CME ACTIVITY

Sponsored by Physicians Postgraduate Press, Inc.

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME). To obtain credit, please read the following article and complete the posttest as instructed on page 809.

CME Objectives

After completing this CME activity, the psychiatrist should be able to:

- Identify the various risk factors and benefits resulting from exposure to light therapy
- Examine the possible parameters of light exposure that may be responsible for specific side effects
- Discuss light therapy regimens that maximize antidepressant response and minimize side effects

Statement of Need and Purpose

Physicians responding to articles in *The Journal of Clinical Psychiatry* and its related CME activities have indicated a need to know more about the diagnosis and management of the side effects and the benefits of bright light therapy in the treatment of seasonal affective disorder. This CME enduring material presents current information to address that need. There are no prerequisites for participating in this CME activity.

Accreditation Statement

Physicians Postgraduate Press, Inc., is accredited by the ACCME to sponsor continuing medical education for physicians. Physicians Postgraduate Press, Inc., takes responsibility for the content, quality, and scientific integrity of this CME activity.

Credit Designation

Physicians Postgraduate Press, Inc., designates this educational activity for a maximum of 1 hour in Category 1 credit toward the American Medical Association Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Faculty Disclosure

In the spirit of full disclosure and in compliance with all ACCME Essentials, Standards, and Guidelines, all faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows:

None of the authors of this article has significant commercial relationships to disclose relative to the presentation.

Bright Light Therapy: Side Effects and Benefits Across the Symptom Spectrum

Michael Terman, Ph.D., and Jiuan Su Terman, Ph.D.

Background: Bright light therapy has been established for treatment of winter depression, or seasonal affective disorder (SAD). Analysis of side effects most often have focused on a narrow set of suspected symptoms, based on clinical observation (e.g., headache, eyestrain, nausea, insomnia, and hyperactivity). This study broadens the purview to a set of 88 physical and subjective symptoms that might emerge, remit, or remain unchanged relative to baseline, thus reducing bias toward assessment of presumed side effects.

Method: Eighty-three patients with SAD (DSM-III-R criteria for mood disorders with seasonal pattern [winter type] and National Institute of Mental Health criteria for SAD) received bright light therapy at 10,000 lux for 30 minutes daily in the morning or evening for 10 to 14 days. They completed a questionnaire (Systematic Assessment for Treatment Emergent Effects), rating symptom severity before and after treatment. Results were compared for morning or evening treatment and for responders and nonresponders.

Results: Several side effects emerged—mostly mildly—including jumpiness/jitteriness (8.8%), headache (8.4%), and nausea (15.9%), mirroring findings of past studies with a less inclusive scope. In most cases, remission rate equalled or exceeded emergence rate. Several nondepressive symptoms also showed large improvement, including poor vision and skin rash/itch/irritation. Being overactive/excited/elated showed greater emergence under morning light and greater remission under evening light. Emergence of nausea was greater than remission in responders.

Conclusion: The dominant effect of light treatment was improvement in bothersome symptoms. Although patients should be advised of side effects and guided in dose manipulations to reduce them, attention also should be drawn to the substantial benefit-to-risk ratio. Improvement of symptoms outside the depressive cluster, seen in both responders and nonresponders, may point to new therapeutic uses of light therapy.

(J Clin Psychiatry 1999;60:799–808)

Received Dec. 1, 1998; accepted June 15, 1999. From the Department of Psychiatry, Columbia University (Dr. M. Terman); and the New York State Psychiatric Institute, New York, N.Y. (both authors).

Supported by grant MH42931 from the National Institute of Mental Health.

The authors thank Donald C. Ross, Ph.D., for statistical consultation, and Jamie Rifkin for editorial comments.

Reprint requests to: Michael Terman, Ph.D., New York State Psychiatric Institute, 1051 Riverside Dr., Unit 50, New York, NY 10032 (e-mail: mt12@columbia.edu).

Light therapy has become a common treatment for seasonal affective disorder (SAD) since the first clinical trial in 1984.[1] Like antidepressant drugs, it is a somatic intervention that may act by serotonergic potentiation,[2] although other mechanisms of action—in particular, circadian rhythm phase shifting[3]—are likely to be involved. In the 2 largest controlled trials to date, bright light administration has been shown to be superior to placebo according to rating scale measures of improvement, categorical remission rate,[4] or both.[5] In contrast to the delayed effect typical of pharmacologic antidepressants, remission or improvement of depressive and atypical neurovegetative symptoms often occurs within a week of light treatment, and adverse side effects appear to be minimal. Systematic investigation of side effects, however, has been quite limited.

Hypomania, irritability, headache, and nausea were noted as occasional side effects in the earliest studies of light therapy for SAD, which used fluorescent light boxes with exposure at 2500 lux for 2 hours/day or longer.[1,6] Some boxes lacked diffusing screens,[6] which might exacerbate symptoms.[7] Side effects were rarely cause for discontinuation. Symptoms usually subsided after several days of treatment or, when persistent, could be alleviated with dose decreases (duration or intensity of light exposure). Recent studies using portable head-mounted units with incandescent bulbs near the eyes have also noted side effects of eyestrain and feeling "wired."[8,9]

The induction of mania or hypomania poses a distinct potential psychiatric concern. Light-induced mania in SAD has been observed only rarely. In our clinic there has been only 1 case in more than 300: a 23-year-old man

with bipolar I disorder who, after about 3 weeks of treatment at 2500 lux for 2 to 4 hours/day, during dose adjustments, required emergency room care and lithium treatment. A case of mania has been reported in a unipolar SAD patient after exposure to bright light that exceeded the recommended dose.[10] There have also been 2 such cases reported in drug-refractory, nonseasonal unipolar depressives after 4 to 5 days of light treatment.[11] Several cases of light-induced agitation and hypomania have also been noted in patients with seasonal or nonseasonal[12] depressions.

