

Bipolar depression

The depressive phase of bipolar disorder has been one of psychiatry’s toughest nuts to crack. The addition of antidepressant drugs to mood stabilizers often leaves the patient depressed, and on a statistical basis, the response to two well-established antidepressants, paroxetine and bupropion (in combination with a mood stabilizer) was no better than to monotherapy with the stabilizer.²³ While it has sometimes been said that light therapy mimics antidepressant drug action, if the response to light therapy were successful for bipolar depression, we might posit that we have a qualitatively different modality.

Ms. E (patient of Milica Stefanovic, M.D.), bipolar II with psychotic features, was a 30-year-old mother with three previous hospitalizations triggered by suicidal ideation and planning. She was readmitted during increasing depression following discontinuation of nortriptyline because of leg-picking behavior. She had become hypersomnic and aphagic, could not care for her children, and contemplated overdosing on lorazepam. She was unresponsive to dose increments of escitalopram, and had experienced worsening under multiple antidepressant and antipsychotic trials. Her mood lightened in the summer, when she received several atypical antipsychotic drugs to control hypomania. After nine unsuccessful ECT sessions and two suicide attempts while on the unit, she began daily 10,000 lux light therapy at 06:30 h (according to her MEQ score, and incremented from 30 to 45 min), while continuing ECT 3 times per week, with olanzapine at bedtime. Suicidal ideation disappeared within 2 days. After 5 days, her affect was significantly improved (and self-acknowledged), appetite and eating normalized, and sleep was stable without hypersomnia. Gradually, she became socially active on the unit, cooperative, with normal rate and volume of speech (but with slight latency of response), normal mood with full range of affect, mood-congruent, brighter, with appropriate smiling and laughter, and linear, nondelusional thinking. She was given passes for family visits and discharged after 3 weeks. Her discharge note states, “It was felt that light therapy was an

adequate antidepressant given that the patient has shown mood fluctuations on antidepressant drug therapy.” At home, she continued with light therapy, olanzapine, lithium and lorazepam, but was later switched to lamotrigine as the sole medication. An attempt to discontinue light therapy at home failed, with immediate recurrence of hypersomnia and depressed mood that quickly resolved after resumption of daily treatment.

Ms. F (patient of Carolyn Douglas, M.D.), was a 44-year-old highly placed professional who suffered schizoaffective disorder, bipolar type, with chronic entrenched delusions. She was able to maintain work function and satisfactory mood with a combination of antidepressant (escitalopram) and antipsychotic (ziprasidone) medication. However, she was hypersomnic (sleep duration 10–12 h) with delayed sleep phase for many years, and could not get to the office before 13:00 h. This embarrassed and frustrated her, and she compensated by working late into the evening. The sedating effect of ziprasidone facilitated (“masked”) sleep onset between 23:00 and 01:00 h, but she could not wake up before 10:30–11:00 h. Her wish was to be able to awaken at 07:00 h, go for a jog (she was in fine physical shape) and arrive for work at 09:30 h. Her MEQ score indicated an “evening type,” for which awakening with light therapy at 07:30 h would be recommended. However, the masked, hypersomnic sleep made this infeasible. We intervened in four ways designed to facilitate a phase advance: (a) bright light therapy at 10:45–11:15 h, followed by a morning jog. The timing was slowly edged earlier over several months as earlier waking became possible, ultimately reaching 07:00 h. The patient showed an immediate, sustained mood lift from ratings of “normal” to nearly “best ever,” yet short of hypomania. Nonetheless, it was difficult to push wake-up earlier. (b) When wake-up reached 09:45 h, we added 0.2 mg controlled released melatonin at 18:45 h (15 h earlier), designed to reinforce and accelerate the phase advances.²⁴ The 15-h time difference was maintained as wake-up time and light therapy were gradually shifted earlier. (c) Likewise, when wake-up reached 09:45 h, we added 90-min dawn simulation at the end of the sleep period, also designed to reinforce and accelerate the phase advances. (d) After taking melatonin in late afternoon or in the evening, the patient wore blue-blocking eyeglass fit-overs while working under fluorescent lighting in the office (often until 22:00 h), designed to minimize the countervailing phase-delaying influence of evening light. After several months, the ziprasidone dose was reduced, and the patient was able to maintain a stable 8 h sleep duration from approximately

23:00–07:00 h. With depression now absent and with high energy, the patient’s delusional thinking also abated. Thinking she was possibly cured, the patient asked to discontinue the chronotherapeutics regimen; her primary provider insisted otherwise, at least until late spring, when outdoor jogs in sunlight might maintain the benefit.

