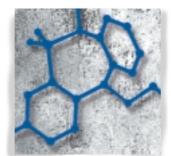# Pharmacological aspects

Light treatment of mood disorders

Barbara L. Parry, MD; Eva L. Maurer, BS

In 1981, seven patients with nonseasonal depression were treated with bright white light. In 1982, bright artificial light was used to treat a manic-depressive patient with a seasonal mood cycle. In the last 20 years, a plethora of studies have further defined the depressive populations, who are responsive to light treatment; the optimal timing, intensity, spectral frequency, and duration of treatment; its comparison with other pharmacological interventions; predictors of response; side-effect profiles; viable placebo-control conditions; alternative devices and forms of administration; potential mechanisms and anatomical pathways mediating light's physiological effects; and its application to other disorders and subsyndromal states. These studies have been conducted across multiple countries with surprisingly consistent results. Further work is needed, as highlighted in this review, to clarify the specific mechanism of action in subtypes of depressive disorders and differential age and gender effects. Although the majority of work in this area is relatively new, it behooves the reader to remember that Solomon, almost 3000 years ago, wrote in Ecclesiastes: "Truly the light is sweet and a pleasant thing it is for the eyes to behold the sun" (11:7).

Keywords: *light treatment; phototherapy; mood disorder; depression; seasonal affective disorder*

Author affiliations: Department of Psychiatry, University of California, San Diego, 9500 Gilman Drive, La Jolla, Calif, USA

Address for correspondence: Department of Psychiatry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0804, USA (e-mail: bparry@ucsd.edu)

Initial studies

In 1981, Kripke[1] exposed seven nonseasonally depressed patients to bright white light shortly before their usual time of arising. Depression scores were reduced on the following day. In a subsequent study,[2] 5 new subjects were added, for a total of 12 subjects, including 11 males with major depressive disorder (MDD) (3 with bipolar illness) according to research diagnostic criteria (RDC),[3] who were on an inpatient psychiatric research ward. In counterbalanced order, the investigators administered either bright white light (1000 to 2000 lux) or dim red light (less than 25 lux) for 1 h, 2 h before the subject's usual time of arising. The bright white light treatment produced significantly lower depression scores on both the Hamilton[4] and Beck[5] ratings as compared with baseline. A follow-up pilot experiment of 12 depressed inpatients[6] showed that there was no indication that 1 h awakening with exposure to dim red light (25 lux) had any antidepressant effect.

After demonstrating that sunlight and bright artificial light could suppress human melatonin secretion, Lewy et al[7] reported on a patient with a bipolar II seasonal mood cycle whose winter depression remitted when his hours of daylight were lengthened with bright fluorescent light (Vital-Lite) of 2000 lux between his time of awakening (6.00 AM) and 9.00 AM, and between 4.00 PM and 7.00 PM, thereby extending his daylength (photoperiod) to 13 h (a spring photoperiod). During light exposure, melatonin levels declined by 88% between 1.00 and 5.00 AM.

Winter depression has been found to improve when patients are exposed to bright full-spectrum light before dawn and after dusk, thereby extending the photoperiod.[8,9] Bright light consisted of 2500 lux of full-spectrum light; dim light was 300 lux. Light was administered from 5.00 AM to 8.00 AM, and 5.30 PM to 8.30 PM every day. Bright light had a marked antidepressant effect, whereas

dim light did not. The response could not be attributed to sleep deprivation.

Thus, the initial studies of light treatment appeared promising, but many questions remained concerning the optimal timing and intensity of treatment intervention.

Methodological issues

Morning versus evening light

Wehr et al[10] found that time of day and suppression of melatonin were not critical for antidepressant effects of phototherapy, indicating that photoperiodic mechanisms were not mediating the efficacy of therapeutic response. A review of efficacy using a pooled clustering technique for light therapy of seasonal affective disorder (SAD)[11] reported that 2500-lux intensity light exposure for 2 h daily for 1 week resulted in significantly more remissions when administered in the early morning (53%) than in the evening (38%) or at midday (32%). All three times were significantly more effective than dim light controls (11%). Exposure to morning plus evening light provided no benefit over morning light alone. In support of the phase-shift hypothesis for winter depression, two groups[12,13] found that morning bright light phase-advanced the dim-light melatonin onset (DLMO) and was more antidepressant than evening light, which phase-delayed it. The DLMO generally was delayed in the patients with winter depression compared with the healthy control subjects. Avery et al[14] also found that improvement was significantly greater with morning light than with evening light in 7 patients with winter depression treated with 7 days of bright light for 2 h daily. Other workers,[15-17] however, found that either morning or evening light therapy improved depressive symptoms in patients with SAD, suggesting that more practical and flexible schedules for light therapy are appropriate for SAD, since time of day is not crucial. As Wirz-Justice and Anderson noted,[18] prior morning light treatment may prevent an evening light response, and it may potentiate responses to subsequent morning light.

Duration of response and treatment

The efficacy of treatment of patients with SAD lasts longer after withdrawal with bright light (>2000 lux) than with dim light (<300 lux).[19,20] Labbate et al[21] reported increased response rates in SAD after 2 weeks rather than 1 week of light treatment: 15% of nonresponders at week 1 responded after week 2 of treatment. Byerley et al[22] found that, in 3 patients with SAD treated with 2 h of morning light exposure, remission of symptoms within 2 to 5 days was sustained during the 2-month treatment period. With regard to daily duration of treatment, 2 h, but not 0.5 h, morning white light was an effective treatment for SAD.[23] Doghramji et al[24] reported that 2 h of evening light was as effective as 4 h in SAD. As Wirz-Justice et al[25] commented, in patients who may be super-sensitive to light, 1 h of 2500 lux may be the minimum light exposure necessary to maintain an antidepressant effect in SAD.

Spectral frequency

Oren et al[26] compared green light and red light, and found that green light induced greater antidepressant effects than red light. Stewart et al,[27] however, observed that white light was more effective than green light in reducing endogenous symptoms, but not the atypical symptoms characteristic of winter depression. Other workers[28] reported that ultraviolet (UV) light reduced depressive symptoms, but that UV-blocked light reduced only atypical depressive symptoms. Bielski et al[29] reported that both broad-spectrum fluorescent light and cool white light were equally effective in reducing SAD symptoms of depression. Brainard et al[30] found that white light had greater benefit than red or blue light in SAD. Levitt et al[31] studied dim versus bright red (light-emitting diode) light, and found there was no significant difference in response rates between the two different illuminances of red light for SAD.

Alternative techniques: dawn simulation

Bright (1700 lux) dawn simulation (4.00-6.00 AM) was not effective in reducing depression scores in seven patients with winter depression compared with a standard bright (1700 lux) morning (6.00-8.00 AM) light treatment and contributed to early morning awakening (EMA).[32] In comparing a gradual dawn signal with a hypothesized placebo condition, a rapid dawn signal, Avery et al[33] found that improvement was similar for both treatments, but that EMA was more common with the gradual dawn condition. In a follow-up study[34] of 22 patients with winter depression, 1 week of treatment with 2-h dawn simu-

lation peaking at 250 lux resulted in significantly lower depression scores than 1 week of treatment with a 30-min dawn simulation peaking at 0.2 lux. Norden and Avery[35] also demonstrated that a slow dawn (a gradually increasing illuminance over 45 min peaking at 100 lux) was better than a rapid dawn (light rapidly increasing over a 4-s period to 100 lux) in 16 patients with subsyndromal winter depression. In a second controlled study of dawn simulation of winter depression, Avery et al[36] showed that 1.5 h of 250 lux dawn simulation with while light resulted in lower depression scores than 1.5 h of a 2 lux, red dawn signal. Linjaerde et al[37] found that symptoms of winter depression improved 57% with lightbox treatment of 1500 to 2500 lux for 2 h in the morning for 6 days compared with 40% for dawn simulation of 60 to 90 min with 100 to 300 lux for 2 weeks. A controlled study of 95 subjects with SAD[38] found that dawn simulation (1.5-h dawn signal from 4.30-6.00 AM peaking at 250 lux), but not bright light treatment (10 000 lux for 30 min from 6.00-6.30 AM), was associated with greater remission rates than placebo (dim red light, 1.5-h dawn signal from 4.30-6.00 AM peaking at 0.5 lux).