In contrast with manic overresponse, light exposure can also exacerbate depression. Three cases of suicidal ideation were reported within 1 month in patients who had received early evening light exposure,[13] although suicidality has shown consistent marked improvement under morning light.[14] A recent study noted that the side effect profile for light treatment, combined with trimipramine in nonseasonal major depressives, may be distinct from that of the antidepressant alone.[15] Of particular interest was increased sedation, which contrasts with the activating effects normally associated with bright light exposure.[16]

Apart from the above-mentioned case reports, there have been only a few studies specifically to assess short- or long-term side effects of light therapy in patients with SAD. In a long-term follow-up survey, about 25% of patients who had used 2500 lux light therapy for several years continued to report headache, eyestrain, and insomnia.[17] The contributing factor of light intensity, however, is still unclear. For example, in a study of patients with nonseasonal depression, which found no therapeutic effect of light, side effects did not differ at high or low intensity.[18]

Two studies have systematically investigated the side effects of light treatment in SAD, using either a 2500 lux unfiltered full-spectrum fluorescent light box[19] or a head-mounted incandescent unit at 60, 600, or 3500 lux.[9] About 25% of patients using the light box reported mild, transient visual side effects (blurring, eyestrain, photophobia) and initial insomnia under evening light. Side effects were more frequent with the head-mounted unit. Across the symptoms assessed (abdominal pain, dizziness, eyestrain, fatigue, feeling "wired," headache, insomnia, muscle pains, nausea, sweating), 58% of 105 patients reported at least 1 symptom, 30% at least 2, and 13% at least 3. Most prevalent were headache (19%), eyestrain (17%), and feeling "wired" (14%). However, these side effects were unrelated to the intensity of illumination or the magnitude of the antidepressant response. Indeed, another study using red light–emitting diodes in a head-mounted unit at 4000 or 96 lux produced similar side effects,[20] although the authors of both visor studies noted generally greater improvement than exacerbation of the same symptoms.[9,20] A question remains about whether side effects are specific to light exposure or some other aspect of the procedure. Similar mild, transient symptoms (headache, eyestrain and irritation, and visual glare) have also been noted at far higher intensity, 10,000 lux fluorescent illumination administered daily for 30 minutes,[21] a procedure now most commonly used for treatment of winter depression.[22]

It remains to be determined how specific parameters of light exposure may be responsible for specific side effects. Factors may include intensity, duration of exposure, spectral content, and illumination method (diffused, focused, direct, indirect). Adverse effects seem more likely to emerge when the light source is close to the eyes, as with head-mounted units. Since 1987, we have conducted clinical trials of light therapy for SAD using a downward-tilted 10,000 lux fluorescent light box covered by an ultraviolet-shielding diffusing screen, with 30 minutes of daily exposures in the morning or evening. This "brief exposure" method produces clinical response rates equal or superior to earlier studies using 2500 lux for longer durations,[23] with maximal response to morning light on awakening.[5] We have investigated potential ocular hazards of 10,000 lux treatment by ophthalmologic examinations and have found no evidence of clinically significant changes even at long-term follow-up.[24,25]

The present report assesses a wide range of potential side effects in subjects who entered treatment between 1987 and 1994. We used a questionnaire version of the Systematic Assessment for Treatment Emergent Effects (SAFTEE),[26] which was originally developed and validated for drug studies. Thus, the scope of symptoms was not restricted to those already suspected to result from light exposure.

METHOD

Subjects

Eighty-three outpatients (63 women, 20 men), aged 18–63 years (mean ± SD = 39.8 ± 9.5) participated. They fulfilled both DSM-III-R criteria for mood disorders with seasonal pattern (winter type) and National Institute of Mental Health criteria for SAD.[27] Sixty-one were diagnosed with major depressive disorder, recurrent (code 296.3); 19, bipolar disorder not otherwise specified (296.7); and 3, bipolar disorder, depressed (296.5). Subjects all had normal medical status and signed informed consent for entry into treatment trials.

Procedure

After onset of a major depressive episode in late fall or winter (severity criteria based on Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version [SIGH-SAD] score,[28] which includes 21 items from the original Hamilton scale with 8 additional items that assess atypical symptoms), subjects were randomly assigned to controlled treatment trials that included bright light presentation in the morning or evening.[5,23] Treatment was at 10,000 lux daily for 30 minutes in the morning (on awakening) or evening (at least 2 hours before bedtime).

Side Effect Inventory

The SAFTEE includes 96 items organized by organ system and body part (head, eyes/vision, ears/hearing, mouth, chest, stomach/abdomen, gastrointestinal, musculoskeletal, skin, depression). There are 88 core symptoms (Table 1) with 8 additional items related to the menstrual cycle, which we did not include because menstrual phase at baseline and during treatment was uncontrolled. In the questionnaire version used, the subject rated each item on a scale of 1 to 5 (1 = not at all, 2 = a little bit, 3 = moderately, 4 = quite a bit, 5 = extremely), using a 1-week evaluation window. The instrument was administered at baseline and at the end of 10 to 14 days of treatment, along with clinical evaluations.

Statistical Analysis

Frequency distributions of symptom severity score were separately derived for each SAFTEE item. Pretreatment to posttreatment change scores were categorized to indicate emergence of a symptom (from a score of 1 ["not at all"] to > 1) or remission (from > 1 to 1). Because of the broad symptom screen and multiple comparisons, statistical significance was not evaluated in terms of α probabilities. Rather, the relative proportion of change scores (emergence vs. remission) was expressed as the effect size of the McNemar chi square, or *w*, where $w = \mathrm{sqrt}(\chi^2/N)$ and N is the total number of change scores in both directions. For comparisons across subgroups (morning vs. evening light, responders vs. nonresponders), the effect size was based on the 2×2 chi-square for change scores. Values of $w \geq 0.5$ were considered to index a large effect size; 0.3, medium; and 0.1, small.[29] Although a symptom with similar rates of emergence and remission results in a negligible effect size, the absolute emergence rate may still cause concern about the acceptability of the treatment for affected patients. Furthermore, items with relatively low frequency can show large effect sizes that warrant attention. In the present sample, all comparisons with large effect size would individually yield α values of .05 or less. However, false positives remain a distinct risk given 88 comparisons. Items with large effect size, especially when unexpected, might merit further investigation in prospective studies.