Mr. G (patient of Carolyn Douglas, M.D.), age 75, lived in an elder care institution. He had experienced severe, recurrent, agitated, and sometime delusional depressions since age 18, interspersed with irritable hypomanic episodes. For the last 7 years the depression was relentless. He was unresponsive to numerous medication trials, and although ECT had provided temporary benefit, cardiac complications during treatment 3 years earlier, which necessitated pacemaker/defibrillator placement, prevented resumption. He showed a distinct pattern of diurnal variation related to nighttime carbohydrate binges. He would fall asleep at 21:00 h, awaken at 23:00 h for a binge, feel better (“almost normal”) for 1–2 h, and resume intermittent sleep with final awakening at 04:00 h. He was exhausted in the morning, and would refuse to leave bed or have breakfast. His phase-advanced sleep suggested use of evening light, and I selected dusk simulation (300 lux from 21:00 to 23:00 h followed by a 90 min fade to 0.001 lux) over bright light, to avoid bright light-induced agitation. The patient immediately responded with coalesced sleep starting during the dusk fade, eliminating the nighttime binge. Within a week he reported, “The [dusk simulation] is slowly making me better.” He awakened at 06:00 h, left bed, ate breakfast in the common room, and for the first time spent time walking outdoors after breakfast. Clinically, his anxiety continued to lessen and he began to enjoy things (e.g., vivid reminiscences of Marilyn Monroe), short of hypomania. After several weeks, brief awakening recurred after 2 h sleep and he resumed eating “a couple of cookies,” but sleep, mood and anxiety remained improved. Despite two intervening hospitalizations during bouts of aggressive and delusional behavior, he has continued the lighting regimen for nearly a year. He complained immediately when power failures aborted dusk presentation on three occasions. Although dusk + dawn simulation for a patient with SAD was reported in a case study many years ago,¹⁰ this may be the first clinical application of dusk-alone therapy. In general, elderly patients given evening bright light therapy have not shown convincing response or adhered to the schedule.²⁵

Clinical trials of light therapy for bipolar depression are in their infancy, but show promise.

Sit et al.²⁶ studied nine women with longstanding nonseasonal bipolar I or II disorder in which mood stabilizers controlled manic phases, but antidepressants did not relieve depressed phases. A placebo lead-in with dim red light administered upon awakening led to minor improvement, with no clinically successful outcome. The first four patients then received 7000 lux morning bright light therapy in a flexible dose-ranging protocol with exposure durations of 7–30 min. One patient showed a full, sustained response at 30 min, while the three others experienced onset of disruptive mixed states characterized by irritability, elevated energy, infeasible multitasking, creativity, aggression, racing thoughts and pressured speech. Light treatment had to be terminated. The time of day of exposure was then switched to early afternoon for five additional patients on the surmise that mixed states could be avoided, based on earlier observations of patients with rapid cycling bipolar disorder.²⁷ Two of these patients showed major improvement at 60 min, two were unsuccessful, and one patient with partial response at 45 min achieved remission when switched to morning light at 37.5 min. The lesson drawn from this study is that light is a potent intervention in nonseasonal bipolar depression, and we will need a more sensitive dosing strategy than has been used for SAD. This is one of the evolving applications of light therapy that surely can win support for major, controlled clinical trials, perhaps even to the point of meta-analytic confirmation of effect.

Benedetti et al. have had remarkable success in reversal of bipolar depression by combining lithium with sleep deprivation and light therapy.^{28,29} The specific contribution of light exposure to this effect, however, is unclear. Importantly, responders with histories of drug resistance were significantly more likely than the others to show relapse over a 9-month follow-up period. Maintenance of the light therapy regimen after hospital discharge might reduce or eliminate this risk of relapse.

Antepartum depression

Rarely is a new line of clinical research sparked directly by critical comments in grant peer review, but here is one happy example. As with standard antidepressant trials, pregnant women routinely have been excluded from SAD light therapy trials out of caution for the fetus. In a politically (and scientifically) correct critique, the protocol was considered discriminatory toward women, especially as the side-effect profile for light therapy was

deemed innocuous. The criticism taken to heart, a group of colleagues at Yale, Case Western Reserve and Columbia sought the pilot data that would justify a funded trial. Our rationale was that no pharmacotherapy is specifically approved for antepartum depression, and a successful alternative to medication would be welcome by many women and their doctors.