Light visor

Stewart et al[39] reported that a portable, head-mounted unit (HMU) was as efficacious as a standard lightbox for the treatment of winter depression. In a study of 105 subjects across five centers,[40] three intensities of a light visor (60, 600, and 3500 lux) for 2 weeks had equal antidepressant efficacy in SAD. Teicher et al[41] found no significant differences in therapeutic response between patients with SAD who were treated with a dim (30 lux) red light or a bright (600 lux) white light visor. In a controlled comparison of a lightbox and a HMU in SAD,[42] there was no significant difference in response rates between patients with SAD who received 2 weeks of light versus patients who received no visible light by an HMU, or between patients who received the lightbox versus the HMU.

Summary

The majority of studies support the beneficial effects of particularly morning light in SAD for 2 h with at least 2500 lux. UV light is not required for response. Dawn stimulation is an effective alternative, although the light visor is not.

Clinical phenomenology

Effects of latitude

In Iceland, Magnusson and Kristbjarnarson[43] found that 10 000-lux white light was more effective than 400-lux red light for 40 min for 8 days for treatment of SAD: patients who improved most on phototherapy also improved most during summer. In Norway, Lingjaerde et al[44] reported that patients with SAD, after treatment with 1500-lux white full-spectrum light for 2 h in the morning for 6 days, had a 48% reduction in symptoms compared with a 56% reduction of patients receiving light and drug treatment. Improvement at 1 week was maintained for the rest of the season.

In a follow-up study of SAD in Switzerland, Graw et al[45] observed that 2 to 5 years after participation in a light therapy trial, 64% of the patients had a reduction in the incidence and severity of depressive episodes and the use of antidepressant drugs. In a study of light therapy for SAD in adolescents in Iceland,[46] light therapy mildly improved the ability to concentrate and wake up in the morning in some students, but did not improve school attendance.

Predictors of response

Lam[47] reported that hypersomnia, hyperphagia, and younger age predicted morning light therapy response in winter depression. Terman et al[48] observed that, in 103 subjects with winter depression given light treatment, responders were characterized by atypical symptoms, especially hypersomnia, afternoon or evening slump, reverse diurnal variation (evening worse), and carbohydrate craving. Nonresponders were characterized mainly by melancholic symptoms. A follow-up study of 59 patients with winter SAD at the National Institute of Mental Health[49] found that 42% remained purely seasonal. The occurrence of nonseasonal depression in 44% of patients was associated with greater severity of illness and less responsiveness to light treatment. There is a greater improvement in mood in summer than with light treatment in winter in patients with SAD.[50] In meta-analysis of dose-response relationships of phototherapy for SAD,[51] no significant effects between strong, medium, and dim light in reducing atypical symptoms of depression were found, but light intensity varied positively with the antidepressant effects for typical symp-

toms. Levitt et al[52] found that response rates were similar in SAD and subsyndromal SAD with morning bright light therapy of 5000 lux for 3 weeks. Longer exposure of 45 to 60 min daily tended to be associated with better outcome. In examining the effects of light therapy on suicidal ideation, Lam et al[53] found that 67% of patients with winter depression were clinical responders: 45% of patients showed a reduction in the suicide item score on the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD).[54]

Prevention

Meesters et al[55,56] observed that administration of light treatment at the first signs of a winter depression prevented it from developing into a full-blown depression. When light exposure was administered at a symptom-free period at the beginning of autumn, however, it was not successful in preventing the development of winter depression.[57] Partonen and Lonnqvist,[58] in contrast, did find that bright light given well in advance of the emerging symptoms of winter SAD prevented a depressive episode.

Effects on hypersomnia

Hypersomnia has been associated with a superior response to morning light.[59] In an open study design, Lam et al[60] found that patients with winter depression who had hypersomnia had greater improvement, particularly in atypical depression symptoms than patients with insomnia. Evening subjective sleepiness improves with morning light, even a short 15-min exposure, in patients with winter depression.[61]

Comparison with antidepressant medication

Wirz-Justice et al[62] described a woman with SAD who, after remitting within a week in each of 6 separate trials of light therapy, remitted within 2 weeks of initiating citalopram, despite the delayed sleep and intermittent awakening induced with citalopram, but not with light therapy. Ruhrmann et al[63] found that 70% of 40 SAD patients treated with bright light (3000 lux 2 h daily) were responders compared with 65% treated with fluoxetine (20 mg daily for 5 weeks). Light treatment improved depression scores faster, while fluoxetine had

a faster effect on atypical symptoms. In 13 SAD patients, Ghadirian et al[64] compared light therapy for 2 weeks or tryptophan for 4 weeks in an open repeated-measures design. Tryptophan was equally effective to light therapy in treating SAD, but relapse after withdrawal of tryptophan occurred more slowly. Improvement of atypical depressive symptoms after 1 h of light therapy positively correlated with improvement after 2 weeks of therapy.[65]

Comparison with natural light

Eastman[66] documented that the perceived sunlight exposure in SAD patients in Chicago was twice as much in summer than in winter: the perceived daylength was 4 to 5 h longer in summer than in winter, with a later perceived dusk contributing more to the lengthening than an earlier perceived dawn.
Wirz-Justice et al[67] observed that 50% of patients with SAD remitted after a daily 1-h morning walk outdoors in natural light, which phase-advanced the onset and/or offset of salivary melatonin secretion, and decreased morning cortisol compared with low-dose artificial light, which did not modify depression self-ratings, or melatonin or cortisol patterns. The effects of bright light treatment (2500 lux) on subsyndromal SAD in the workplace have been studied,[68] and both morning and afternoon exposure resulted in similar levels of improvement in mood, energy, alertness, and productivity.

Side effects

Terman et al[69] reviewed the ocular effects of particularly the more recent treatment approach of using approximately 10 000 lux light exposure for 30 min. Although ophthamological examinations have thus far revealed no induced abnormalities, precaution is warranted with use of photosensitizing antidepressant drugs that may enhance UV– and visible-light–induced lesions. Bauer et al[70] observed the induction of hypomania in winter depressives treated with 4 weeks of light treatment. Seasonality—but not diagnosis of major depression, bipolar disorder with seasonal pattern, or control subject—predicted the emergence of manic symptoms.

The influence of comorbid and other disorders

Stewart et al[71] questioned whether SAD and atypical depression might be subtypes of the same disorder.

Bright artificial light (2500 lux, 6.00-8.00 AM and 6.00-8.00 PM), however, was less effective in treating patients with atypical depression than with SAD, suggesting that the two disorders are separate with a different underlying pathophysiology. Partonen and Lonnqvist[72] observed that in patients with comorbid personality disorder, the remission rate with light treatment was similar to that of patients with recurrent winter depression, although there was a more variable course and an increased risk of an earlier onset of a depressive episode. A controlled trial in 28 children (aged 7-17 years)[73] investigated the efficacy of light therapy for the treatment of pediatric SAD. In a primary care setting,[74] patients with SAD improved after light therapy, but bright white versus dim red light was not associated with greater improvement.

Response to placebo

Eastman et al[75] observed that 32 patients with SAD responded equally to 1 h of morning light (7000 lux) and 1 h of morning placebo treatment (a deactivated negative ion generator). Richter et al,[76] comparing exposure to real bright light and placebo bright light perceived through hypnosis, concluded that the findings did not support the hypothesis that the long-term results of light treatment in SAD were merely placebo effects. Terman and Terman[77] reported that 58% of patients with SAD responded to high-density negative ionizer treatment, whereas 15% responded to low-density ion generator treatment. A placebo-controlled trial of bright (6000 lux) morning light, bright evening light, or morning placebo (a sham negative ion generator) for 1.5 h daily for 4 weeks,[78] found that by using strict response criteria from the SIGH-SAD[54] (50% decrease of baseline and ≤8), 61% of SAD patients responded to morning light, 50% to evening light, and 32% to placebo; however, there was no significant benefit on mean Hamilton depression rating scores. A controlled trial of timed bright light and negative air ionization (6 groups) in 158 patients with winter depression,[79] reported that low-density ion response was inferior to all other groups, that evening light response was reduced when preceded by treatment with morning light, and when stringent remission criteria were used, a higher response rate to morning than evening light.
In summary, SAD patients, in particular, are responsive to light treatment. Carbohydrate craving and hyper-

somnia are predictors of response. Acute intervention is more efficacious than prophylactic treatment. Light administration is as effective as antidepressant treatment or natural light exposure. Side effects are minimal, with the exception of the induction of mania in bipolar patients, and there may be significant placebo effects.