RESULTS

Symptom Frequency Before and After Treatment

Table 1 lists the frequency of all symptoms on the SAFTEE reported as more than mildly bothersome—i.e., moderate (3) to extreme (5)—in the order the items appear on the questionnaire. At baseline, there was a wide range of symptoms with frequency above 10%. These included symptoms that might also be predicted to emerge as side effects after treatment (e.g., eye irritation, 12.1%), symptoms of ailments typical in winter (e.g., coughing, 11.0%), symptoms of depression (e.g., fatigue, 79.3%), physical symptoms often associated with depression and anxiety (e.g., dry mouth, 18.1%), and symptoms that might be associated either with depression or hypomania (e.g., initial, middle, and late insomnia, 15.9% to 25.6%). Some items fall into more than 1 class (e.g., headache [27.7%], a suspected side effect also associated with both depression and anxiety).

Depressive symptoms were always prominent at baseline (e.g., irritability, 62.2%), and they uniformly decreased after treatment (19.8%). However, the trend toward decrease from baseline to posttreatment was nearly ubiquitous throughout the range of SAFTEE items, with exceptions falling into 2 classes as follows: (1) physical symptoms (e.g., breast tenderness, nausea, fever, all with frequencies of 7.4% or less), and (2) symptoms consistent with hypomania (e.g., increased sexual interest, 14.9%; excessive energy, 6.3%; and being overactive/excited/elated, 7.4%). Despite the general improvement under light therapy, the most prevalent posttreatment symptoms fell into the depressive cluster (e.g., anxiety, 22.2%) or were physical symptoms potentially associated with depression and anxiety (e.g., gas, 12.1%); these could be either true side effects or residuals of the depressive episode.

The SAFTEE includes several pairs of contrasting symptoms (e.g., appetite decrease and increase) that, however, do not necessarily show opposite results in the group as a whole. This complicates interpreting emergent side effects, since a depressive episode may be associated with atypical features (e.g., appetite increase), melancholic features (e.g., appetite decrease), or neither.

Table 1. SAFTEE Inventory: Percentage of Cases Symptomatic Before and After Treatment[a]

Class	Symptom	Baseline	Post-treatment
Head	Headaches	27.7	8.4
	Dizziness/faintness	4.9	1.2
	Loss of consciousness	0.0	0.0
	Seizures	0.0	0.0
Eyes	Eye irritation	12.1	1.2
	Eye swelling	7.2	0.0
	Blurred vision	2.4	0.0
	Double vision	1.2	0.0
	Poor vision	2.4	0.0
	Light bothersome to eyes	6.0	2.4
Ears	Earache	1.2	0.0
	Ear discharge	0.0	0.0
	Hearing loss	3.6	2.4
	Noise/ringing in ears	2.5	2.6
Mouth	Mouth sores	3.6	1.2
	Dry mouth	18.1	7.2
	Excess salivation	2.4	2.4
	Swollen/sore tongue	2.4	0.0
	Bleeding gums	3.6	0.0
	Dental problems	3.7	0.0
Nose/throat	Nasal congestion	26.5	19.5
	Nasal bleeding	1.2	0.0
	Sore throat	9.6	10.8
	Laryngitis	3.6	3.6
	Difficulty swallowing	0.0	1.2
	Chest pain	2.4	3.6
Chest	Shortness of breath	2.4	2.4
	Wheezing	4.8	1.2
	Coughing	11.0	7.2
	Breast pain/discharge	0.0	1.2
	Breast tenderness	2.4	7.2
Heart	Rapid heartbeat	9.6	1.2
	Irregular heartbeat	1.2	2.4
Stomach/ abdomen	Abdominal discomfort	20.5	15.7
	Nausea	3.7	7.3
	Vomiting	0.0	2.4
	Heartburn	8.4	4.9
Intestinal	Diarrhea	12.1	4.9
	Constipation	7.2	3.6
	Gas	24.1	12.1
	Change in stool color	3.6	1.2
	Hemorrhoids	4.8	1.2
	Painful bowel movements	2.4	0.0
Appetite/weight	Appetite increase	42.2	18.1
	Appetite decrease	12.1	8.4
	Weight gain	26.5	7.2
	Weight loss	4.8	3.6
	Change in taste	4.9	1.2
	Increased thirst	16.8	4.8
Urinary	Painful urination	0.0	2.4
	Urinary burning	0.0	2.4
	Difficulty urinating	0.0	2.4
	Decreased urinary pressure	2.5	3.7
	Frequent urination	14.8	7.3
	Change in urine color	1.2	2.5
Genital	Genital discomfort	0.0	2.7
	Genital swelling/discharge	0.0	1.3
	Decreased sexual interest	45.3	9.3
	Increased sexual interest	9.3	14.9
	Difficulties with orgasm	6.2	4.8
	Difficulty with erection (N = 20)	18.2	10.0
Musculoskeletal	Muscle/bone/joint pain	27.5	14.6
	Leg/arm swelling	2.5	1.2
	Hand/foot numbness	10.0	6.1
	Unsteady on feet	4.9	0.0
	Difficulty moving	13.4	3.8
	Unwanted body movement	0.0	0.0
	Restlessness	20.7	3.8
	Shaking	1.2	1.2
	Rigidity/stillness	3.7	2.5
Skin	Rash/itch/irritation	3.7	4.9
	Bruising	1.2	0.0
	Sunlight irritation	0.0	0.0
	Sweating	2.4	0.0
	Fever/chills	3.7	7.4
Depression	Fatigue	79.3	30.9
	Excessive energy	2.5	6.3
	Jumpiness/jitteriness	26.8	3.8
	Overactive/excited/elated	4.9	7.4
	Initial insomnia	25.6	12.4
	Middle insomnia	22.0	9.9
	Late insomnia	15.9	9.9
	Hypersomnia	40.7	16.1
	Drowsiness	70.7	21.3
	Thought/concentration/ memory problems	60.0	16.1
	Feeling depressed/ "down"/"blue"	85.9	24.1
	Anxiety	59.8	22.2
	Irritability	62.2	19.8

