Insurance Reimbursement Information Kit:

Most major insurance companies now authorize or reimburse the purchase of light therapy equipment for Seasonal Affective Disorder (SAD) To improve your chances of receiving reimbursement for your light therapy device, make sure to send your insurance company the following documents/articles:

- Prescription from your psychiatrist or general practitioner
- Invoice from Apollo for the light therapy device
- Letter of medical necessity (included in this packet). See instructions with letter
- Your own cover letter to the insurance company (See below.)
    - Include all pertinent member information, policy #, referring physician and his/her number, date of service, and invoice for light therapy device.

Additional necessary information is also included in this packet:

- HCPCS and Procedure Codes for SAD.
- Abstracts from professional journals (on reverse side of letter of medical necessity).
- *"Beginning to See the Light"* article from Archives of General Psychiatry.
- *"Medical Reimbursement for Light Therapy"*, from the American Journal of Psychiatry; A case history of the cost effectiveness of light therapy vs. medication
- *"The Efficacy of Light Therapy in the Treatment of Mood Disorders: A Review and Meta-Analysis of the Evidence"* from the American Journal of Psychiatry
- *Efficacy of Light Therapy*: Official recommendations and references for light therapy.

The American Journal of Psychiatry article (*Efficacy*) is a current review of all light therapy studies, and officially recommends light for SAD. Because of this article, most insurers now accept light therapy as the treatment of choice. The Archives article is also perfect for sending to insurance companies. It is from the AMA and states that, "Light is now recommended as the treatment of choice for SAD. "Highlight these statements and also write at letter to your insurance that says something like this:

To Whom it May Concern:

My doctor has prescribed the use of a 10,000-lux lightbox for the treatment of Seasonal Affective Disorder (DSMIV 296.3). The American Psychiatric Association recommends light therapy as the treatment of choice for SAD (See attached article: Am J. of Psychiatry 2006). The American Academy of Sleep Medicine and the U.S. Public Health Service Agency for Health Care Policy and Research also recommend light therapy (See attachment). Please review this request for reimbursement.

Sincerely,

(Your Name)

Relevant Codes:

HCPCS Code:

E0203:	Therapeutic lightbox, 10,000 lux tabletop model
A4634:	Replacement bulb for therapeutic lightbox, tabletop model

CPT Code: 96900

ICD-9 Diagnosis Code:

296.00 – 296.99	Affective psychosis
300.4	Neurotic depression
301.10-301.13	Affective personality disorder
311	Depressive disorder, not elsewhere classified

Letter of Medical Necessity: See following page

Below is an example of a letter of medical necessity that might be sent (taken from Rosenthal, Norman E. *Winter Blues; Seasonal Affective Disorder What It Is and How to Overcome It*. New York: The Gillard Press, 1993). This letter is for the doctor/medical professional to fill out. It describes the symptoms and proper diagnosis for SAD. It also describes the cost effectiveness over conventional antidepressant medication.

To whom it may concern,

This is to certify that has been a patient of mine since_____, 20____. I have treated him/her for recurrent major depressions (DSM-IV 296.3), with a seasonal pattern. This condition, also known as Seasonal Affective Disorder (SAD), has been shown in many studies in the United States and elsewhere in the world to respond to treatment with bright environmental light (light therapy). Light therapy is no longer considered experimental, but is a mainstream type of psychiatric treatment, described in the *Task Force Report of the American Psychiatric Association: Treatment of Psychiatric Disorders*, Vol. 3, pages 1890-1896, APA Press, 1989. In order to administer light therapy adequately, a quality light box, such as the Apollo Brite Lite or goLITE is required (see attached invoice).

Although a light box is an expensive piece of equipment, the experience of clinicians who have used it for many patients indicates that it saves a great deal of money in the long run, by reducing the number of doctors' visits and laboratory investigations of persistent symptoms, as well as the indirect costs of lost productivity. I contend that in _____'s case the use of the Brite Lite or goLITE should be regarded not only as a medical necessity, to be used in preference to (or in addition to) other forms of treatment, but also as a means of reducing his/her overall medical costs.

Sincerely,

Efficacy of Light Therapy

In the 20 years since the initial discovery of light therapy and circadian rhythms, thousands of studies involving several thousand participants have demonstrated the validity of light therapy for the treatment of these chronobiological disturbances.[i] [ii] Dozens of medical journals report on the efficacy of light therapy (See appendix for a partial list). The National Institute of Health as well as major research universities and medical associations have established light therapy as a mainstream medical treatment. [iii] [iv] [v] [vi] [vii] [viii] These studies have been confirmed through multiple independent replications of placebo-controlled trials. Most northern US hospitals, and all Canadian hospitals have SAD clinics.

Treatment of Choice

Reviews in Archives of General Psychiatry, JAMA and other medical journals recommend light therapy as the treatment of choice SAD.[ix x xi xii xiii] Light is generally recommended first because of the quick response and high response rate. Most patients respond within a week. Although some studies show response rates as high as 90%, large clinical trials show response rates of 65% and 75%.[xiv xv] Another reason light is preferred is that it is more effective than drugs or other treatments and side effects are more benign and better tolerated.[xvi xvii] One recent journal concluded, "[Light] meets 3 essential criteria for use in clinical practice: (1) specific antidepressant efficacy as gauged against placebo controls, (2) lack of clinically significant ocular changes, and (3) a favorable side effect profile.[xviii]

Official Recommendations

SAD and its treatment are described in the DSM IV.[xix] Light therapy is also recommended by the Society for Light Treatment and Biological Rhythms (SLTBR),[i xx] the U.S. Public Health Service Agency for Health Care Policy and Research,[xxi] [xxii]American Psychiatric Association,[xxiii] and the American Academy of Sleep Medicine (for sleep disturbances).[xxiv] The American Medical Association is currently reviewing recommendation guidelines for its Recognition Program.[xxv]

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[i] National Library of Medicine search on 'Circadian Rhythms' and 'Light Therapy'. February 2004. Source: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