Light treatment of nonseasonal mood disorders

Major depressive disorder

In an open trial with unmatched patient groups, Yerevanian et al[80] found that 1 to 2 weeks of light treatment with ≥2000 lux was effective in reducing depressive symptoms in seasonal, but not nonseasonal patients, whose functioning was more impaired (by unpaired *t* tests). Although the patient groups were unmatched, in a comparison of bright white light (2500 lux) and dim light (50 lux) from approximately 7.00 to 9.00 AM for 7 days in up to 42 patients who met RDC for nonseasonal MDD, other workers[81-83] observed a significant reduction in depressive symptomatology in all patients, but the difference between bright and dim light was not significant. In a 10-day study of morning (6.00-8.00 AM) or evening (6.00-8.00 PM) bright (1500 lux) light room treatment of 90 patients with either seasonal or nonseasonal MDD,[84] patients with seasonal pattern improved significantly more than those with a nonseasonal pattern, irrespective of time of treatment, atypical symptoms, or carbohydrate craving. Yamada et al[85] administered bright or dim light in the morning or evening to 27 unmedicated patients with nonseasonal depression by *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R)*[86] criteria and found that bright, but not dim, light significantly improved clinical symptoms of depression, independent of the time of treatment. The circadian rhythm of body temperature was more sensitive to the entraining effects of bright light in depressed versus normal control subjects, but was not related to clinical improvement. In a reassessment of the speed, efficacy, and combined treatment effects for nonseasonal depression, Kripke[87] observed that light treatment produced net benefits in the range of 12% to 35% often within a week, and that the effects for nonseasonal and seasonal depression were comparable and produced faster antidepressant benefits than psychopharmacological treatment.

Pharmacological aspects

Inpatient studies

In the setting of a psychiatric hospital, Wirz-Justice et al[88] reported that 61% of 37 nonmedicated patients with major depression responded to light treatment in a 10-day open trial using ceiling lights of 3000 lux either for 8 h (5.00-9.00 AM and 4.00-8.00 PM) or 4 h only (5.00-9.00 AM). Results of pilot data using 2 h of 10 000 lux light also suggested that further controlled trials were warranted in this population. In a controlled trial of hospitalized veterans with nonseasonal MDD or depressed forms of bipolar disorder, Kripke et al[89] found that the 25 patients treated with bright white light (2000-3000 lux) improved in measures of depression compared with the 26 patients randomized to dim red light placebo-control treatment. Two patients treated with bright white light became hypomanic. Partial relapse appeared within 2 days. Patients treated in winter responded as well as those treated in summer. Beauchemin and Hays[90] observed that in a psychiatric inpatient unit, depressed patients in sunny rooms had a significantly shorter hospital stay than those in dull rooms. In a follow-up study,[91] they randomly assigned depressed inpatients to high and low levels of artificial light and found that both unipolar and bipolar depressed patients responded more to bright than dim light when used as an adjunct to pharmacotherapy. Benedetti et al[92] also found that length of hospitalization for 415 unipolar and 187 bipolar depressed inpatients was reduced in bipolar patients in eastern rooms exposed to direct sunlight in the morning compared with western rooms. No effect was found in unipolar inpatients. In a placebo-controlled, crossover study of bright light treatment of depression in institutionalized older adults, Sumaya et al[93] found that 50% of patients were no longer in the depressed range after 1 week treatment with 10 000 lux, but their depression scores were unchanged after placebo (300 lux) or control (no treatment) conditions. Patients with higher depression scores, associated with longer duration of institutionalization, experienced the greatest improvement with the 10 000 lux treatment.

Interaction with medication and other antidepressant treatment

Levitt et al[94] administered a 2-week course of bright light therapy to 10 patients who presented during the winter months with major depression and who had failed an adequate trial of antidepressants, or who had relapsed following a successful course of antidepressants and found that augmentation with bright lights resulted in substantial improvement in 7 of the 10 patients. Holsboer-Trachsler et al[95] reported that adjunctive treatment with bright light or sleep deprivation did not hasten the onset of antidepressant action of the antidepressant trimipramine, but the groups were not balanced on baseline prognostic factors. Neumeister et al[96] administered bright (3000 lux) or dim (100 lux) light for 6 days to depressed patients from the morning after they underwent partial sleep deprivation (PSD) treatment. In responders to PSD, bright light therapy prevented the relapse after the next night of sleep and significantly prolonged the antidepressant effects of PSD up to 7 days. Patients treated with dim light relapsed after a recovery night of sleep and showed no further improvement of their depressive symptoms after 1 week of dim light treatment. PSD nonresponders did not benefit from light treatment. Muller et al[97] found that the side effects of adjunct bright light therapy as compared with antidepressant (trimipramine) monotherapy included aggravated sedation, restlessness, sleep disturbance, decreased appetite, and vertigo. Prasko et al[98] treated inpatients with recurrent nonseasonal depression with (i) bright light (5000 lux from 6.00-8.00 AM) and imipramine 150 mg/day; (ii) bright light and placebo; or (iii) dim red light (500 lux from 6.00-8.00 AM) and imipramine 150 mg/day. Patients in all 3 groups improved significantly, but the improvement of patients with bright light plus placebo was nonsignificantly superior to the other two groups. Loving et al[99] found that in 13 patients with MDD who underwent a half night of home wake therapy (sleep deprivation), those who subsequently received 10 000 lux bright white light for 30 min between 6.00 and 9.00 AM improved 27% in 1 week, compared with those receiving dim red (placebo) light at a comparable time.

Bipolar illness

The effects of 2 weeks of bright light and 1 week of dim light were investigated in patients with bipolar II SAD versus controls[100] and bright light was found to reduce or eliminate all group differences and variability in behavioral engagement, a mood dimension specifically associated with depression. Papatheodorou and Kutcher[101] treated persistent depressive symptoms in adolescent-onset bipolar disorder with adjunctive light therapy (10

000 lux twice per day): out of 7 patients, 3 showed a marked (70%) decrease in symptoms, 2 had a moderate (40%) decrease, and 2 had mild to no response. In 2 patients with bipolar disorder and 1 with recurrent MDD, Praschak-Rieder et al[102] observed that within the first week after beginning bright light therapy, 2 subjects attempted suicide and the third patient developed suicidal thoughts that were so acute and overwhelming that the light therapy had to be discontinued. In a patient with rapid-cycling bipolar illness, Wirz-Justice et al[103] found that extending the dark/rest period to 14 h (plus a 1-h midday nap) immediately stopped the rapid cycling and when midday, then morning light therapy was added, depression gradually improved achieving near-euthymia. In 115 bipolar depressed inpatients treated with total sleep deprivation,[104] morning light therapy (150 or 2500 lux) and ongoing lithium treatment significantly enhanced and sustained the effects of total sleep deprivation on mood, with no additional benefit when the two treatments were combined.

Women's mood disorders

The efficacy of light treatment has been studied in women with premenstrual (late luteal phase) dysphoric disorder.[105-108] In an open trial of morning light therapy for treatment of antepartum depression, Oren et al[109] observed that, after 3 weeks of treatment, mean depression ratings improved by 49%. Benefits were seen through 5 weeks of treatment and there was no evidence of adverse effects of light therapy on pregnancy. In two patients with postpartum depression,[110] there was a 75% reduction in depressive symptoms with light therapy.
In summary, the emerging evidence suggests the potential efficacy of light treatment in MDD, in inpatients and outpatients, and in women's mood disorders. Light treatment may also enhance the efficacy of other antidepressant modalities.

Proposed mechanisms

Circadian timing

Lewy et al[111] proposed that the timing of bright light is critical for its antidepressant effect in SAD: the mechanism was related to a phase-advance of circadian rhythms that corrected a pathogenic phase-delay. Terman et al[112] found that the antidepressant effect of light in SAD was poten-tiated by early-morning administration in circadian time, optimally about 8.5 h after melatonin onset or 2.5 h after the sleep midpoint, suggesting the importance of phase relationships in treatment response.