[a]Abbreviation: SAFTEE = Systematic Assessment for Treatment Emergent Effects. Symptoms rated moderate (3) to extreme (5). N = 83 (range, 70 to 83; denominator adjusted for missing cases). Items with substantially lower sample size are all related to genital/sexual issues.

Bidirectional Change

Although the SAFTEE was designed to detect side effects, the inclusion of items associated with depression also leads it to detect posttreatment improvement. Given the high frequency of many symptoms at baseline, the detection of emergent side effects requires that change scores be analyzed for individual subjects, rather than for the group as a whole. Table 2 shows remission and emergence rates for 55 of the 88 items that showed change frequencies (in either direction) of 5% or more.

Emergence. About half (27/55) of the items listed in Table 2 show emergence rates of 5% or more, whereas only 9 items showed rates of 10% more. Several symptoms might be suspected as potential side effects of bright light exposure (e.g., headache, 8.4%; eye irritation, 6.0%; jumpiness/jitteriness, 8.8%; nausea, 15.9%), although

Table 2. Symptom Change Before and After Light Treatment[a]

Class	Symptom	Percentage of Cases[b] Emerged	Remitted	Effect Size, *w*
Head	Headaches	8.4	15.7	0.25
Eyes	Eye irritation	6.0	16.9	0.42
	Eye swelling	1.2	7.2	0.57
	Blurred vision	0.0	8.4	0.86
	Poor vision	0.0	13.4	0.91
	Light bothersome to eyes	3.6	14.5	0.53
Mouth	Mouth sores	8.4	3.6	0.30
	Dry mouth	3.6	15.7	0.56
	Bleeding gums	1.2	8.4	0.63
Nose/throat	Nasal congestion	12.2	15.9	0.09
	Sore throat	8.4	8.4	0.00
Chest	Chest pain	4.8	9.6	0.25
	Shortness of breath	6.0	8.4	0.08
	Coughing	14.6	15.9	0.00
	Breast tenderness	6.0	7.2	0.00
Heart	Rapid heartbeat	3.6	12.0	0.46
Stomach/ abdomen	Abdominal discomfort	9.6	16.9	0.23
	Nausea	15.9	9.8	0.19
	Vomiting	6.1	2.4	0.29
	Heartburn	2.5	9.9	0.50
Intestinal	Diarrhea	13.4	9.8	0.11
	Constipation	2.4	14.5	0.64
	Gas	3.6	19.3	0.63
Appetite/ weight	Appetite increase	14.5	38.6	0.43
	Appetite decrease	19.3	20.5	0.00
	Weight gain	9.6	36.1	0.55
	Weight loss	19.3	7.2	0.41
	Change in taste	1.2	12.3	0.73
	Increased thirst	3.6	22.9	0.68
Urinary	Frequent urination	3.7	13.6	0.50
Genital	Decreased sexual interest	6.7	46.7	0.73
	Increased sexual interest	17.6	8.1	0.32
	Difficulties with orgasm	6.3	17.5	0.40
	Difficulty with erection (N = 20)	5.0	20.0	0.40
Musculoskeletal	Muscle/bone/joint pain	7.5	20.0	0.41
	Leg/arm swelling	0.0	6.2	0.80
	Hand/foot numbness	1.3	11.3	0.70
	Unsteady on feet	4.9	7.4	0.10
	Difficulty moving	3.7	18.5	0.61
	Restlessness	2.5	22.2	0.75
Skin	Rash/itch/irritation	3.7	14.8	0.53
	Fever/chills	7.4	8.6	0.00
Depression	Fatigue	2.5	25.9	0.78
	Excessive energy	5.1	5.1	0.00
	Jumpiness/jitteriness	8.8	25.0	0.44
	Overactive/excited/elated	9.9	9.9	0.00
	Initial insomnia	7.4	19.8	0.41
	Middle insomnia	4.9	23.5	0.61
	Late insomnia	13.6	14.8	0.00
	Hypersomnia	8.6	32.1	0.55
	Drowsiness	0.0	38.8	0.97
	Thought/concentration/ memory problems	3.8	28.8	0.73
	Feeling depressed/"down"/ "blue"	0.0	43.6	0.97
	Anxiety	4.9	37.0	0.74
	Irritability	4.9	33.3	0.71

[a]Items included showed ≥ 5.0% emergence or remission; symptomatic range, mild (2) to extreme (5).
[b]N = 83 (range, 70 to 83, denominator adjusted for missing cases). Items with substantially lower sample size are all related to genital/sexual issues.

some may also reflect exacerbated depression given ineffective treatment. Feeling depressed/ "down"/"blue" necessarily had a zero rate of emergence, since all patients reported depression at baseline. Other emergent symptoms are commonly associated with winter depression (e.g., hypersomnia, 8.6%; weight gain, 9.6%) or hypomania (e.g., being overactive/excited/elated, 9.9%), but do not necessarily indicate an abnormal mood state. Yet others are neither associated with depression nor suspected as side effects of light exposure; rather, they emerge in winter throughout the population (e.g., nasal congestion, 12.2%; fever/chills, 7.4%). Finally, several emergent symptoms may represent desired treatment outcomes (e.g., appetite decrease, 19.3%; increased sexual interest, 17.6%).