[ii] Kripke, D. Estimating Circadian Rhythm and Light Therapy Studies on Patients. Correspondence with Apollo February 19, 2004

[iii] Terman M. et al. Light therapy for seasonal affective disorder. A review of efficacy. Neuropsychopharmacol 1989;2:1-22

[iv] Blehar MC. et al. Seasonal mood disorder: Consensus and controversy. Psychopharmacol Bull 1990; 26:465-494

[v] Lam RW. et al. Phototherapy for depressive disorders: A review. Can J Psychiatry 1989; 34:14-147

[vi] Rosenthal NE et al. (eds): Seasonal Affective Disorders and Phototherapy. New York, Guilford, 1989

[vii] Thompson C, et al. (eds): Seasonal Affective Disorders. London, CNS, 1989

[viii] Society for Light Treatment and Biological Rhythms: Consensus statement on the efficacy of light treatment for SAD. Light Treatment and Biol Rhythms 1990;3:5-9

[ix] Depression Guideline Panel. *Depression in Primary Care: Volume 2. Treatment of Major Depression.* Washington, DC: Agency for Health Care Policy and Research. Dept of Health and Uman Services; 1993. Publication 93-0551.

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i The SLTBR was formed in 1990 by medical researchers and manufacturers to determine the effectiveness and safety of light therapy. The SLTBR holds annual conferences, offers CME credit and publishes studies on light therapy in the *Journal of Biological Rhythms* and *Chronobiology International* as well as other medical journals.

[x] Rsenthal NE. Diagnosis and treatment of seasonal affective disorder. JAMA. 1993;270:2717-2720
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[xii] Lamburg, L. Dawn's early light to twilight's last gleaming. JAMA 1998; 280:1556-1558
[xiii] Singer, EA. Seasonal affective disorder: Autumn onset, winter gloom (Board Review). Clinician Reviews 2001; 11: Issue 11
Lam, R. et al. Light therapy for depressive disorders: Indications and efficacy. Mod Probl Pharmacopsychiatry 1997; 25:215-234
[xiv] Lam R, Levitt A. (eds): Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder. Clinical and Academic Publishing
[xv] Partonin T. Light Therapy. In: Partonen, T, eds. Seasonal Affective Disorder. Oxford UK: Oxford University Press, 2001 65-78
[xvi] Lam, R. et al. (ed): Light therapy for depressive disorders: Indications and efficacy. In: Mood Disorders. Systematic Medication Management. Mod Probl Pharmacopsychiatry Basel Karger 1997; 25:215-234
[xvii] Wirz-Justice, A.
[xviii] Terman M, Terman JS. Bright Light Therapy: Side effects and benefits across the spectrum. J Clin Psychiatry. 1999;60:799-808
[xix] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision, Washington DC: American Psychiatric Association; 2000:356,365,427
[xx] Society for Light Treatment and Biological Rhythms. Consensus statements on the safety and effectiveness of light therapy of depression and disorders of biological rhythms. Light Treatment Biol Rhythms. 1991;3:45-50
[xxi] Terman M, Terman JS. Light therapy for Winter Depression: Report to the Depression Guidelines Panel USPHS Agency for Health Care Policy and Research. New York, NY: New York State Psychiatric Institute; 1991
[xxii] Agency for Health Care Policy and Research. Depression in Primary Care: Treatment of Major Depression. Clinical Practice Guideline No. 5. Rockville, Md: US Department of Health and Human Services; 1993
[xxiii] American Psychiatric Association. Practice guideline for major depressive disorder in adults. Am J Psychiatry. 1993;150(suppl):1-26
[xxiv] Chesson AL, et al. Practice parameters for the use of light thrapy in the treatment of sleep disorders. Sleep. 1999;22:641-660
[xxv] Terman M, Terman JS. Light Therapy. In: Kryger MH, Roth T, Dement WC, eds. Principles and Practices of Sleep Medicine. Philadelphia, W.B. Saunders, 2000;1258-1274

The Efficacy of Light Therapy in the Treatment of Mood Disorders: A Review and Meta-Analysis of the Evidence

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Objective: The purpose of this study was to assess the evidence base for the efficacy of light therapy in treating mood disorders.

Method: The authors systematically searched PubMed (January 1975 to July 2003) to identify randomized, controlled trials of light therapy for mood disorders that fulfilled predefined criteria. These articles were abstracted, and data were synthesized by disease and intervention category.

Results: Only 13% of the studies met the inclusion criteria. Meta-analyses revealed that a significant reduction in depression symptom severity was associated with bright light treatment (eight studies, having an effect size of 0.84 and 95% confidence interval [CI] of 0.60 to 1.08) and dawn simulation in seasonal affective disorder (five studies; effect size=0.73, 95% CI=0.37 to 1.08) and with bright light treatment in nonseasonal depression (three studies; effect size=0.53, 95% CI=0.18 to 0.89). Bright light as an adjunct to antidepressant pharmacotherapy for nonseasonal depression was not effective (five studies; effect size=–0.01, 95% CI=–0.36 to 0.34).

Conclusions: Many reports of the efficacy of light therapy are not based on rigorous study designs. This analysis of randomized, controlled trials suggests that bright light treatment and dawn simulation for seasonal affective disorder and bright light for nonseasonal depression are efficacious, with effect sizes equivalent to those in most antidepressant pharmacotherapy trials. Adopting standard approaches to light therapy's specific issues (e.g., defining parameters of active versus placebo conditions) and incorporating rigorous designs (e.g., adequate group sizes, randomized assignment) are necessary to evaluate light therapy for mood disorders.

(Am J Psychiatry 2005; 162:656–662)

The development of light therapy in psychiatry is closely intertwined with the original description of the syndrome of seasonal affective disorder. Two decades ago, Rosenthal and colleagues (1) described a series of patients with histories of recurrent depressions that developed in the fall or winter and spontaneously remitted during the following spring or summer. Their initial report also included preliminary findings indicating that bright artificial light, administered in a manner that would in essence extend the photoperiod, was more effective than dim light in treating seasonal affective disorder. The article presented an underlying hypothesis about the pathophysiology of the syndrome (i.e., depressogenic effects of melatonin), which in turn shaped the selection of treatment parameters: the intensity, duration, and timing of bright light exposure were designed to suppress the release of melatonin and lengthen the photoperiod.