Melatonin

Terman et al[113] proposed that early morning and evening light exposure impacted a photosensitive interval in SAD patients, in which melatonin secretion overshoots its normal nocturnal phase. Despite equal suppression of plasma melatonin levels, altered timing of light treatments has differential effects on mood.[114] Danilenko et al[115] found that daytime (12 noon and 4.00 PM) serum melatonin levels were higher in women with SAD compared with controls in winter; this difference disappeared in the summer and after light treatment in the winter. Light treatment and change in season also resulted in a phase-advance shift of melatonin in the SAD patients, associated with a decline in symptoms of hyperphagia and carbohydrate craving. Partonen[116] hypothesized that the induction of arousing stimuli mediated by effects of melatonin and the blockade of serotonin uptake mechanisms in the suprachiasmatic nucleus is necessary for the antidepressant effects of light in SAD. In patients with SAD who underwent light treatment with full-spectrum or cool white light,[117] both treatments reduced depression scores, advanced the timing of the salivary melatonin rhythm (in both responders and nonresponders), and increased its concentration. In light treatment of patients with seasonal and nonseasonal depression, melatonin amplitude was decreased by light and its phase position was advanced by morning light and delayed by evening light, but therapeutic outcome was not related to baseline melatonin phase position, the degree of light suppression of melatonin or the rebound effect of serum melatonin levels following bright light exposure.[118]

Serotonin

A study of patients with nonseasonal depression and healthy subjects[119,120] found that both bright as well as dim light augmented blood serotonin throughout the day. The influence of light was more pronounced on serotonin than on melatonin metabolism. Mellerup et al[121] examined platelet paroxetine binding as an indirect measure of the effect of light therapy on serotonin

Pharmacological aspects

uptake capacity in patients with winter depression. They found that in responders, but not in nonresponders, platelet serotonin transporters decreased significantly following treatment. An extended study of the seroton-ergic agent *meta*-chlorophenylpiperazine (m-CPP)[122] replicated the finding that m-CPP–induced activation-euphoria responses in untreated depressed patients with SAD, reflecting a state marker for the illness. This study also showed blunted corticotropin and norepinephrine responses to m-CPP, suggesting trait abnormalities. Mood improvement after light treatment was associated with lowering of nocturnal core temperatures, compat-ible with deficient serotonin transmission during winter depression. In a study of platelet serotonergic functions in SAD, Stain-Malmgren et al[123] found that responders to light therapy had higher K_m and lower B_{max} for parox-etine binding than nonresponders, suggesting abnor-malities in the serotonin uptake mechanism with enhanced serotonin 5-HT$_2$ receptor density that may reflect an upregulation.

Effects of tryptophan depletion

Rapid tryptophan depletion reverses the antidepressant effect of bright light therapy in patients with SAD,[124,125] suggesting that the therapeutic effects of bright light in this disorder may involve a serotonergic mechanism. Neumeister et al[126] also demonstrated that catecholamine depletion reversed the beneficial effects of light therapy, suggesting that brain catecholaminergic systems may also be involved.

Other neurotransmitters

In studies of platelet [³H]imipramine binding in patients with or without SAD, and healthy controls, Szadoczky et al[127,128] observed that, after incandescent light treatment, B_{max} values increased in SAD patients parallel with clin-ical improvement. In patients with SAD, light therapy produced a decrease in the urinary output of norepi-nephrine and its metabolites in association with signifi-cant decreases in depression ratings.[129] In contrast, Rudorfer et al[130] measured cerebrospinal fluid concen-trations of the principal metabolites of norepinephrine, serotonin, and dopamine and did not find differences between SAD and healthy controls. Neither the trans-mitter measures nor their interrelatedness was affected by phototherapy.

Endocrine function

On the basis of observed low serum prolactin concentra-tion in women with winter depression that was indepen-dent of season and bright light treatment, Partonen[131] hypothesized a role for estrogen and serotonergic func-tion in SAD. Normal thyroid function in SAD does not alter with light treatment.[132] Serum cortisol does not dif-fer between SAD and non-SAD patients, and no signifi-cant changes were seen as a result of light treatment, although melatonin appears to serve as a coordinating hormone transducing light information for the phase posi-tion of cortisol.[133] Partonen[134] also hypothesized that bright light, by normalizing increased corticotropin-releasing fac-tor (CRF) activity in the evening in SAD, might thereby normalize subjective sleepiness via its effects on neurons of the paraventricular nucleus of the hypothalamus. In studies of growth hormone (GH), Yatham et al[135] reported that GH responses to sumatriptan (a 5-HT$_{1D}$ receptor agonist) were significantly blunted during winter depres-sion in SAD patients compared with healthy controls and were normalized following light treatment. These findings suggest a role for the serotonergic system in the mecha-nism of action of light therapy. In contrast, Shiah et al[136] found that GH response to the γ-aminobutyric acid (GABA)$_B$ receptor agonist, baclofen, was not altered in SAD or by light therapy. On the basis of evidence that heme moieties and bile pigments in plants and animals mediate some of the nonvisual influences of light on bio-logical rhythms, Oren[137] hypothesized that bilirubin, which is a proposed photoreceptor given its similarity to the chromophore of phytochrome (a primary time-setting plant molecule), plays an evolutionary role in the regula-tion of rapid-eye movement (REM) sleep and in mediat-ing some of the antidepressant effects of light. He and his colleagues[138] found that nocturnal bilirubin levels were lower in patients with winter depression compared with controls, and that levels increased in both groups during the night and increased in patients after 2 weeks of morn-ing light treatment that improved mood.

Sleep, hemispheric, and EEG changes

Bright light shortens sleep onset, decreases number of awakenings, increases REM latency, attenuates REM length, and improves morning alertness in patients with MDD.[139] In SAD patients, Partonen et al[140] found no sleep electroencephalographic (EEG) changes after

treatment with bright light, although morning sleepiness was reduced. SAD patients have the expected pattern of EEG frontal asymmetry when depressed and following light-induced remission, although right hemisphere coherence is a state-dependent indicator of seasonal depression.[141] Winter depression is associated with a shift of laterality from the left to the right that was normalized by bright light treatment.[142] Brunner et al[143] documented normal homeostatic sleep regulation in SAD; although sleep EEG spectra in SAD, but not controls, showed modifications resembling those of recovery sleep after light treatment (perhaps reflecting sleep curtailment), the authors concluded that the effects of light treatment in SAD were unlikely to be mediated by changes in sleep. A positive response to total sleep deprivation in major depression is predictive of a beneficial outcome of subsequent light therapy.[144]

Temperature regulation

In a review of the neurobiological effects of artificial bright light, Dilsaver[145] reported that, based on measures of core temperature, bright light subsensitizes muscarinic and nicotinic mechanisms. Although temperature curves between SAD and controls were similar, light treatment enhanced the amplitude of the core body temperature rhythm in SAD patients during winter.[146] There were no abnormalities in the baseline phase or amplitude of the temperature rhythm in SAD patients versus controls,[147] and antidepressant responses to light treatment were unrelated to changes in the temperature rhythm. In constant routine conditions, Avery et al[148] documented a phase-delay of temperature and cortisol rhythms in hypersomnic winter depression that phase-advanced with bright light treatment. Schwartz et al[149] observed that core temperature minima were lower during the extended photoperiod of summer compared with winter in SAD patients, but not controls. In studying the oscillations of facial skin and core temperatures in relation to slow-wave activity during sleep, Schwartz et al[150] found that brain cooling activity, which oscillates in an ultradian manner during sleep, is reduced during winter depression, providing support for the hypothesis that brain temperatures are elevated during winter depression.

Functional anatomic and retinal sensitivity factors

Seggie et al[151] observed that antidepressant medication (sinuequan) reversed the increased sensitivity to light in depression. Terman and Terman[152] reported heightened retinal sensitivity with increased light exposure and supersensitivity of SAD patients relative to controls in winter. UVA-spectrum light did not increase the antidepressant response[153] and illumination applied in the upper visual field was most effective.[154] An increase in cerebral blood flow is associated with recovery following light treatment for SAD.[155]

Other

Patients with non-SAD major depression show a more pronounced light-associated increment of parasympathetically controlled cardiac functions compared with other depressed patients and controls.[156] Light therapy normalizes transducin (G_1 protein) levels observed to be reduced in winter depression.[157] No effects of light therapy were noted on basal glucagon levels in SAD and comparison subjects.[158] Immune-inflammatory markers are increased in SAD patients but are not altered by successful light therapy.[159]

In summary, the proposed mechanisms for light treatment primarily involve effects on the circadian timing system, melatonin, serotonin, and temperature regulation.