Emergence versus remission. Emergence of a symptom in some patients must be judged against remission in others. Several emergent symptoms were offset by greater gains in remission (e.g., jumpiness/jitteriness, 8.8% vs. 25.0%), with medium-to-large effect sizes. When emergence and remission rates are similar (e.g., nasal congestion, 12.2% vs. 15.9%), the symptom may appear intermittently throughout the winter season, irrespective of light exposure. A treatment success may be indicated when remission greatly overshadows emergence (e.g., hypersomnia or dry mouth [a somatic symptom of anxiety]). Surprisingly, several symptoms outside the depressive spectrum showed similar improvement (e.g., poor vision, light bothersome to eyes, and skin rash/itch/irritation). Several symptoms showed greater emergence than remission, but with only medium effect size. Two of these—increased sexual interest and weight loss—suggest benefits of light therapy. Several gastrointestinal symptoms (nausea, vomiting, and diarrhea) emerged either with low frequency or small effect size, but merit attention since they might be triggered by light exposure.

Subgroup Analyses

Because specific side effects may be related to the time of day of light treatment or the response to treatment, we compared data for (1) patients given morning or evening light, and (2) responders and nonresponders. For example, evening light might selectively induce initial insomnia through an activating or circadian phase-delaying effect.[16,30] Twelve potential side effects showed 5% emer-

Table 3. Side Effect Analysis: Morning vs. Evening Light

	Morning Light (N = 54)[a]			Evening Light (N = 29)[b]			Morning vs Evening Effect Size, *w*		
Symptom	Emerged[c]	Remitted[c]	Effect Size, *w*	Emerged[c]	Remitted[c]	Effect Size, *w*	Emergence	Remission	Bidirectional Change[d]
Headaches	7.4	20.4	0.40	10.3	6.9	0.00	0.05[f]	0.18	0.30
Eye irritation	5.6	22.2	0.53	6.9	6.9	0.00	0.03[f]	0.20	0.28
Nasal congestion	14.8	18.5	0.06	7.1	10.7	0.00	0.11	0.10	0.04
Shortness of breath	3.7	9.3	0.29	10.3	6.9	0.00	0.13[f]	0.04	0.31
Abdominal discomfort	11.1	20.4	0.24	6.9	10.3	0.00	0.07	0.13	0.04
Nausea	17.0	13.2	0.06[e]	13.8	3.5	0.40[e]	0.04	0.16	0.21[f]
Diarrhea	15.1	13.2	0.00[e]	10.3	3.5	0.25[e]	0.07	0.16	0.18[f]
Skin rash/itch/irritation	5.7	11.3	0.22	0.0	21.4	0.83	0.15	0.13[f]	0.41[f]
Jumpiness/jitteriness	9.6	25.0	0.39	7.1	25.0	0.44	0.05	0.00	0.06[f]
Overactive/excited/elated	13.2	3.8	0.44[e]	3.6	18.5	0.57	0.16	0.28[f]	0.60[f]
Initial insomnia	3.8	17.0	0.55	14.3	25.0	0.18	0.19[f]	0.09[f]	0.20
Late insomnia	11.3	15.1	0.07	17.9	14.3	0.00	0.09[f]	0.02	0.12

[a]Range, 51 to 54, due to missing cases.
[b]Range, 27 to 29, due to missing cases.
[c]Percentage of cases.
[d]Emergence vs. remission across groups.
[e]Emergence > remission.
[f]Evening > morning.

Table 4. Side Effect Analysis: Responders vs. Nonresponders

	Responders (N = 51)[a]			Nonresponders (N = 32)[b]			Responders vs Nonresponders Effect Size, *w*		
Symptom	Emerged[c]	Remitted[c]	Effect Size, *w*	Emerged[c]	Remitted[c]	Effect Size, *w*	Emergence	Remission	Bidirectional Change[d]
Headaches	5.9	19.6	0.46	12.5	9.4	0.00[e]	0.12[f]	0.13	0.34
Eye irritation	7.8	17.7	0.31	3.1	15.6	0.50	0.10	0.03	0.15[f]
Nasal congestion	7.8	17.7	0.31	19.4	12.9	0.10[e]	0.18[f]	0.06	0.29
Shortness of breath	5.9	7.8	0.00	6.3	9.4	0.00	0.01[f]	0.03[f]	0.03
Abdominal discomfort	11.8	19.6	0.19	6.3	12.5	0.17	0.09	0.09	0.04
Nausea	18.0	8.0	0.31[e]	12.5	12.5	0.00	0.07	0.07[f]	0.19
Diarrhea	17.7	9.8	0.21[e]	6.5	9.7	0.00	0.16	0.00	0.22
Skin rash/itch/irritation	6.1	12.2	0.22	0.0	19.4	0.83	0.16	0.11[f]	0.41[f]
Jumpiness/jitteriness	8.3	22.9	0.40	9.7	29.0	0.42	0.03[f]	0.08[f]	0.02[f]
Overactive/excited/elated	10.2	14.3	0.08	9.7	3.2	0.25[e]	0.00	0.18	0.29[f]
Initial insomnia	6.1	20.4	0.46	9.7	19.4	0.22	0.07[f]	0.01	0.11
Late insomnia	12.2	18.4	0.13	16.1	9.7	0.13[e]	0.06[f]	0.12	0.22

[a]Range, 48 to 51, due to missing cases.
[b]Range, 30 to 32, due to missing cases.
[c]Percentage of cases.
[d]Emergence vs. remission across groups.
[e]Emergence > remission.
[f]Nonresponders > responders.

gence or greater in at least 1 of the conditions (Tables 3 and 4).