Both seasonal affective disorder and bright light therapy quickly captured considerable attention, both in the scientific community and with the general public. Several research groups launched clinical trial programs, and soon this experimental treatment was extended to other conditions, including nonseasonal mood disorders, Alzheimer's disease, circadian-related sleep disorders and jet lag, eating disorders, and other behavioral syndromes (2, 3). An international organization (the Society for Light Treatment and Biological Rhythms) was created, and several journals that emphasized phototherapy and biological rhythms emerged. Despite the growth in clinical and research programs, there remained an absence of recognition and support for light therapy within many segments of the psychiatric treatment community. Most insurers do not offer reimbursement for this treatment, most residency training programs do not provide clinical training in phototherapy, and there is a sense that "the biological psychiatry establishment has regarded light therapy with a certain disdain and relegated it to the edge of the paradigm" (4).

The American Psychiatric Association (APA) Council on Research requested that the APA Committee on Research on Psychiatric Treatments use the principles of evidence-based medicine to examine the efficacy of light therapy (J. Greden, personal communication). A work group was formed from members of the committee as well as outside consultants with expertise and experience in relevant disciplines. The work group completed a comprehensive literature review and meta-analyses. This report contains our findings about the efficacy of light therapy in the treatment of mood disorders in adult patients.

Method

Search Strategy

We searched PubMed for medical literature published from Jan. 1, 1975, to July 25, 2003. The search terms included "phototherapy" (which was the original term applied to light therapy) and any of the following terms: 1) "seasonal affective disorder"; 2) "depressive disorder"; 3) "bipolar disorder"; 4) "sleep" or "sleep disorder"; 5) "circadian rhythm" or "jet lag" or "melatonin"; 6) "Alzheimer's disease" or "dementia"; 7) "premenstrual dysphoric disorder" or "premenstrual syndrome" or "late luteal phase dysphoric disorder"; 8) "eating disorder" or "bulimia" or "obesity"; 9) "serotonin"; and 10) "attention" or "vigilance" or "reaction time." We limited our search strategy to clinical trials reported in English. We supplemented these sources by using the same search terms in MEDLINE, searching the Cochrane Collaboration Library, and searching the bibliographies of prior reviews and relevant original articles. In this article, we present our findings for studies of light therapy for mood disorders.

Selection Criteria

Study groups were limited to adults who met a criterion-based mood disorder diagnosis. We restricted the age range to 18–65 years in an effort to define a standard for adequate treatment. We recognized that at each end of the age spectrum, the requirements for light therapy dosing may differ. For example, children and adolescents may differ from adults in the needed dose of light therapy, while elderly patients may require a higher dose of photons given the normal age-related clouding of the lens and ocular media, as well as possible reduction in the number of retinal photoceptors in that population. Accepted criterion standards were DSM-III, DSM-III-R, DSM-IV, the Research Diagnostic Criteria (5), and the Rosenthal criteria (1). Subsyndromal diagnoses were excluded.

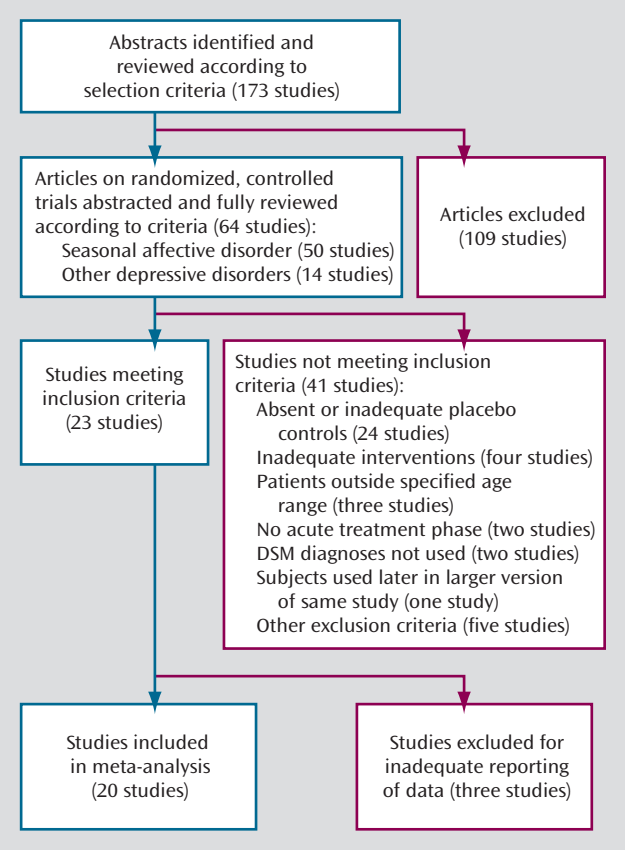
The included studies were required to be randomized, controlled trials of patients in the acute phase of treatment and to have a credible placebo control condition. Defining a minimum treatment dose (lux by time) for the experimental bright light treatment intervention was complicated by the absence of an accepted standard definition of adequate dosing. In some studies, we found that the "placebo condition" consisted of light exposure that was greater than that for the "active condition" in other studies. After we reviewed standard textbooks and consulted with expert clinicians in the field, we arrived at a priori definitions of adequate light therapy dose and duration. For bright light treatment of seasonal affective disorder, the definition was a minimum of 4 days of at least 3,000 lux-hours (e.g., 1,500 lux for 2 hours or 3,000 lux for 1 hour). We required placebo comparison groups to receive a maximum of 300 lux. For dawn simulation studies, we required that the active intervention consist of increasing light exposure from 0 to 200–300 lux over 1.0–2.5 hours and that the placebo condition consist of an increase that was less than 5 lux and/or less than 15 minutes in duration. For studies of bright light augmentation, we applied the same minimum lux criteria as those for bright light treatment of seasonal affective disorder and required that bright light therapy was the primary adjunct to the standard treatment under investigation.