In the initial group, 16 women with major depression received 3–5 weeks of 10,000 lux morning light therapy and showed orderly improvement, more than half with Hamilton scores indicative of remission.³⁰ The response was no greater among women who reported histories of seasonality and those who did not. Two women reported nausea under light therapy (which is the most common side effect in patients with SAD³¹), ameliorated in one case by dose reduction to 45 min light exposure.

On this promising basis, we applied for federal funding of a controlled trial but were refused for two primary reasons: (a) we had not demonstrated superiority relative to placebo; and (b) since standard antidepressants already were known to relieve antepartum depression, it was not a priority to establish a non-drug alternative. So, with seed funding from a private foundation we conducted a randomized, controlled pilot trial that compared response to 7000 lux vs. 500 lux light in 10 women.³² Although 5 weeks were insufficient to demonstrate a significant effect, by 10 weeks—which included dose adjustments—the superiority of bright light was clear. Nonetheless, a second application for federal funding failed for two primary reasons: (a) the placebo light in the pilot study may have been active (low dose vs. inert) and we had not established a result for the proposed 50-lux substitute; and (b) this work did not merit a multicenter effort. By contrast, a parallel application by Anna Wirz-Justice to the Swiss National Science Foundation received a top-rated review and a 5-year randomized, controlled clinical trial is actually underway.

Beyond depression

A prescient 1998 collection was entitled *Seasonal Affective Disorder and Beyond: Light Treatment for SAD and Non-SAD Conditions*,³³ yet its novelty lay mainly in extension to nonseasonal depressions (e.g., premenstrual dysphoric disorder) and comorbid conditions (e.g., bulimia nervosa, insomnia). In principle, circadian rhythm disturbance and chronotherapeutics should not be restricted to depressive illness, and there have been continual

attempts to expand the purview, at least within the psychiatric domain.

Attention deficit hyperactivity disorder (ADHD)

As with earlier work on bulimia nervosa, which began with observations of winter exacerbation,³⁴ light therapy for adult ADHD was initially construed in conjunction with SAD and the circadian rhythm phase delay characteristic in winter.³⁵ However, 29 patients were selected on the basis of ADHD criteria regardless of seasonal mood pattern. A 3-week open trial of morning bright light therapy produced clinically meaningful, statistically significant improvement in core ADHD symptoms irrespective of depression status. Importantly, increased score on the MEQ—a proxy measure of circadian rhythm phase advance—was a strong correlate of ADHD improvement, while depression status was not.

The underlying circadian concept is reinforced by direct measurement of endogenous melatonin and sleep patterns in children with ADHD, ages 6–12, with or without chronic idiopathic sleep onset insomnia.³⁶ Both melatonin and sleep onset were approximately 1 h phase-delayed in the children with insomnia. Although morning light therapy for the insomniacs, with special attention to ADHD symptoms, is an obvious next step, it would be worthwhile also to test the children with normal sleep. In SAD, for example, light-evoked circadian rhythm phase advances appear salutary even for patients without delayed wintertime sleep.⁷

Dementia

The disrupted rest–activity pattern that accompanies dementia has long been a target of light therapy studies, but results have been weak or negative.³⁷ Not only is this disruption a major reason for institutionalization, but the stability and amplitude of actigraphic data are significantly correlated with cognitive and functional capacity and emotional state.³⁸ There are hints that further work will pay off. In a recent controlled study of 46 patients with Alzheimer’s disease, 1 h of morning light exposure (2500 lux and above) for 10 weeks did not provide superior outcome to normal room light exposure, though there was improvement in a subgroup of patients with the most disrupted rest–activity cycles.³⁹ Anna Wirz-Justice’s group administered dusk and dawn simulation (white light peaking at 200 lux or a dim red placebo) at the

bedside of 13 demented patients for 3 weeks.⁴⁰ Globally, there was no improvement in circadian rhythm stability or amplitude. However, the dusk-to-dawn signal advanced nocturnal sleep onset by more than 1 h, with commensurate increases in sleep duration and nocturnal quiescence.

A recent controlled study of 189 patients presented a stronger intervention—daylong bright light exposure (~1000 lux vs. ~375 lux) coupled with high-dose melatonin (2.5 mg) before bedtime in both groups. The bright light group showed enhanced stability and amplitude of the rest–activity rhythm, improved mood and reduced cognitive deterioration.^{41,42} By contrast, mood deteriorated under the normal room light control, which might suggest a risk of melatonin monotherapy in chronotherapy for dementia.