Morning versus evening light (Table 3). Under morning light, the symptoms showing greatest emergence were nausea (17.0%) and diarrhea (15.1%), but they were counterbalanced by similar remission rates (both 13.2%), resulting in negligible effect sizes. Being overactive/excited/elated emerged in 13.2% of cases and remitted only in 3.8%. Although possibly a cause for concern, such reports may also reflect posttreatment relief from depression or the response to circadian phase advances under morning light with earlier awakening.[5] We did not detect any manic episodes or clinically significant hypomania in posttreatment clinical evaluations.[31] The only large changes under morning light were in initial insomnia and eye irritation, both of which improved.

Under evening light, nausea showed greater emergence than remission (13.8% vs. 3.5%), an effect not observed under morning light. Being overactive/excited/elated showed lower emergence than remission (3.6% vs.

18.5%), a large effect opposite that seen under morning light; this may reflect the lower clinical efficacy of evening light or the lack of circadian phase advances with earlier awakening.[5] Although initial insomnia showed 14.3% emergence, it was offset by a remission rate of 25.0%. Furthermore, the emergence rates of initial and late insomnia were similar. Surprisingly, skin rash/itch/irritation showed the largest relative improvement of any symptom under evening light (0.0% vs. 21.4%). Indeed, all patients with preexisting skin rash/itch/irritation reported complete remission of this symptom. (As shown below, this improvement was unrelated to the antidepressant response.)

When emergence and remission rates for morning and evening light were separately compared (Table 3, right section), no item showed a large effect size. The greatest contrast in remission rates, while only of medium effect size, was for being overactive/excited/elated (morning, 3.8%; evening, 18.5%). When the groups were compared for bidirectional change, this item showed a large effect ($w = 0.60$) that reflects the balance toward emergence under morning light and the balance toward remission under evening light. However, both clinical evaluations and self-ratings on the SAFTEE indicated that disruptive overexcitation was very rare: 83% of subjects reported not being overactive/excited/elated; 9% reported "a little bit"; 6%, "moderately"; 1%, "quite a bit"; and none, "extremely." Unfortunately, the SAFTEE does not discriminate being overactive from being elated, nor does it define elation as a supernormal response. Two other symptoms, headache and shortness of breath, also showed bidirectional changes consistent with a differential advantage of morning light.

Responders versus nonresponders (Table 4). Responders were defined as those whose pretreatment to posttreatment reduction in SIGH-SAD score was 50% or greater, with the component Hamilton and atypical scale scores both below 8, and Clinical Global Impressions rated "much improved" or "very much improved."[32] Among responders, nausea and diarrhea, which both occurred in about 18% of cases, were the only symptoms with greater emergence than remission. Being overactive/excited/elated emerged and remitted at indistinguishable rates (10.2% vs. 14.3%). Headache and jumpiness/jitteriness both showed a balance toward improvement after treatment.

Among nonresponders, the emergence and remission of nausea was identical, which contrasts with the balance toward emergence seen in responders. Being overactive/excited/elated emerged about 3 times more frequently than it remitted. The improvement in initial insomnia among responders was less pronounced among nonresponders. However, jumpiness/jitteriness showed clear improvement among both responders and nonresponders, and thus was unrelated to the treatment effect. The 2 symptoms showing greatest relative improvement among nonresponders were eye irritation and skin/rash/itch irritation, potential benefits that may be independent of the antidepressant response.

In summary, the side effect profiles reveal no dramatic differences between responders and nonresponders. Although emergence of nausea outweighed remission among responders, the contrast with nonresponders was negligible ($w = 0.07$). Headache showed a balance toward improvement only in responders. There was no difference in emergence of being overactive/excited/elated, but remission of these symptoms was largely restricted to nonresponders. The greatest group difference was in skin rash/itch/irritation, which failed to emerge in any nonresponder; overall, however, both nonresponders and responders reported reduced skin irritation.

DISCUSSION

A difficulty in interpreting this multisymptom survey of side effects lies in the criteria for ascertaining a clinically or statistically significant outcome. The items are not mutually exclusive (e.g., nausea and diarrhea), and, given 88 items, statistical correction for multiple testing would prevent detection of even prominent side effects. Instead, we have focused attention on the effect size of changes. The SAFTEE was designed with drug side effects in mind. Thus, it might overlook some light-related symptoms that would be reported spontaneously or clinically observed. However, the SAFTEE does include most side effects reported in previous light therapy studies, although equivalences may be inexact (e.g., feeling "wired"[8,9] vs. jumpiness/jitteriness and irritability). Some side effects may fluctuate, and thus be underreported in a snapshot posttreatment evaluation, although the 1-week window of the SAFTEE matches that of standard depression rating scales, including the SIGH-SAD[28] administered to these patients.[5]

After 10 to 14 days of light therapy, 9 symptoms emerged with frequencies greater than 10%, 17 symptoms greater than 8%, and 27 symptoms greater than 5% (see Table 2). Several of these are troublesome side effects (e.g., nausea, headache). They fall into 2 classes, depending on corresponding remission rates, as follows: (1) Greater emergence than remission: nausea, for example,

showed a distinct balance toward emergence and should be considered a direct side effect of light exposure. Indeed, emergence was accentuated in responders, with 18% frequency (see Table 4). (2) Greater remission than emergence: headache, for example, showed a distinct balance toward remission (see Table 2). Since nonresponders were more likely to show headache, it may represent exacerbated depression or a direct light-induced side effect. When describing potential side effects to patients, the risk of emergence needs to be weighed against the likelihood of improvement.

For several of the symptoms studied, emergence represents a treatment benefit (e.g., weight loss against a baseline of weight gain). One surprise was the large improvement in skin rash/itch/irritation. The SAFTEE does not adequately characterize such irritation or localize it to light-exposed or unexposed skin. Although improvement may reflect reduction in anxiety-related dermatitis or dermatosis (J. Prystowsky, Ph.D., M.D., oral communication, November 1998), it was also strongly evident in nonresponders.