We required that the outcomes be psychiatric symptom measures, e.g., Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (6). Studies were excluded if gross protocol violations occurred (e.g., the study design was changed during the course of the trial).

Study Selection Process

Selection of the studies for inclusion involved two steps. First, two authors (R.N.G. and B.N.G.) independently reviewed the abstracts of all articles identified by the literature searches and excluded those for which they agreed that the eligibility criteria were not met. Next, the remaining articles were abstracted in detail (as described in the following) and the two authors made a final decision about inclusion or exclusion by consensus.

FIGURE 1. Selection of Studies for Meta-Analysis of Trials of Light Therapy for Mood Disorders



A total of 173 articles were identified and reviewed according to the selection criteria. This first step produced potentially relevant articles reporting 64 randomized, controlled trials (Figure 1). Of these, 50 involved patients with seasonal affective disorder and 14 involved patients with other depressive illnesses. These 64 trials received detailed abstraction, including clarification of subject group and selection, study design characteristics, and intervention parameters, to determine final eligibility. In addition, baseline demographic information and psychiatric outcome data were collected to allow direct comparisons of the experimental and control groups.

Data Analysis

All studies meeting the inclusion criteria were grouped by disorder and treatment type to produce four categories: bright light for seasonal affective disorder, bright light for nonseasonal depression, dawn simulation for seasonal affective disorder, and bright light as adjunctive treatment combined with conventional antidepressant pharmacotherapy for nonseasonal depression. The statistical information required for inclusion of a trial consisted of the mean score and standard deviation on a psychiatric symptom outcome measure and the number of subjects for each treatment condition; a trial was also included if the report contained sufficient information from which we could calculate the preceding data. For the articles in which the reported statistical detail was inadequate to allow meta-analytic procedures, several attempts were made to contact the corresponding author to gain

TABLE 1. Randomized, Controlled Trials of Bright Light and Dawn Simulation in the Treatment of Mood Disorders

Treatment, Diagnosis, and Study	Duration of Trial (days)	Experimental Group				Control Group				Effect Size
		Condition	Illuminance (lux)	Time (hours/day)	Number of Patients	Condition	Illuminance (lux)	Time (hours/day)	Number of Patients	
Bright light										
Seasonal affective disorder										
Avery et al., 2001 (9)	42	White light	10,000	0.5	33	Red light	0.5	1.5	31	0.09
Eastman et al., 1998 (10)	24	White light	6,000	1.5	49	Deactivated negative air ionizer		1.5	22	0.19
Michalon et al., 1997 (11)	14	White light	2,500	2.0	15	Red light	<300	2.0	14	1.53
Rosenthal et al., 1984 (1)	14	White light	2,500	6.0	9	Yellow light	100	6.0	9	2.08
Rosenthal et al., 1985 (12)	7	White light	2,500	6.0	13	Yellow light	≤300	6.0	13	1.19
Rosenthal et al., 1987 (13)	7	White light	2,500	5.0	7	White light	≤300	5.0	7	2.11
Schwartz et al., 1997 (14)	21	White light	10,000	1.5	17	Active light avoidance (dark goggles outdoors)			17	2.01
Terman et al., 1998 (15)	10–14	White light	10,000	0.5	85	Negative ion density (1.0×10^4 ions/cm^3)		0.5	19	1.05
Nonseasonal depression										
Baumgartner et al., 1996 (16)	7	White light	2,500	2.0	19	Red light	50	2.0	15	0.40
Kripke et al., 1992 (17)	7	White light	>2,000	3.0	25	Red light	<50	3.0	26	0.78
Volz et al., 1991 (18)	7	White light	2,500	2.0	22	Red light	50	2.0	20	0.35
Dawn simulation for seasonal affective disorder										
Avery et al., 1992 (19)	7	White light ("gradual dawn")	0–275	2.5	9	White light ("rapid dawn")	0–275	0.2	9	0.25
Avery et al., 1993 (20)	7	White light ("gradual dawn")	0–250	2.0	13	White light ("rapid dawn")	0–0.2	0.5	9	1.16
Avery et al., 1994 (21)	7	White light ("gradual dawn")	0–250	1.5	10	Red light	0–2	1.5	9	1.10
Avery et al., 1998 (22)	7	White light ("gradual dawn")	0–250	1.5	6	Red light	0–2	1.5	6	1.33
Avery et al., 2001 (9)	42	White light ("gradual dawn")	0–250	1.5	31	Red light	0–0.5	1.5	31	0.54
Bright light as adjunctive treatment of nonseasonal depression										
Beauchemin and Hays, 1997 (23)[a]	7	White light	10,000	2.0	8	White light	2,500	0.5	11	1.31
Fritzsche et al., 2001 (24)[b]	14	White light	2,500	2.0	21	Red light	50	2.0	19	0.09
Holsboer-Trachsler et al., 1994 (25)[c]	16	White light	5,000	2.0	14	No light treatment			14	–0.74
Muller et al., 1997 (26)[c]	28	White light	5,000	2.0	14	No light treatment			14	–0.80
Neumeister et al., 1996 (27)[d]	6	White light	3,000	4.0	10	White light	100	4.0	10	0.81

[a] The other treatments were lithium, valproate, lorazepam, fluoxetine, desipramine, sertraline, clonazepam, haloperidol, benztropine, paroxetine, flurazepam, temazepam, amitriptyline, venlafaxine, zopiclone, diazepam, and pimozide; one patient received no drugs. The subjects continued their medications throughout the trial.

[b] The other treatments were tricyclic antidepressants (N=32), selective serotonin reuptake inhibitors (SSRIs) (N=15), neuroleptics in low doses (N=15), and lithium or carbamazepine (N=6); 10 of the patients were treated with monotherapy and 30 with combinations. The medications were started before the light therapy and kept constant during the trial as much as possible.