For light therapy to be more generally effective in elderly dementia—or old age in general—we may need: (a) substantially enhanced light exposure protocols that compensate for reduced ocular transmission and retinal sensitivity; (b) individualized timing anchored to circadian rhythm phase; and (c) strategies that enhance rhythmic amplitude, above and beyond phase shifting.

Parkinson’s disease

Though it might be hypothesized that light therapy would reduce the depressive symptoms often seen in Parkinson’s disease, it would be surprising also to obtain improvement in core motor symptoms, the targets of dopamine replacement therapy. A 12-patient case series, using late evening light exposure of 1000–1500 lux, found a majority of patients who, within 2 weeks, showed clinically significant reduction in bradykinesia and rigidity (but not tremor) in parallel with the antidepressant effect.⁴³ The choice of evening light exposure was based on the presumption of advanced melatonin onset and peak phases, which are especially prominent under dopamine replacement therapy.⁴⁴ Despite such phase advances, initial insomnia is prevalent in these patients, and evening light surprisingly served to reduce sleep onset latency. Of note, under light therapy many patients were able to sustain up to 50% dose reduction of dopaminergic medication without loss of symptom control, which offers promise for alleviating treatment-emergent levodopa-related motor complications. Open questions are: (a) the effect of evening light therapy on circadian rhythm phase; (b) the comparative efficacy of morning light; and, of course, (c) the outcome of a randomized, placebo-controlled trial.

Toward integrated chronotherapeutics

The observation of remarkable, often instantaneous remissions from major depression after one night of sleep deprivation⁴⁵ holds a key to a new therapeutic strategy unmatched by medication. The downside has been the often-instantaneous relapse following the next night's recovery sleep. The challenge has been to maintain the improvement, if only as a booster toward eventual medication response. Promising strategies include multiple sleep deprivations with interspersed recovery sleep,^{28,46} earlier bedtime and wake-up following sleep deprivation (sleep phase advance),⁴⁷ and initiation of daily morning light therapy following sleep deprivation.⁴⁸ Such protocols for depressed inpatients are under active investigation at centers in Copenhagen, Irvine, Milan and New York.

In a consensus formulation (Benedetti F, Wirz-Justice A, Terman M, in preparation), we are developing a chronotherapeutic combination strategy for general clinical use, initially for inpatients under close observation. Overnight sleep deprivation (rechristened wake therapy), morning light therapy and sleep schedule advances are introduced sequentially over 1–2 weeks, depending on the patient's day-to-day response. At entry, the patient is allowed to sleep at his or her habitual hours, in contrast to enforced ward schedules. Timing of the chronotherapies is anchored to habitual sleep time, the MEQ score or both. Treatment begins with a night of wake therapy followed by the first light therapy session. A decision tree guides the sequence of procedures based on remission, partial improvement, nonresponse, or worsening or relapse following transient remission. In cases of instantaneous remission, light therapy is repeated each morning to maintain the effect. With partial or no improvement, bedtime the next day is 5 h earlier than normally, with wake-up for the second half of the night and continued light therapy in the morning. The patient may receive a second night of wake therapy followed by sleep beginning 3 h before habitual bedtime. If necessary, the patient receives a third night of wake therapy followed by sleep beginning 1 h before habitual bedtime. Light exposure duration is increased in 15 min steps every 3 days, up to 60 min, if response continues to fall short of remission. The chronotherapeutics ensemble is compatible with concurrent standard medication; indeed, lithium appears to magnify the success rate in patients with bipolar depression.⁴⁹ The consensus group is preparing guidelines for clinical administration,

to be published as *Psychiatric Chronotherapeutics: A Treatment Manual*.

Conclusions

Depending on one's research background or experience in clinical practice, the finding that daily doses of light exposure can rapidly and profoundly alleviate mood, sleep and cognitive disturbances will seem either remarkable or self-evident. Contraindications for light therapy are few, and its compatibility with medication and other modes of psychiatric treatment augurs well for its incorporation into standard practice. However, successful administration of light therapy requires grounding in the principles of chronobiology, with individual tailoring of the regimen.