A distinct set of nondepressive ocular symptoms also showed large improvement (eye swelling, blurred vision, "poor" vision, and "light bothersome to eyes"; see Table 2). These results are surprising considering earlier reports of exacerbation of ocular symptoms under bright light,[8,9,19–21] although 2 studies also noted improvement in other patients.[9,20] Since improvement was found in both responders and nonresponders, it appears to be independent of the antidepressant effect. In one case, a patient with best-corrected visual acuity of 20/200 (V_{SC}) and 20/25 (V_{CC}) was able to stop using prescription lenses after many years. If such results are sustained using objective measurements rather than self-ratings, a distinct, new application for light therapy might be identified. In a recent study by the authors,[33] the photopic (cone-mediated) visual threshold of SAD patients, but not of normal controls, decreased significantly from winter to summer, which may be due to the seasonal increase in light exposure.[33] Indeed, animal research suggests that the cones rely on adequate light stimulation to maintain viability and that prolonged darkness serves to degrade or even destroy normal cone function.[34] In "syntonic" optometry, colored lights have long been used in training regimens to improve visual sensory performance,[35] although controlled clinical trials are lacking.

The spontaneous seasonal contrast in SAFTEE symptoms provides further insight into light-treatment–related side effects. In paired comparisons of springtime symptom frequencies (after remission of the depression) and winter frequencies (at baseline, while depressed), the only symptoms to predominate in spring were being overactive/excited/elated, increased sexual interest, and weight and appetite decrease.[36] We compared data for the 40 treatment responders who also completed a spring evaluation. For each item, we computed the conditional probability of being symptomatic after treatment given that the symptom was absent in the spring (treatment emergence relative to spring), and being symptomatic in spring given that the symptom was absent after treatment (springtime emergence relative to treatment). Five of the 12 side effects listed in Tables 3 and 4 (eye irritation, abdominal discomfort, skin rash/itch/irritation, jumpiness/jitteriness, late insomnia) showed similar rates of treatment and springtime emergence and thus appear unrelated to artificial light exposure. However, 7 symptoms emerged more often after treatment: headache, nasal congestion, shortness of breath, nausea, diarrhea, initial insomnia, and jumpiness/jitteriness. Of these, nausea was the most prominent ($w = 0.88$). Nasal congestion is more likely associated with the winter season than with treatment.

The particular pattern of side effects to bright light may be influenced by the apparatus configuration and treatment parameters (e.g., timing and dose). It will be difficult to make generalizations about light therapy unless a common core of symptoms is found across procedures; for example, nearly all studies have noted nausea. One seeks apparatus and therapeutic regimens that maximize the antidepressant response while minimizing side effects. Because high-intensity light box exposure (10,000 lux) provides treatment more efficiently than lower intensity (2500 lux),[23] a key objective is to reduce headache and ocular disturbance, especially aversive visual glare. Bright light from horizontally positioned light boxes and ones tilted upward toward the eyes—both are common in commercial designs—induce greater perceptual glare than boxes with a downward tilt. Light boxes with smaller illuminating surfaces, bordered by a relatively dark periphery in the visual field, induce more glare than larger boxes. Lamps of high color temperature with a balance toward blue induce more glare and visual disturbance than lamps balanced toward longer wavelengths.[7] Indeed, specific blue-blocking filters provide marked glare reduction and increased perceptual brightness and acuity while barely affecting illuminance (lux level).[37,38] We have used such lenses beneficially in open treatment of photophobic and headache-prone patients. The diffusing screen in a light box affects glare according to its refraction properties. Commonly used prismatic surfaces, for example, are inferior to surfaces with textured sur-

faces or flat, smooth white sheets. Diffusers also differ markedly in their transmission of visible wavelengths and short wavelength cutoffs.[7]

None of the side effects reported has caused sufficient disturbance for more than a few patients to discontinue treatment. The single patient who experienced mania, who was not part of this study, resumed use of lights after beginning lithium treatment. The combination of light therapy with mood stabilizers is now common in open treatment of bipolar I patients with SAD and nonseasonal depression.[22,39] Posttreatment nausea was rarely severe (82% of our subjects were asymptomatic; 11% reported mild disturbance; 4%, moderate disturbance; and 3%, "quite a bit" or extreme disturbance). Although headache remitted more often than it emerged, it can present a serious impediment to treatment for those affected. In open treatment, dose reduction (session duration or light intensity) can alleviate or eliminate headache, but there have been several intractable cases. Even with dose reduction, 2 of our patients (who were not subjects in this study) have experienced continued difficulty: one had to discontinue treatment, while the other continued when the frequency of headache fell by half.

In summary, bright light therapy for SAD—using a 10,000 lux UV-shielded, diffused white fluorescent light from a downward-tilted light box, 30 minutes daily for 2 weeks (and longer)—meets 3 essential criteria for use in clinical practice: (1) specific antidepressant efficacy as gauged against placebo controls,[5,23] (2) lack of clinically significant ocular changes,[25] and (3) a favorable side effect profile.