[c] All patients received trimipramine beginning 1 week before the light therapy period and continuing throughout the trial.

[d] The other treatments were monotherapy with tricyclic antidepressants (N=6) or SSRIs (N=11) and combinations of these (N=3). The medications were started at least 3 weeks before the beginning of the study and kept constant during the trial.

TABLE 2. Significance of Effect Sizes for Studies of Bright Light and Dawn Simulation in the Treatment of Mood Disorders

Diagnosis and Treatment	Number of Studies	Effect Size	95% CI	p (z test)
Seasonal affective disorder				
Bright light	8	0.84	0.60 to 1.08	<0.0001
Dawn simulation	5	0.73	0.37 to 1.08	<0.0001
Nonseasonal depression				
Bright light	3	0.53	0.18 to 0.89	<0.003
Adjunctive bright light	5	–0.01	–0.36 to 0.34	>0.95

access to the necessary raw data. For articles presenting outcomes from several treatment or control conditions, we pooled and analyzed the resulting statistics within conditions in order to use the largest study group available.

We employed standard meta-analytical methods, as described by Lipsey and Wilson (7). For each study, the standardized mean difference effect size and its 95% confidence interval (CI) were calculated and adjusted with the Hedges correction for small sample bias (8). For each of the four meta-analyses, the weighted mean of the component effect sizes and its 95% CI was calculated with the inverse variance weights from each study. The statistical significance of each weighted mean effect size was tested nondirectionally at the 0.05 level by using the z test.

If the number of subjects was sufficient, we performed homogeneity analyses of our results. If the required data were available, we calculated odds ratios for the likelihood of remission, defined a priori as a final score on the Hamilton Depression Rating Scale of 8 or less. We also applied the Q test, which uses the chi-square distribution to test the homogeneity of effect sizes across studies.

Results

Only 23 of the 173 studies identified during our literature search met our selection criteria (Figure 1). Of these, 20 distinct articles had sufficient data to allow inclusion in our meta-analysis (Table 1). One article (18) appeared to include a subset of patients who had been the subjects in a trial reported earlier (28), so the latter paper was excluded from this analysis. An additional report (9) contained the results of two experiments, one involving light therapy and another involving dawn simulation. Each was included in the appropriate, separate meta-analysis.

The results of the meta-analyses are shown in Table 2. We demonstrated significant effect sizes for bright light treatment of seasonal affective disorder (Figure 2), dawn simulation for seasonal affective disorder (Figure 3), and bright light treatment of nonseasonal depression (Figure 4). The effect size for bright light as an adjunctive treatment for nonseasonal depression was not significant (Figure 5).

Homogeneity analysis of the eight studies of bright light treatment of seasonal affective disorder was performed (for the other three meta-analyses, the number of studies was not large enough to support a Q test). The Q test indicated significant ($p<0.0001$) heterogeneity among studies; however, the effect sizes were consistently positive.

FIGURE 2. Effect Sizes in Studies of Treatment of Seasonal Affective Disorder With Bright Light

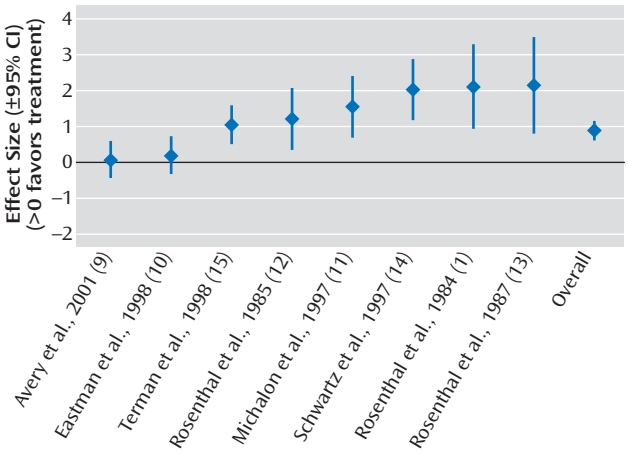
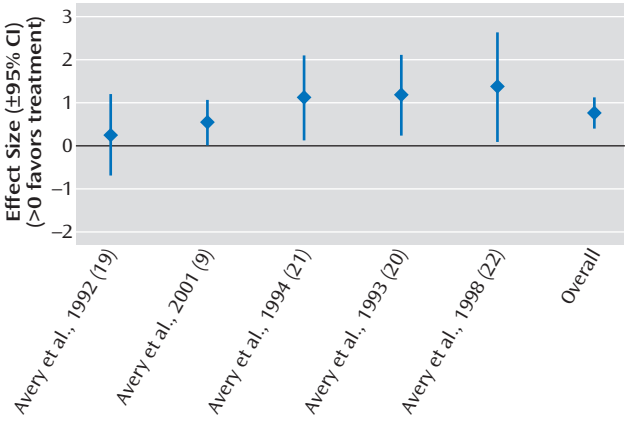


FIGURE 3. Effect Sizes in Studies of Treatment of Seasonal Affective Disorder With Dawn Simulation



Odds ratios and their 95% CIs were calculated for the subset of four studies of bright light treatment of seasonal affective disorder for which the number of subjects who experienced remission was known. The summary estimate of risk of remission given treatment was an odds ratio of 2.9 (95% CI=1.6 to 5.4). The four study-specific odds ratios were significantly heterogeneous ($p<0.04$) but consistently positive.

Discussion

In our literature review, we found that most of the published research reports on the effects of light therapy in mood disorders did not meet recognized criteria for rigorous clinical trial design. There are several potential explanations for this observation. First, there are inherent challenges in creating an acceptable placebo (or even an active control) condition for light therapy. While it is relatively easy to create a placebo pill or capsule that is identical in appearance to an active medication formulation, it is more difficult to "blind" a subject when broad-spectrum intense white light is the active experimental intervention.