Conclusions

Light treatment is efficacious for SAD (winter-type) and an increasing database suggests that it has beneficial effects in nonseasonal depression as well. In toto, bright light (>2500 lux) results in greater improvement than dim light; morning light of at least 3 to 4 days duration results in more responders than evening light in SAD; UV-spectrum wavelengths are not required for antidepressant effects; and dawn-stimulation is an effective alternative. Light visors, in contrast, are not efficacious. Carbohydrate craving is a predictor of response and there are minimal side effects with the exception of the risk of inducing mania in bipolar patients. Further investigation is warranted with respect to light treatment's mechanism of action. ❏

Pharmacological aspects

Fototerapia de los trastornos afectivos

En 1981 siete pacientes con depresión no estacional fueron tratados con luz blanca brillante. En 1982 se utilizó luz artificial brillante para tratar a un paciente maníaco-depresivo con un ciclo de ánimo estacional. En los últimos 20 años gran cantidad de estudios han permitido definir con mayor precisión, además de las poblaciones de pacientes depresivos que responden a la fototerapia, el momento óptimo de la aplicación, la intensidad, la frecuencia del espectro y la duración del tratamiento. También se la ha comparado con otras intervenciones farmacológicas, se han estudiado los predictores de respuesta, el perfil de efectos colaterales, el uso de placebos adecuados a estos estudios, diversos aparatos y formas de administración, potenciales mecanismos y vías anatómicas que median los efectos farmacológicos de la luz y su aplicación a otros trastornos y estados subsindromáticos. Estos estudios se han realizado en varios países con resultados sorprendentemente constantes. Se requiere de futuros trabajos, como se destaca en esta revisión, para aclarar el mecanismo de acción específico en subtipos de trastornos depresivos y diferenciar efectos según edad y sexo. Aunque la mayor parte del trabajo en esta área es relativamente nuevo, le corresponde al lector recordar que Salomón, hace casi 3000 años, escribió en el Eclesiastés (11:7) "Verdaderamente la luz es dulce y es algo placentero para los ojos contemplar el sol."

Luminothérapie des troubles de l'humeur

En 1981, sept patients atteints de dépression non saisonnière ont été traités par lumière blanche intense. En 1982, la lumière artificielle intense a été utilisée pour traiter un patient maniacodépressif souffrant d'un trouble cyclothymique saisonnier. Durant ces 20 dernières années, une pléthore d'études ont mieux identifié les populations dépressives sensibles à la luminothérapie ; le rythme optimal du traitement, son intensité, sa fréquence spectrale et sa durée ; sa comparaison avec d'autres types de traitement ; les facteurs prédictifs de réponse ; les effets secondaires ; les conditions placebo/témoin adaptées ; les techniques alternatives et les différentes méthodes d'administration ; les voies anatomiques et les mécanismes potentiels véhiculant les effets physiologiques de la lumière ; et ses applications aux autres troubles et états sous-syndromiques. Ces études ont été conduites dans de nombreux pays, la concordance des résultats étant tout à fait surprenante. Comme le souligne cet article, d'autres travaux sont nécessaires afin de clarifier les mécanismes d'action spécifiques dans les sous-types de troubles dépressifs et l'influence de l'âge et du sexe. Bien que la majorité des travaux dans ce domaine soit relativement récente, il incombe au lecteur de se souvenir de ce que Salomon, il y a presque 3 000 ans, écrivit dans l'Ecclésiaste (XI, 7) : « Douce est la lumière et il plaît aux yeux de voir le soleil ».

REFERENCES

1. Kripke DF. Photoperiodic mechanisms for depression and its treatment. In: Perris C, Struwe G, Jansson B, eds. *Biological Psychiatry*. Amsterdam, The Netherlands: Elsevier; 1981:1249.

2. Kripke DF, Risch SC, Janowsky D. Bright white light alleviates depression. *Psychiatry Res*. 1983;10:105-112.

3. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. *Arch Gen Psychiatry*. 1978;35:773.

4. Hamilton M. A rating scale for depression. *J Psychiatry Neurol Neurosurg*. 1960;23:56.

5. Beck At, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561.

6. Kripke DF, Risch S, Janowsky DS. Lighting up depression. *Psychopharmacol Bull*. 1983;19:526-530.

7. Lewy AJ, Kern HA, Rosenthal NE, Wehr TA. Bright artificial light treatment of a manic-depressive patient with a seasonal mood cycle. *Am J Psychiatry*. 1982;139:1496-1498.

8. Rosenthal NE, Sack DA, Gillin JC, et al. Seasonal affective disorder: a description of the syndrome and preliminary findings with light treatment. *Arch Gen Psychiatry*. 1984;41:72-80.

9. Rosenthal NE, Sack DA, Carpenter CJ, Parry BL, Mendelson WB, Wehr TA. Antidepressant effects of light in seasonal affective disorder. *Am J Psychiatry*. 1985;142:163-170.

10. Wehr TA, Jacobsen FM, Sack DA, Arendt J, Tamarkin L, Rosenthal NE. Phototherapy of seasonal affective disorder. *Arch Gen Psychiatry*. 1986;43:870-875.

11. Terman M, Terman JS, Quitkin FM, McGrath PJ, Stewart JW, Rafferty B. Light therapy for seasonal affective disorder: a review of efficacy. *Neuropsychopharmacology*. 1989;2:1-22.

12. Lewy AJ, Bauer VK, Cutler NL, et al. Morning vs evening light treatment of patients with winter depression. *Arch Gen Psychiatry*. 1998;55:890-896.

13. Sack RL, Lewy AJ, White DM, Singer CM, Fireman MJ, Vandiver R. Morning vs evening light treatment for winter depression: evidence that the therapeutic effects of light are mediated by circadian phase shifts. *Arch Gen Psychiatry*. 1990;47:343-351.

14. Avery DH, Khan A, Dager SR, Cox GB, Dunner DL. Bright light treatment of winter depression: morning versus evening light. *Acta Psychiatr Scand*. 1990;82:335-338.

15. James SP, Wehr TA, Sack DA, Parry BL, Rosenthal NE. Treatment of seasonal affective disorder with light in the evening. *Br J Psychiatry*. 1985;147:424-428.

16. Wirz-Justice A, Graw P, Krauchi K, et al. Light therapy in seasonal affective disorder is independent of time of day or circadian phase. *Arch Gen Psychiatry*. 1993;50:929-937.

17. Lafer B, Sachs GS, Labbate LA, Thibault A, Rosenbaum JF. Phototherapy for seasonal affective disorder: a blind comparison of three different schedules. *Am J Psychiatry*. 1994;151:1081-1083.

18. Wirz-Justice A, Anderson J. Morning light exposure for the treatment of winter depression: the one true light therapy? *Psychopharmacol Bull*. 1990;26:511-519.

19. Wirz-Justice A, Bucheli C, Graw P, Kielholz P, Fisch HU, Woggon B. Light treatment of seasonal affective disorder in Switzerland. *Acta Psychiatr Scand*. 1986;74:193-204.

20. Grota LJ, Yerevaian, Gupta K, Kruse J, Zborowski L. Phototherapy for seasonal major depressive disorder: effectiveness of bright light of high or low intensity. *Psychiatry Res*. 1989;29:29-35.

21. Labbate LA, Lafer B, Thibault A, Rosenbaum JF, Sachs GS. Influence of phototherapy treatment duration for seasonal affective disorder: outcome at 1 vs 2 weeks. *Biol Psychiatry*. 1995;38:747-750.

22. Byerley WF, Brown J, Lebegue B. Treatment of seasonal affective disorder with morning light. *J Clin Psychiatry*. 1987;48:447-448.

23. Wirz-Justice A, Schmid AC, Graw P, et al. Dose relationships of morning bright white light in seasonal affective disorder. *Experientia*. 1987;43:574-576.

24. Doghramji K, Gaddy JR, Stewart KT, Rosenthal NE, Brainard GC. Two-versus four-hour evening phototherapy of seasonal affective disorder. *J Nerv Mental Dis*. 1990;178:257-260.

25. Wirz-Justice A, Bucheli C, Schmid A, Graw. A dose relationship in bright white light treatment of seasonal depression. *Am J Psychiatry*. 1986;143:932-933.

26. Oren DA, Brainard GC, Johnston SH, Joseph-Vanderpool JR, Sorek E, Rosenthal NE. Treatment of seasonal affective disorder with green light and red light. *Am J Psychiatry*. 1991;148:509-511.

27. Stewart KT, Gaddy JR, Byrne B, Miller S, Brainard GC. Effects of green or white light for treatment of seasonal depression. *Psychiatry Res*. 1991;38:261-270.

28. Lam RW, Buchanan A, Clark CM, Remick RA. Ultraviolet versus non-ultraviolet light therapy for seasonal affective disorder. *J Clin Psychiatry*. 1991;52:213-216.

29. Bielski RJ, Mayor J, Rice J. Phototherapy with broad spectrum white fluorescent light: a comparative study. *Psychiatry Res*. 1992;43:167-175.

30. Brainard GC, Sherry RG, Skwerer RG, Waxler M, Kelly K, Rosenthal NE. Effects of different wavelengths in seasonal affective disorder. *J Affect Disord*. 1990;20:209-216.

31. Levitt AJ, Joffe RT, King E. Dim versus bright red (light-emitting diode) light in the treatment of seasonal affective disorder. *Acta Psychiatr Scand*. 1994;89:341-345.