Drug name: trimipramine (Surmontil).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

REFERENCES

1. Rosenthal NE, Sack DA, Gillin C, et al. Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. Arch Gen Psychiatry 1984;4:72–80
2. Lam RW, Zis AP, Grewal AK, et al. Effects of tryptophan depletion in patients with seasonal affective disorder in remission with light therapy. Arch Gen Psychiatry 1996;53:41–44
3. Lewy AJ, Sack RL, Miller LS, et al. Antidepressant and circadian phase-shifting effects of light. Science 1987;235:352–354
4. Eastman CI, Young MA, Fogg LF, et al. Light therapy for winter seasonal affective disorder is more than a placebo. Arch Gen Psychiatry 1998;55: 883–889
5. Terman M, Terman JS, Ross DC. A controlled trial of timed bright light and negative air ionization for treatment of seasonal affective disorder. Arch Gen Psychiatry 1998;55:875–882
6. Wirz-Justice A, Bucheli C, Graw P. Light treatment of seasonal affective disorder in Switzerland. Acta Psychiatr Scand 1986;74:193–204
7. Reme CE, Rol P, Grothmann K, et al. Bright light therapy in focus: lamp emission spectra and ocular safety. Technol Health Care 1996;4:403–413
8. Rosenthal NE, Moul DE, Hellekson CJ, et al. A multicenter study of the light visor for seasonal affective disorder: no difference in efficacy found between two different intensities. Neuropsychopharmacology 1993;8: 151–160
9. Levitt AJ, Joffe RT, Moul DE, et al. Side effects of light therapy in seasonal affective disorder. Am J Psychiatry 1993;150:650–652
10. Chan PKY, Lam RW, Perry KF. Mania precipitated by light therapy for patients with SAD [letter]. J Clin Psychiatry 1994;55:454
11. Schwitzer J, Neudorfer C, Blecha H-G, et al. Mania as a side effect of phototherapy. Biol Psychiatry 1990;28:532–534
12. Kripke DF, Mullaney DJ, Lauber MR, et al. Controlled trial of bright light for nonseasonal major depressive disorders. Biol Psychiatry 1992;31: 119–134
13. Praschak-Rieder N, Neumeister A, Hesselmann B, et al. Suicidal tendencies as a complication of light therapy for seasonal affective disorder: a report of three cases. J Clin Psychiatry 1997;58:389–392
14. Lam RW, Tam EM, Shiah I-S, et al. Effects of light therapy on suicidal ideation in patients with winter depression. J Clin Psychiatry. In press
15. Muller MJ, Seifritz E, Hatzinger M, et al. Side effects of adjunct light therapy in patients with major depression. Eur Arch Psychiatry Clin Neurosci 1997;247:252–258
16. Campbell SS, Dijk D-J, Boulos Z, et al. Light treatment for sleep disorders: consensus report, III: alerting and activating effects. J Biol Rhythms 1995;10:113–128
17. Oren DA, Shannon NJ, Carpenter CJ, et al. Usage patterns of phototherapy in seasonal affective disorder. Compr Psychiatry 1991;32:147–152
18. Volz HP, Mackert A, Stieglitz RD. Side-effects of phototherapy in nonseasonal depressive disorder. Pharmacopsychiatry 1991;24:141–143
19. Labbate LA, Lafer B, Thibault A, et al. Side effects induced by bright light treatment for seasonal affective disorder. J Clin Psychiatry 1994;55: 189–191
20. 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
21. Kogan AO, Guilford PM. Side effects of short-term 10,000-lux light therapy. Am J Psychiatry 1998;155:293–294
22. Terman M, Terman JS, Williams JBW. Seasonal affective disorder and its treatments. J Pract Psychiatry Behav Health 1998;5:287–303
23. Terman JS, Terman M, Schlager D, et al. Efficacy of brief, intense light exposure for treatment of winter depression. Psychopharmacol Bull 1990; 26:3–11
24. Terman M, Reme CE, Rafferty B, et al. Bright light therapy for winter depression: potential ocular effects and theoretical implications. Photochem Photobiol 1990;51:781–793
25. Gallin PF, Terman M, Reme CE, et al. Ophthalmologic examination of patients with seasonal affective disorder, before and after bright light therapy. Am J Ophthalm 1995;119:202–210
26. National Institute of Mental Heath. Systematic Assessment for Treatment Emergent Effects (SAFTEE). Rockville, Md: National Institute of Mental Health; 1986
27. Rosenthal NE, Sack DA, Carpenter CJ, et al. Antidepressant effects of light in seasonal affective disorder. Am J Psychiatry 1985;142:163–170
28. Williams JBW, Link MJ, Terman M, et al. Structured Interview Guide for the Hamilton Depression Scale-Seasonal Affective Disorder Version (SIGH-SAD), rev. ed. New York, NY: New York State Psychiatric Institute; 1998
29. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988
30. Terman M, Lewy AJ, Dijk D-J, et al. Light treatment for sleep disorders: consensus report, IV: sleep phase and duration disturbances. J Biol Rhythms 1995;10:135–150
31. Goel N, Terman M, Terman JS, et al. Summer mood in winter depressives:

validation of a structured interview. Depress Anxiety 1999;9:83–91
32. Terman M, Amira L, Terman JS, et al. Predictors of response and nonresponse to light treatment for winter depression. Am J Psychiatry 1995;153: 1423–1429
33. Terman M, Terman JS. Photopic and scotopic light detectability in patients with seasonal affective disorder and normal controls. Biol Psychiatry. In press
34. Reme CE, Wirz-Justice A, Terman M. The visual input stage of the mammalian circadian pacemaking system, I: is there a clock in the mammalian eye? J Biol Rhythms 1991;6:5–29
35. Liberman J. The effect of syntonic (colored light) stimulation on certain visual and cognitive functions. Int J Biosocial Res 1986;8:169–184
36. Terman M. On the specific action and clinical domain of light treatment. In: Lam RA, ed. Seasonal Affective Disorder and Beyond: Light Treatment of SAD and Non-SAD Conditions. Washington, DC: American Psychiatric Press; 1997:91–115
37. Zigman S. Vision enhancement using a short wavelength light-absorbing filter. Optom Vis Sci 1990;67:100–104
38. Zigman S. Light filters to improve vision. Optom Vis Sci 1992;69: 325–328
39. Kripke DF. Light treatment for nonseasonal depression: speed, efficacy, and combined treatment. J Affect Disord 1998;49:109–117