FIGURE 4. Effect Sizes in Studies of Treatment of Nonseasonal Depression With Bright Light

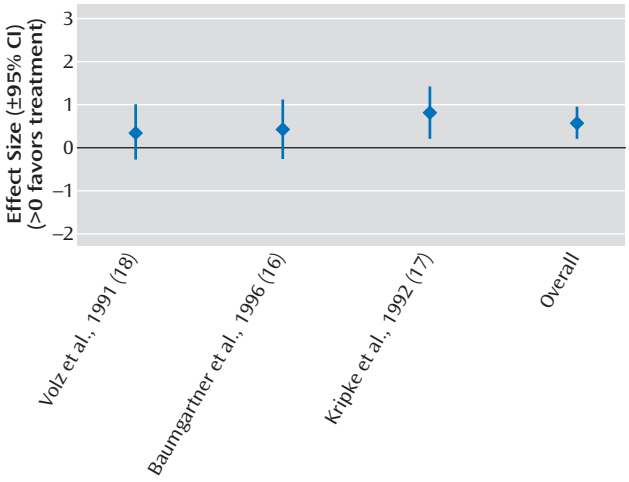
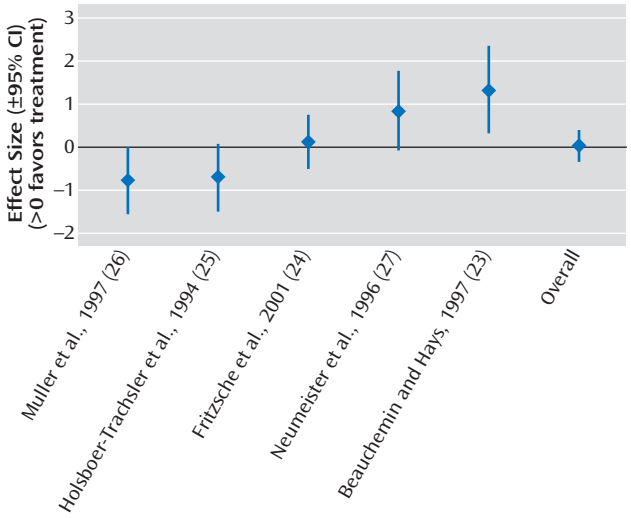


FIGURE 5. Effect Sizes in Studies of Treatment of Nonseasonal Depression With Bright Light as Adjunctive Treatment



The pharmaceutical industry, which has considerable resources devoted to research and development activities, funds much of the clinical trial research for potential new antidepressant pharmacotherapies. In contrast, there has not been a similarly endowed industry nor as sizable a market in place to support the development and testing of light therapy treatments. The history of the development of light therapy, which is inextricably interwoven with the development of the concept of seasonal affective disorder, not surprisingly was dominated in its early stages by a series of relatively small, investigator-initiated pilot projects. These researchers did not have access to resources of the magnitude of those available when pharmaceutical companies seek recognition by the U.S. Food and Drug Administration of the safety and efficacy of a new medication. Unfortunately, a consensus about standard approaches to study design issues (such as lux parameters for the active treatment, duration of an adequate light therapy trial, and characteristics of placebo control conditions) was not established in the early years of light therapy research. In too many cases, high standards of research design (such as random assignment to treatment conditions, adequate reporting of results statistics) were not followed. Not surprisingly, these conditions produced inconsistencies in the research literature. We found substantial variability in the selection of study groups and in the doses of both the active and control interventions for those trials meeting our selection criteria.

All of these factors have limited the conclusions that can be drawn from light therapy research. Past efforts to synthesize the available body of literature have been as challenging as the proverbial comparison of apples and oranges. More important, the limitations in much of the literature on light therapy research may have created the unsubstantiated impression that the treatment itself has limitations in terms of its efficacy.

When we analyzed the data from all available randomized, controlled trials that met our a priori standards, we demonstrated a significant reduction in depression symptom severity following bright light therapy in seasonal affective disorder and in nonseasonal depression, as well as a significant effect with dawn simulation in seasonal affective disorder. In other words, when the "noise" from unreliable studies is removed, the effects of light therapy are comparable to those found in many antidepressant pharmacotherapy trials (29).

Earlier reviews of light therapy yielded similar findings. Terman et al. (30) pooled data from 14 research groups that collectively studied 332 patients who received bright light therapy for seasonal affective disorder over a 5-year period, and they applied a pooled clustering technique in their analysis. Twenty-nine data sets were included. Unfortunately, the vast majority were not available for inclusion in our current analysis, because they consisted of personal communications, unpublished posters presented at meetings, and book chapters, as well as a few additional reports that did not meet our inclusion criteria. Thus, only two of their 29 data sets overlap with the 20 studies included in our meta-analyses, i.e., two studies by Rosenthal et al. (1, 12). Terman et al. (30) found that 2,500-lux light exposure for at least 2 hours/day for 1 week resulted in significantly more remission when administered in the early morning than in the evening or at midday. Treatments at each of these three administration times were significantly more effective than control treatments with dim light. Tam et al. (31) concluded that bright light therapy that utilized at least 2,500-lux white light for 2 hours/day and treatment with 10,000 lux for 30 minutes/day had comparable response rates and that both treatments were efficacious. They noted that more studies were needed before conclusions could be drawn about the efficacy of dawn simula-

tion. They highlighted the methodological limitations of the literature, which included brief treatment periods, small study groups, and lack of replication.

Several caveats and limitations in our review and analyses should be noted. First, we limited our focus to *efficacy* and did not study the other key feature of all treatments, *safety*. Very few reports of the controlled studies contained data on side effects or toxicity. Several side effects of bright light therapy have been described elsewhere, including headache, eye strain, nausea, and agitation (32, 33). To our knowledge, there have been no reports to date of retinal toxicity in association with bright light treatment, and a 5-year follow-up study showed no adverse ocular effects (34). However, some psychotropic medications may increase photosensitivity, and further study of potential adverse effects of combined pharmacotherapy and light therapy is indicated. Light therapy, like other antidepressants, may be associated with a switch to hypomania or mania in vulnerable bipolar patients (35). Other rare potential side effects from bright light treatment may emerge only after the treatment has become more widely applied. Thus, any potential recommendation of light therapy for mood disorders, based on findings of efficacy in our meta-analyses, must be tempered by the acknowledgment that safety must also be considered. This important aspect of light therapy merits careful examination with additional long-term follow-up studies.