32. Avery D, Bolte MA, Millet M. Bright dawn simulation compared with bright morning light in the treatment of winter depression. *Acta Psychiatr Scand*. 1992;85:430-434.

33. Avery DH, Bolte AP, Cohen S, Millet MS. Gradual versus rapid dawn simulation treatment of winter depression. *J Clin Psychiatry*. 1992;53:359-363.

34. Avery DH, Bolte MA, Dager SR, et al. Dawn simulation treatment of winter depression: a controlled study. *Am J Psychiatry*. 1993;150:113-117.

35. Norden MJ, Avery DH. A controlled study of dawn simulation in sub-syndromal winter depression. *Acta Psychiatr Scand*. 1993;88:67-71.

36. Avery DH, Bolte AP, Wolfson JK, Kazaras AL. Dawn simulation compared with a dim red signal in the treatment of winter depression. *Biol Psychiatry*. 1994;36:181-188.

37. Lingjaerde O, Foreland AR, Dankertsen J. Dawn simulation vs lightbox treatment in winter depression: a comparative study. *Acta Psychiatr Scand*. 1998;98:73-80.

38. Avery DH, Eder DN, Bolte MA, et al. Dawn simulation and bright light in the treatment of SAD: a controlled study. *Biol Psychiatry*. 2001;50:205-216.

39. Stewart KT, Gaddy JR, Benson DM, Byrne B, Doghramji K, Brainard GC. Treatment of winter depression with a portable head-mounted phototherapy device. *Prog Neuropsychopharmacol Biol Psychiatry*. 1990;14:569-578.

40. Joffe RT, Moul DE, Lam RW, et al. Light visor treatment for seasonal affective disorder: a multicenter study. *Psychiatry Res*. 1993;46:29-39.

41. Teicher MH, Glod CA, Oren DA, et al. The phototherapy light visor: more to it than meets the eye. *Am J Psychiatry*. 1995;152:1197-1202.

42. Levitt AJ, Wesson VA, Joffe RT, Maunder RG, King EF. A controlled comparison of light box and head-mounted units in the treatment of seasonal depression. *J Clin Psychiatry*. 1996;57:105-110.

43. Magnusson A, Kristbjarnarson H. Treatment of seasonal affective disorder with high-intenisty light. A phototherapy study with an Icelandic group of patients. *J Affect Disord*. 1991;21:141-147.

44. Lingjaerde O, Reichborn-Kjennerud T, Haggag A, Gartner I, Berg EM, Narud K. Treatment of winter depression in Norway. Short- and long-term effects of 1500-lux white light for 6 days. *Acta Psychiatr Scand*. 1993;88:292-299.

45. Graw P, Gisin B, Wirz-Justice A. Follow-up study of seasonal affective disorder in Switzerland. *Psychopathology*. 1997;30:208-214.

46. Magnusson A. Light therapy to treat winter depression in adolescents in Iceland. *J Psychiatry Neurosci*. 1998;23:118-122.

47. Lam RW. Morning light therapy for winter depression: predictors of response. *Acta Psychiatr Scand*. 1994;89:97-101.

48. Terman M, Amira L, Terman JS, Ross DC. Predictors of response and non-response to light treatment for winter depression. *Am J Psychiatry*. 1996;153:1423-1429.

49. Schwartz PJ, Brown C, Wehr TA, Rosenthal NE. Winter seasonal affective disorder: a follow-up study of the first 59 patients of the National Institute of Mental Health Seasonal Studies Program. *Am J Psychiatry*. 1996;153:1028-1036.

50. Postolache TT, Hardin TA, Myers FS, et al. Greater improvement in summer than with light treatment in winter in patients with seasonal affective disorder. *Am J Psychiatry*. 1998;155:1614-1616.

51. Lee TMC, Chan CCH. Dose-response relationship of phototherapy for seasonal affective disorder: a meta-analysis. *Acta Psychiatr Scand*. 1999;99:315-323.

52. Levitt AJ, Lam RW, Levitan R. A comparison of open treatment of seasonal major and minor depression with light therapy. *J Affect Disord*. 2002;71:243-248.

53. Lam RW, Tam EM, Shiah IS, Yatham LN, Zis AP. Effects of light therapy on suicidal ideation in patients with winter depression. *J Clin Psychiatry*. 2000;61:30-32.

54. Williams JBW, Link MJ, Rosentahl NE, et al. *Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD)*. New York, NY: New York State Psychiatric Institute; 1998.

55. Meesters Y, Lambers PA, Jansen JHC, Bouhuys AL, Beersma DGM, van den Hoofdakker RH. Can winter depression be prevented by light treatment? *J Affect Disord*. 1991;23:75-79.

56. Meesters Y, Jansen JH, Beersma DGM, Bouhuys AL, van den Hoofdakker RH. Early light treatment can prevent an emerging winter depression from developing into a full-blown depression. *J Affect Disord*. 1993;29:41-47.

57. Meesters Y, Jansen JHC, Beersma DGM, Bouhuys AL, van den Hoofkadder RH. An attempt to prevent winter depression by light exposure at the end of September. *Biol Psychiatry*. 1994;35:284-286.

58. Partonen T, Lonnqvist J. Prevention of winter seasonal affective disorder by bright-light treatment. *Psychol Med*. 1996;26:1075-1080.

59. Avery DH, Khan A, Dager SR, Cohen S, Cox GB, Dunner DL. Morning or evening bright light treatment of winter depression. The significance of hypersomnia. *Biol Psychiatry*. 1991;229:117-126.

60. Lam RW, Buchanan A, Mador JA, Corral MR. Hypersomnia and morning light therapy for winter depression. *Biol Psychiatry*. 1992;31:1062-1064.

61. Partonen T. Effects of morning light treatment on subjective sleepiness and mood in winter depression. *J Affect Disord*. 1994;30:99-108.

62. Wirz-Justice A, van der Velde P, Bucher A, Nil R. Comparison of light treatment with citalopram in winter depression: a longitudinal single case study. *Int Clin Psychopharmacol*. 1992;7:109-116.

63. Ruhrmann S, Kasper S, Hawellek B, et al. Effects of fluoxetine versus bright light in the treatment of seasonal affective disorder. *Psychol Med*. 1998;28:923-933.

64. Ghadirian AM, Murphy BEP, Gendron MJ. Efficacy of light versus tryptophan therapy in seasonal affective disorder. *J Affect Disord*. 1998;50:23-27.

65. Sher L, Matthews JR, Turner EH, Postolache TT, Katz KS, Rosenthal NE. Early response to light therapy partially predicts long-term antidepressant effects in patients with seasonal affective disorder. *J Psychiatry Neurosci*. 2001;26:336-338.

66. Eastman C. Natural summer and winter sunlight exposure patterns in seasonal affective disorder. *Physiol Behav*. 1990;48:611-616.

67. Wirz-Justice A, Graw P, Krauchi K, et al. Natural light treatment of seasonal affective disorder. *J Affect Disord*. 1996;37:109-120.

68. Avery DH, Kizer D, Bolte MA, Hellekson C. Bright light therapy of subsyndromal seasonal affective disorder in the workplace: morning vs afternoon exposure. *Acta Psychiatr Scand*. 2001;103:267-274.

69. Terman M, Reme CE, Rafferty B, Gallin PF, Terman JS. Bright light therapy for winter depression: potential ocular effects and theoretical implications. *Photochem Photobiol*. 1990;51:781-792.

70. Bauer MS, Kurtz JW, Rubin LB, Marcus JG. Mood and behavioral effects of 4-week light treatment in winter depressives and controls. *J Psychiatr Res*. 1994;28:135-145.

71. Stewart JW, Quitkin FM, Terman M, Terman JS. Is seasonal affective disorder a variant of atypical depression? Differential response to light therapy. *Psychiatry Res*. 1990;33:121-128.

72. Partonen T, Lonnqvist J. The influence of comorbid disorders and of continuation light treatment on remission and recurrence in winter depression. *Psychopathology*. 1995;28:256-262.

73. Swedo SE, Allen AJ, Glod CA. A controlled trial of light therapy for the treatment of pediatric seasonal affective disorder. *J Am Acad Child Adolesc Psychiatry*. 1997;36:816-821.

74. Wileman SM, Eagles JM, Andrew JE. Light therapy for seasonal affective disorder in primary care. *Br J Psychiatry*. 2001;178:311-316.

75. Eastman CI, Lahmeyer HW, Watell LG, Good GD, Young MA. A placebo-controlled trial of light treatment for winter depression. *J Affect Disord*. 1992;26:211-222.