Research agenda

Given the probable effectiveness of light therapy for a range of depressive as well as other neuropsychiatric disorders, we need to determine whether:

1. The basic dosing and timing regimens established for seasonal affective disorder must be reconsidered for each new application,
2. Specific circadian rhythm parameters (e.g., phase relative to local time or sleep) characterize each disorder, and whether these parameters respond specifically to light therapy,
3. Light therapy should be used to complement the effect of medication regimens or can serve to replace them.

Practice points

In order to meaningfully supervise light therapy:

1. Clinicians need to gauge its effect on circadian rhythm phase re-adjustment.
2. Patients need to maintain daily records of treatment sessions, sleep time, mood and energy ratings, and medication doses and timing.
3. The interplay with medication needs to be continually monitored.

References

- *1. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry* 2005;162:656–62.
2. Eastman CI, Young MA, Fogg LF, et al. Bright light treatment for winter depression: a placebo-controlled trial. *Arch Gen Psychiatry* 1998;55:883–9.
3. Terman M, Terman JS, Ross DC. A controlled trial of timed bright light and negative air ionization for treatment of winter depression. *Arch Gen Psychiatry* 1998;55:875–82.
4. Lewy AJ, Bauer VK, Cutler NL, et al. Morning vs. evening light treatment of patients with winter depression. *Arch Gen Psychiatry* 1998;55:890–6.
5. Wirz-Justice A. Beginning to see the light. *Arch Gen Psychiatry* 1998;55:861–2.
6. Lam RW, Gorman CP, Michalon M, et al. Multicenter, placebo-controlled study of fluoxetine in SAD. *Am J Psychiatry* 1995;152:1765–70.
7. Terman JS, Terman M, Lo ES, et al. Circadian time of morning light administration and therapeutic response in winter depression. *Arch Gen Psychiatry* 2001;58:69–75.
8. Horne JA, Östberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol* 1976;4:97–110.
- *9. Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety and side effects. *CNS Spectr* 2005;10:647–63.
10. Terman M, Schlager D, Fairhurst S, et al. Dawn and dusk simulation as a therapeutic intervention. *Biol Psychiatry* 1989;25:966–70.
11. Terman M, Terman JS. Controlled trial of naturalistic dawn simulation and negative air ionization for seasonal affective disorder. *Am J Psychiatry* 2006;163:2126–33.
12. Modell JG, Rosenthal NE, Harriett AE, et al. Seasonal affective disorder and its prevention by anticipatory treatment with bupropion XL. *Biol Psychiatry* 2005;58:658–67.
13. Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. *Cochrane Database Sys Rev* 2005;2:CD004050.
14. Benedetti F, Colombo C, Pontiggia A, et al. Morning light treatment hastens the antidepressant effect of citalopram: a placebo-controlled trial. *J Clin Psychiatry* 2003;64:648–53.
15. Martiny K. Adjunctive bright light in non-seasonal major depression. *Acta Psychiatr Scand Suppl* 2004;425:7–28.
16. Terman M. Review: light therapy is an effective treatment for seasonal affective disorder. *Evid Based Ment Health* 2006;9:21.
- *17. Wirz-Justice A, Benedetti F, Berger M, et al. Chronotherapeutics (light and wake therapy) in affective disorders. *Psychol Med* 2005;25:939–44.
18. Wirz-Justice A, Terman M, Oren DA, et al. Brightening depression [letter]. *Science* 2004;303:467–9.
19. Terman M. On the question of mechanism in phototherapy for seasonal affective disorder: considerations of clinical efficacy and epidemiology. *J Biol Rhythms* 1988;3:155–72.
20. Rosenthal NE, Bradt GH, Wehr TA. *Seasonal Pattern Assessment Questionnaire*. Bethesda, MD: National Institute of Mental Health; 1987.
- *21. Goel N, Terman M, Terman JS, et al. Controlled trial of bright light and negative air ions for chronic depression. *Psychol Med* 2005;35:945–55.
22. Stewart JW, Terman M, Mangurian C, et al. Light therapy augmentation of MAOI treatment in refractory depression. *Chronobiol Int* 2005;23:740–1.
23. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med* 2007 Mar 28 [Epub ahead of print].
24. Lewy AJ, Lefler BJ, Emens JS, et al. The circadian basis of winter depression. *Proc Natl Acad Sci USA* 2006;103:7414–9.
25. Campbell SS, Terman M, Lewy AJ, et al. Light treatment for sleep disorders: consensus report. V. Age-related disturbances. *J Biol Rhythms* 1995;10:151–4.
26. Sit D, Wisner KL, Hanusa BH, et al. Light therapy for bipolar disorder: a case series in women. *Bipolar Disord*, in press.
27. Leibenluft E, Turner EH, Feldman-Naim S, et al. Light therapy in patients with rapid cycling bipolar disorder: preliminary results. *Psychopharmacol Bull* 1995;31:707–10.
- *28. Benedetti F, Barbini B, Fulgosi MC, et al. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. *J Clin Psychiatry* 2005;66:1535–40.
29. Benedetti F, Barbini B, Colombo C, et al. Chronotherapeutics in a psychiatric ward. *Sleep Med Rev* 2007;11:509–22.
30. Oren DA, Wisner KL, Spinelli M, et al. An open trial of morning light therapy for treatment of antepartum depression. *Am J Psychiatry* 2002;159:666–9.
31. Terman M, Terman JS. Bright light therapy: side effects and benefits across the symptom spectrum. *J Clin Psychiatry* 1999;60:799–808.
32. Epperson CN, Terman M, Terman JS, et al. Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. *J Clin Psychiatry* 2004;65:421–5.
33. Lam RW, editor. *Seasonal affective disorder and beyond: light treatment of SAD and non-SAD conditions*. Washington, DC: American Psychiatric Press; 1998.
34. Lam RW, Goldner EM, Solyom L, et al. A controlled study of light therapy for bulimia nervosa. *Am J Psychiatry* 1994;151:744–50.
- *35. Rybak YE, McNeely HE, Mackenzie BE, et al. An open trial of light therapy in adult attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2006;67:1527–35.
36. van der Heijden KB, Smits MG, van Someren EJ, et al. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *J Am Acad Child Adolesc Psychiatry* 2007;46:233–41.
37. Ancoli-Israel S, Martin JL, Kripke DF, et al. Effect of light treatment on sleep and circadian rhythms in demented nursing home patients. *J Am Geriatr Soc* 2002;50:282–9.
38. Carvalho-Bos SS, Riemersma-van der Lek RF, Waterhouse J, et al. Strong association of the rest-activity rhythm with well-being in demented elderly women. *Am J Geriatr Psychiatry* 2007;15:92–100.
39. Dowling GA, Hubbard EM, Mastick J, et al. Effect of morning bright light treatment for rest-activity disruption in institutionalized patients with severe Alzheimer's disease. *Int Psychogeriatr* 2005;17:221–36.
40. Fontana-Gasio P, Kräuchi K, Cajochen C, et al. Dawn–dusk simulation light therapy of disturbed circadian rest–activity cycles in demented elderly. *Exp Gerontol* 2003;38:207–16.
41. Riemersma RF, Swaab DF, Hoogendijk WJG, et al. Light and melatonin: effect on sleep, mood and cognition in demented elderly. *Neurobiol Aging* 2004;25(S2):194.
42. van Someren EJ, Riemersma-van Der Lek RF. Live to the rhythm, slave to the rhythm. *Sleep Med Rev* 2007;11:465–84.