Another limitation in this study, as described in our methods section, is that we restricted our analyses to studies of a relatively homogeneous, clearly defined population (i.e., nongeriatric adult patients). There are published reports of light therapy for seasonal affective disorder in children (e.g., references 36 and 37) and for mood disorders in the elderly (38). These important patient populations merit separate consideration, and there is a need for a larger evidence base in these areas. An additional potential application of light therapy lies in the treatment of depression during pregnancy and in the postpartum period, when safe and effective alternatives to pharmacotherapy without potential toxicity for the fetus or newborn would be clearly desirable (39, 40). It should be noted that all of the studies of dawn simulation in our meta-analysis came from a single research group, and confirmation of their findings by others at different locations would be especially important in determining the generalizability of their results. Finally, by setting a reasonably high standard for study inclusion in our meta-analysis, we excluded many of the published reports in this area. One could argue, as Smith et al. (41) did in another context, that many small, "imperfect" studies can "converge on a true conclusion." However, we agree with those who believe that meta-analyses based on flawed studies are not useful and that some bodies of data are inadequate for supporting a proper meta-analysis (42).

This study suggests that certain types of light therapy are effective in the treatment of seasonal affective disorder and other forms of depression. Much of the available literature is limited in terms of study design, and additional randomized, controlled trials with appropriate numbers of subjects are needed. Remaining questions of efficacy, safety, optimum dose, and the proper place of light therapy in the psychiatrist's toolbox may be answered only after investigators in the field define and consistently adhere to standard approaches to essential components, such as definitions of acceptable parameters for active treatment and control conditions.

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Beginning to See the Light

Light is the first treatment in psychiatry to evolve directly out of modern neuroscience. Yet paradoxically, the biological psychiatry establishment has regarded light therapy with a certain disdain and relegated it to the edge of the paradigm—not molecular enough, a bit too Californian-alternative, a bit too media overexposed, merely a placebo response by mildly neurotic middle-aged women who don't like nasty drugs.

But light is as effective as drugs, perhaps more so. Three articles in this issue provide the best evidence to date that light is an effective antidepressant in seasonal affective disorder (SAD).[1-3] Placebo response[4] and nonspecific factors[5] are an issue in all clinical trials: for light therapy, "blindness" is not simply an oxymoron. Many psychiatrists are unaware that the advantage of antidepressant drugs over placebo in controlled trials is so small that only multicenter studies can answer questions of relevance.[4,6,7] That 2 single centers[1,2] in large, controlled, blind trials are able to show that light therapy works better than a convincing placebo is therefore extremely important.

The idea of light therapy came from research into mammalian seasonality, where changes in sleep, eating behavior, and weight, for example, are exquisitely tuned, for each species, to day length at the latitude inhabited.[8] The circadian pacemaker in the suprachiasmatic nuclei acts as a "clock for all seasons": the window of responsivity to light at dawn and dusk is dependent on prior photoperiod.[9] Humans too have retained their intrinsic seasonal responses,[10] though these are mostly masked by splendid isolation in living boxes where lighting and temperature are manipulated at will. Indeed, such "unnatural" behavior may be one of the factors precipitating seasonal mood decline in vulnerable individuals.

In the 15 years since the pioneer National Institute of Mental Health study describing SAD and its treatment by bright light,[11] a remarkable research interest has developed worldwide, not only in the dark northern fastnesses of Alaska, Canada, Scandinavia, and Siberia, but also in India, Italy, Japan, and the inverse winter of the southern hemisphere. Light therapy is widely used, in spite of the skepticism of colleagues who do not "believe" in a syndrome they have never seen (only about 10% of patients with SAD have ever been hospitalized[8]). Since many study patients are recruited via newspaper advertisements, these psychiatrists consider them merely high placebo responders. The new evidence indicates that they are not.

New York, NY, at 41°N, Chicago, Ill, at 42°N, and Portland, Ore, at 45°N: these 3 articles,[1-3] with the largest numbers so far in individual studies, scan the United States from east to west at around the same northerly latitude. In spite of the differences in design, some important correspondences emerge with respect to remission rates (Table).

The 2 placebo-controlled trials[1,2] (what a very cunning idea that negative-ion generator was!) have nearly identical results: both morning and evening light are better than placebo, and morning light is superior to evening light. The third study[3] also demonstrates a morning light superiority but has overall lower improvement rates. In emphasizing the similarities—and not dissecting out why certain differences are found between these populations, or in European studies[12,13]—we have to be cognizant that these comparisons of therapeutic outcome are based on very stringent criteria for remission, not just response, within a rather short time (2-4 weeks). Such stringent criteria, when applied to a 5-week multicenter trial of fluoxetine in patients with SAD, did not differentiate between drug (33%, n=36) and placebo (28%, n=32).[14] Patients with SAD treated with light for 5 weeks tended to remit more (50%, n=20) than those treated with fluoxetine (25%, n=20; P=.10).[15]

The Society for Light Treatment and Biological Rhythms (www.websciences.org/sltbr/) has played an important role in the last decade to establish guidelines, standards, and consensus statements for light

therapy. Light is now recommended as the treatment of choice for SAD.[16,17] However, in spite of international recognition, only in Switzerland has the additional economic argument that light is cheaper than drugs attained government endorsement and mandatory reimbursement by medical insurance. In addition to SAD, new applications for light have recently been summarized in the Society for Light Treatment and Biological Rhythms Task Force commissioned by the American Sleep Disorders Association: for circadian-related sleep disorders, aging and Alzheimer's disease, jet lag, and shift work.[18]

But few psychiatrists have yet recognized that light therapy should be considered a mainstream antidepressant modality. Seasonality of depression can also overlap other diagnoses, such as chronic and intermittent depressions, rapid brief depression, dysthymia, bulimia, premenstrual dysphoric disorder, etc. Long-term follow-up documentation indicates that whereas some patients may flip in and out of modes, most remain seasonally susceptible.[19] There is intriguing preliminary evidence for light treatment beyond SAD.[20] Kripke has carried out a systematic comparison of light and antidepressant drug studies in nonseasonal major depression.[7] He argues that we should routinely prescribe light for nonseasonal depression[7]—at least as a drug adjuvant—even before waiting for results from large multicenter trials (which may not even begin, since there is no industrial interest in them).