76. Richter P, Bouhuys AL, van den Hoofdakker RH, et al. Imaginary versus real light for winter depression. *Biol Psychiatry*. 1992;31:531-537.

77. Terman M, Terman JS. Treatment of seasonal affective disorder with a high-output negative ionizer. *J Altern Complementary Med*. 1995;1:87-92.

78. Eastman CI, Young MA, Fogg LF, Liu L, Meaden PM. Bright light treatment of winter depression. A placebo-controlled trial. *Arch Gen Psychiatry*. 1998;55:883-889.

79. 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;55:875-882.

80. Yerevanian BI, Anderson JL, Grota LJ, Bray M. Effects of bright incandescent light on seasonal and nonseasonal major depressive disorder. *Psychiatry Res*. 1986;18:355-364.

81. Volz HP, Mackert A, Stieglitz RD, Muller-Oerlinghausen B. Effect of bright white light therapy on non-seasonal depressive disorder. *J Affect Disord*. 1990;19:15-21.

82. Mackert A, Volz HP, Stieglitz B, Muller-Oerlinghausen B. Effects of white light on non-seasonal depressive disorder. *Pharmacopsychiatry*. 1990;23:151-154.

83. Mackeert A, Volz HP, Stieglitz, Muller-Oerlinghausen B. Phototherapy in nonseasonal depression. *Biol Psychiatry*. 1991;30:257-268.

84. Thalen BE, Kjellman BF, Morkrid L, Wibom R, Wetterberg L. Light treatment in seasonal and nonseasonal depression. *Acta Psychiatr Scand*. 1995;91:352-360.

85. Yamada N, Martin-Iverson MT, Daimon K, Tsujimoto T, Takahashi S. Clinical and chronobiological effects of light therapy on nonseasonal affective disorders. *Biol Psychiatry*. 1995;37:866-873.

86. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed, revised. Washington, DC: American Psychiatric Association; 1987.

87. Kripke DF. Light treatment for nonseasonal depression: speed, efficacy and combined treatment. *J Affect Disord*. 1998;49:109-117.

88. Wirz-Justice A, Graw P, Roosli H, Glauser G, Fleischhauer J. An open trial of light therapy in hospitalized major depression. *J Affect Disord*. 1999;52:291-292.

89. Kripke DF, Mullaney DJ, Klauber MR, Risch SC, Gillin JC. Controlled trial of bright light for nonseasonal major depressive disorders. *Biol Psychiatry*. 1992;31:119-134.

90. Beauchemin KM, Hays P. Sunny hospital rooms expedite recovery from severe and refractory depressions. *J Affect Disord*. 1996;40:49-51.

91. Beauchemin KM, Hays P. Phototherapy is a useful adjunct in the treatment of depressed in-patients. *Acta Psychiatr Scand*. 1997;95:424-427.

92. Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E. Morning sunlight reduces length of hospitalization in bipolar depression. *J Affect Disord*. 2001;62:221-223.

93. Sumaya IC, Rienzi BM, Deegan JF, Moss DE. Bright light treatment decreases depression in institutionalized older adults: a placebo-controlled crossover study. *J Gerontol*. 2001;56A:M356-M360.

94. Levitt AJ, Joffe RT, Kennedy SH. Bright light augmentation in antidepressant nonresponders. *J Clin Psychiatry*. 1991;52:336-337.

95. Holsboer-Trachsler E, Hemmeter U, Hatzinger M, Seifritz E, Gerhard U, Hobi V. Sleep deprivation and bright light as potential augmenters of antidepressant drug treatment-neurobiological and psychometric assessment of course. *J Psychiatr Res*. 1994;28:381-399.

96. Neumeister A, Goessler R, Lucht M, Kapitany T, Bamas C, Kasper S. Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. *Biol Psychiatry*. 1996;39:16-21.

97. Muller MJ, Seifritz E, Hatzinger M, Hemmeter U, Holsboer-Trachsler E. Side effects of adjunct light therapy in patients with major depression. *Eur Arch Psychiatry Clin Neurosci*. 1997;247:252-258.

98. Prasko J, Horacek J, Klaschka J, Kosova J, Ondrackova I, Sipek J. Bright light therapy and/or imipramine for inpatients with recurrent non-seasonal depression. *Neuroendocrinol Lett*. 2002;23:109-113.

99. Loving RT, Kripke DF, Shuchter SR. Bright light augments antidepressant effects of medication and wake therapy. *Depress Anxiety*. 2002;16:1-3.

100. Krauss SS, Depue RA, Aribisi PA, Spoont M. Behavioral engagement level, variability and diurnal rhythm as a function of bright light in bipolar II seasonal affective disorder: an exploratory study. *Psychiatry Res*. 1992;43:147-160.

101. Papatheodorou G, Kutcher S. The effect of adjunctive light therapy on ameliorating breakthrough depressive symptoms in adolescent-onset bipolar disorder. *J Psychiatry Neurosci*. 1995;20:226-232.

102. Praschak-Rieder N, Neumeister A, Hesselmann B, Willeit M, Barnas C, Kasper S. Suicidal tendencies as a complication of light therapy for seasonal affective disorder: a report of three cases. *J Clin Psychiatry*. 1997;58:389-392.

103. Wirz-Justice A, Quinto C, Cajochen C, Werth E, Hock C. A rapid-cycling bipolar patient treated with long nights, bedrest, and light. *Biol Psychiatry*. 1999;45:1075-1077.

104. Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E. Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. *Psychiatry Res*. 2000;95:43-53.

105. Parry BL, Rosentahl NE, Tamarkin L, Wehr TA. Treatment of a patient with seasonal premenstrual syndrome. *Am J Psychiatry*. 1987;144:762-766.

106. Parry BL, Berga SL, Mostofi N, Sependa PA, Kripke DF, Gillin JC. Morning versus evening bright light treatment of late luteal phase dysphoric disorder. *Am J Psychiatry*. 1989;146:1215-1217.

107. Parry BL, Mahan AM, Mostofi N, Klauber MR, Lew GS, Gillin JC. Light therapy of late luteal phase dysphoric disorder: an extended study. *Am J Psychiatry*. 1993;150:1417-1419.

108. Lam RW, Carter D, Misri S, Kuan AJ, Yatham LN, Zis AP. A controlled study of light therapy in women with late luteal phase dysphoric disorder. *Psychiatry Res*. 1999;86:185-192.

109. Oren DA, Wisner KL, Spinelli M, et al. An open trial of morning light therapy for treatment of antepartum depression. *Am J Psychiatry*. 2002;159:666-669.

110. Corral M, Kuan A, Kostaras D. Bright light therapy's effect on postpartum depression. *Am J Psychiatry*. 2000;157:303-304.

111. Lewy AJ, Sack RL, Miller S, Hoban TM. Antidepressant and circadian phase-shifting effects of light. *Science*. 1987;235:352-354.

112. Terman JS, Terman M, Lo ES, Cooper TB. Circadian time of morning light administration and therapeutic response in winter depression. *Arch Gen Psychiatry*. 2001;58:69-75.

113. Terman M, Terman JS, Quitkin FM, et al. Response of the melatonin cycle to phototherapy for seasonal affective disorder. *J Neural Transm*. 1988;72:147-165.

114. Winton F, Corn T, Huson LW, Franey C, Arendt J, Checkley SA. Effects of light treatment upon mood and melatonin in patients with seasonal affective disorder. *Psychol Med*. 1989;19:585-590.

115. Danilenko KV, Putilov AA, Russkikh GS, Duffy LK, Ebbesson SOE. Diurnal and seasonal variations of melatonin and serotonin in women with seasonal affective disorder. *Arct Med Res*. 1994;53:137-145.