*The most important references are denoted by an asterisk.

43. Willis GL, Turner EJD. Primary and secondary features of Parkinson's disease improve with strategic exposure to bright light: a case series study. *Chronobiol Int* 2007;**24**:521–37.
44. Bordet R, Devos D, Briquet S, et al. Study of circadian melatonin secretion pattern at different stages of Parkinson's disease. *Clin Neuropharmacol* 2003;**26**:65–72.
- *45. Wirz-Justice A, van den Hoofdakker RH. Sleep deprivation in depression: what do we know, where do we go? *Biol Psychiatry* 1999;**46**:445–53.
46. Kuhs H, Farber D, Borgstadt S, et al. Amitriptyline in combination with repeated late sleep deprivation versus amitriptyline alone in major depression. A randomised study. *J Affect Disord* 1996;**37**:31–41.
47. Voderholzer U, Valerius G, Schaerer L, et al. Is the antidepressive effect of sleep deprivation stabilized by a three day phase advance of the sleep period? A pilot study. *Eur Arch Psychiatry Clin Neurosci* 2003;**253**: 68–72.
- *48. Neumeister A, Goessler R, Lucht M, et al. Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. *Biol Psychiatry* 1996;**39**:16–21.
49. Benedetti F, Barbini B, Campori E, et al. Sleep phase advance and lithium to sustain the antidepressant effect of total sleep deprivation in bipolar depression: new findings supporting the internal coincidence model? *J Psychiatr Res* 2001;**35**:323–9.

Available online at www.sciencedirect.com