116. Partonen T. Involvement of melatonin and serotonin in winter depression. *Medical Hypotheses*. 1994;43:165-166.

117. Rice J, Mayor J, Tucker A, Bielski RJ. Effect of light therapy on salivary melatonin in seasonal affective disorder. *Psychiatry Res*. 1995;56:221-228.
118. Thalen BE, Kjellman BF, Morkrid L, Wetterberg L. Melatonin in light treatment of patients with seasonal and nonseasonal depression. *Acta Psychiatr Scand*. 1995;92:274-284.
119. Rao ML, Muller-Oerlinghausen BM, Mackert A, Stieglitz RD, Strebel B, Volz HP. The influence of phototherapy on serotonin and melatonin in nonseasonal depression. *Pharmacopsychiatry*. 1990;23:155-158.
120. Rao ML, Muller-Oerlinghausen B, Macker A, Strebel B, Stieglitz RD. Blood serotonin, serum melatonin and light therapy in healthy subjects and in patients with nonseasonal depression. *Acta Psychiatr Scand*. 1992;86:127-132.
121. Mellerup ET, Errebo I, Molin J, Plenge P, Dam H. Platelet paroxetine binding and light therapy in winter depression. *J Affect Disord*. 1993;29:11-15.
122. Schwartz PJ, Murphy DL, Wehr TA, et al. Effects of *meta*-chorophenylpiperazine infusions in patients with seasonal affective disorder and healthy control subjects. *Arch Gen Psychiatry*. 1997;54:375-385.
123. Stain-Malmgren R, Kjellman BF, Aberg-Wistedt A. Platelet serotonergic functions and light therapy in seasonal affective disorder. *Psychiatry Res*. 1998;78:163-172.
124. Lam RW, Zis AP, Grewal A, Delgado PL, Charney DS, Krystal JH. Effects of rapid tryptophan depletion in patients with seasonal affective disorder in remission after light therapy. *Arch Gen Psychiatry*. 1996;53:41-44.
125. Neumeister A, Praschak-Rieder P, Hesselmann B, Rao ML, Gluck J, Kasper S. Effects of tryptophan depletion on drug-free patients with seasonal affective disorder during a stable response to bright light therapy. *Arch Gen Psychiatry*. 1997;554:133-138.
126. Neumeister A, Turner E, Matthews JR, et al. Effects of tryptophan depletion vs catecholamine depletion in patients with seasonal affective disorder in remission with light therapy. *Arch Gen Psychiatry*. 1998;55:524-530.
127. Szadoczky E, Falus A, Arato M, Nemeth A, Teszeri G, Moussong-Kovacs E. Phototherapy increases platelet imipramine binding in patients with winter depression. *J Affect Disord*. 1989;16:121-125.
128. Szadoczky E, Falus A, Nemeth A, Teszeri G, Moussong-Kovacs E. Effect of phototherapy on 3H-imipramine binding sites in patients with SAD, non-SAD and in healthy controls. *J Affect Disord*. 1991;22:179-184.
129. Anderson JL, Vasile RG, Mooney JJ, Bloomingdale KL, Samson JA, Schildkraut JJ. Changes in norepinephrine output following light therapy for fall/winter seasonal depression. *Biol Psychiatry*. 1992;32:700-704.
130. Rudorder MV, Skwerer RG, Rosenthal NE. Biogenic amines in seasonal affective disorder: effects of light therapy. *Psychiatry Res*. 1993;46:19-28.
131. Partonen T. Prolactin in winter depression. *Medical Hypotheses*. 1994;43:163-164.
132. Lingjaerde O, Reichborn-Kjennerud T, Haug E. Thyroid function in seasonal affective disorder. *J Affect Disord*. 1995;33:39-45.
133. Thalen BE, Morkrid L, Kjellman BF, Wetterberg L. Cortisol in light treatment of seasonal and non-seasonal depression: relationship between melatonin and cortisol. *Acta Psychiatr Scand*. 1997;96:385-394.
134. Partonen T. A mechanism of action underlying the antidepressant effect of light. *Medical Hypotheses*. 1995;45:33-34.
135. Yatham LN, Lam RW, Zis AP. Growth hormone response to sumatriptan (5-HT$_{1D}$ agonist) challenge in seasonal affective disorder: effects of light therapy. *Biol Psychiatry*. 1997;42:24-29.
136. Shiah IS, Robertson HA, Lam RW, Yatham LN, Tam EM, Zis AP. Growth hormone response to baclofen in patients with seasonal affective disorder: effects of light therapy. *Psychonueroendocrinology*. 1999;24:143-153.
137. Oren D. Bilirubin, REM sleep, and phototransduction of environmental time cues. A hypothesis. *Chronobiol Int*. 1997;14:319-329.
138. Oren DA, Desan PH, Boutros N, Anand A, Charney DS. Effects of light on low nocturnal bilirubin in winter depression: a preliminary report. *Biol Psychiatry*. 2002;51:422-425.

139. Dietzel M, Saletu B, Lesch OM, Sieghart W, Schjerve M. Light treatment in depressive illness. Polysomnographic, psychometic and neuroendocrinological findings. *Eur Neurol Suppl*. 1986;25:93-103.
140. Partonen T, Appelberg B, Partinen M. Effects of light treatment on sleep structure in seasonal affective disorder. *Eur Arch Psychiatry Clin Neurosci*. 1993;242:310-313.
141. Allen JJ, Iacono WG, Depue RA, Arbisi P. Regional electroencephalographic asymmetries in bipolar seasonal affective disorder before and after exposure to bright light. *Biol Psychiatry*. 1993;33:642-646.
142. Volf NV, Senkova NI, Danilenko KV, Putilov AA. Hemispheric language lateralization in seasonal affective disorder and light treatment. *Psychiatry Res*. 1993;47:99-108.
143. Brunner DP, Krauchi K, Dijk DJ, Leonhardt G, Haug HJ, Wirz-Justice A. Sleep electroencephalogram in seasonal affective disorder and in control women: effects of midday light treatment and sleep deprivation. *Biol Psychiatry*. 1996;40:485-496.
144. Fritzsche M, Heller R, Hill H, Kick H. Sleep deprivation as a predictor of response to light therapy in major depression. *J Affect Disord*. 2001; 62:207-215.
145. Dilsaver SC. Neurobiologic effects of bright artificial light. *Brain Res Rev*. 1989;14:311-333.
146. Rosenthal NE, Levendosky AA, Skwerer RG, et al. Effects of light treatment on core body temperature in seasonal affective disorder. *Biol Psychiatry*. 1990;27:39-50.
147. Eastman CI, Gallo LC, Lahmeyer HW, Fogg LF. The circadian rhythm of temperature during light treatment for winter depression. *Biol Psychiatry*. 1993;34:210-220.
148. Avery DH, Dahl K, Savage MV, et al. Circadian temperature and cortisol rhythms during a constant routine are phase-delayed in hypersomnic winter depression. *Biol Psychiatry*. 1997;41:1109-1123.
149. Schwartz PJ, Rosentahl NE, Turner EH, Drake CL, Liberty V, Wehr TA. Seasonal variation in core temperature regulation during sleep in patients with winter seasonal affective disorder. *Biol Psychiatry*. 1997;42:122-131.
150. Schwartz PJ, Rosenthal NE, Kajimura N, et al. Ultradian oscillations in cranial thermoregulation and electroencephalographic slow-wave activity during sleep are abnormal in humans with annual winter depression. *Brain Res*. 2000;866:152-167.
151. Seggie J, Canny C, Mai F, McCrank E, Waring E. Antidepressant medication reverses increased sensitivity to light in depression: preliminary report. *Prog Neuropsychopharmacol Biol Psychiatry*. 1989;13:537-541.
152. Terman S, Terman M. Photic and scotopic light detection in patients with SAD and control subjects. *Biol Psychiatry*. 1999;46:1642-1648.
153. Lam RW, Buchanan A, Mador JA, Corral MR, Remick RA. The effects of ultraviolet-A wavelengths in light therapy for seasonal depression. *J Affect Disord*. 1992;24:237-244.
154. Lasko TA, Kripke DF, Elliot JA. Melatonin suppression by illumination of upper and lower visual fields. *J Biol Rhythms*. 1999;14:122-125.
155. Vasile RG, Sachs G, Anderson JL, Lafer B, Matthews E, Hill T. Changes in regional cerebral blood flow following light treatment for seasonal affective disorder: responders versus nonresponders. *Biol Psychiatry*. 1997;42:1000-1005.
156. Rechlin T, Weis M, Schneider K, Zimmermann U, Kaschka WP. Does bright-light therapy influence autonomic heart-rate parameters? *J Affect Disord*. 1995;34:131-137.
157. Avissar S, Schreiber G, Nechamkin Y, et al. The effects of seasons and light therapy on G protein levels in mononuclear leukocyctes of patients with seasonal affective disorder. *Arch Gen Psychiatry*. 1999;56:178-183.
158. Oren DA, Berman RM, Anand A, Charney DS. No effect of light on basal glucagon levels in winter seasonal depressives and comparison subjects. *Psychiatry Res*. 2000;94:263-266.
159. Leu SJ, Shiah IS, Yatham LN, Cheu YM, Lam RW. Immune-inflammatory markers in patients with seasonal affective disorder: effects of light therapy. *J Affect Disord*. 2001;63:27-34.