We need to separate 2 issues: clinical efficacy of light vs mechanisms of action. These clinical trials[1-3] clearly support the claim that light is antidepressant, rather than elucidating how it works. Interpretation of the available data requires multiple levels of explanation. Light targets a neuroanatomical region (the circadian clock), and the SAD literature provides experimental support for both the "phase-shift hypothesis" and the "too-few-photons hypothesis," rather than the original "photoperiod hypothesis." Circadian and serotonergic hypotheses of the pathophysiological mechanisms of SAD are not incompatible: light also acts on a neurochemical substrate within that clock, the serotonergic input from the median raphe. Here we need further research to tease out mechanisms.

The evidence is in that light is an active neurobiological agent. But light therapy has little chance to be widely and properly used for a variety of ills, as long as it appears to the policymakers and grant-givers to lie uncomfortably between pharmaceutical company neglect (for obvious reasons) and the molecular reductionism of academe. These attitudes strikingly contrast with patients' acceptance of light therapy. Light therapy is easy to administer in outpatient settings, lacks major side effects, and, importantly, is cost-effective. Whatever its mode of action, it demands inclusion in the antidepressant armamentarium, now.

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(*Arch Gen Psychiatry*. 1998;55:861-862)

Neuroleptic Malignant Syndrome and Low-Dose Olanzapine

TO THE EDITOR: Neuroleptic malignant syndrome is a rare yet potentially fatal adverse reaction generally associated with typical neuroleptics (1). Some case reports describe neuroleptic malignant syndrome associated with olanzapine, an atypical neuroleptic, at high doses or when combined with other neuroleptics (2–5). We report on a patient taking a low dose of olanzapine who developed neuroleptic malignant syndrome. Upon his recovery, neuroleptic malignant syndrome recurred after olanzapine was restarted.

Mr. A, an 86-year-old man with an 8-month history of dementia with paranoia, was successfully treated for several months with olanzapine, 5 mg/day, until signs of parkinsonism led to a dose decrease to 2.5 mg/day. Two months later, when the daytime temperature was 96°F, he came to the hospital with uncontrollable shaking, confusion, a temperature of 105.6°F, and significant cogwheel rigidity. Paramedics believed his apartment's temperature had exceeded 110°F. His admission and 2-hour blood pressures were notable for fluctuation: 110/72 mm Hg and 162/62 mm Hg, respectively. The results of laboratory tests included an aspartate aminotransferase level of 72 U/liter (normal=10–47), a creatinine kinase level of 1184 U/liter (normal=45–230), and a mildly elevated cardiac isoenzyme level of 39 U/liter (normal=0–6), with a relative index of 3.3 (normal=0–2.5). Mr. A was diagnosed with myocardial infarction, and olanzapine was suspended, given presumptive neuroleptic malignant syndrome.

By hospital day 5, Mr. A's tremors had resolved, his cogwheel rigidity had minimized, his alertness had improved, his temperature had returned to normal, his creatinine kinase level had decreased to 245 U/liter, and his aspartate aminotransferase level had returned to normal. That night, he was rechallenged with one dose of olanzapine, 2.5 mg. The next morning, he was shaking vigorously, his temperature was 100.6°F, and he was notably more rigid. Olanzapine was discontinued, and his temperature again returned to normal, his tremor disappeared, and his cogwheel rigidity decreased substantially. His creatinine kinase level returned to normal, and he was treated with quetiapine, 25 mg/day, for several days with no signs of neuroleptic malignant syndrome.

This case differs from prior reports of neuroleptic malignant syndrome with olanzapine in that the olanzapine dose was notably lower and olanzapine was not given with other dopamine-blocking agents. The rechallenge symptoms also strengthen the association. Dehydration is a possible risk factor for neuroleptic malignant syndrome, and the overheated apartment may have contributed to it (1). It is unlikely that the patient's symptoms can be attributed to heatstroke, which generally is seen with hypotension and limb flaccidity—not fluctuating blood pressure and rigidity (1). Furthermore, the myocardial infarction does not account for the increased skeletal muscle breakdown, rigidity, tremors, fever, or rechallenge exacerbation. Clinicians should be aware that neuroleptic malignant syndrome can occur with low doses of olanzapine and that extremes of heat may precipitate such cases.

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Medicaid Reimbursement for Light Therapy

TO THE EDITOR: Medicaid does not reimburse patients for light therapy. Dr. Wirz-Justice (1) has commented, "Light is now recommended as the treatment of choice for seasonal affective disorder. However, in spite of international recognition, only in Switzerland has the additional economic argument that light is cheaper than drugs attained government endorsement and mandatory reimbursement by medical insurance." The following case report strikingly illustrates the shortsightedness of that policy.

Ms. A, a 40-year-old Guatemalan woman living in a family shelter with four school-age children, never experienced clinical depression before moving to New York 15 years ago. Since then, she regularly experienced winter depression accompanied by hyperphagia, hypersomnia, and cravings for sweets. These bouts of depression led to her losing a nurse's aide job and being abandoned by her husband. Treatment with venlafaxine, 375 mg/day, and later fluoxetine, 40 mg/day, provided minimal benefit in winter, but there was dramatic improvement in spring and summer. When Ms. A was initially evaluated, she was depressed and ready to drop out of a medical technician training program. We loaned her a 10,000-lux light box, which she used 30 minutes each morning. Within 2 weeks, she improved markedly. Subsequently, she finished her training and began working as a medical technician and living independently.

This case illustrates three major points:

1. Although patients with seasonal affective disorder are rarely ill enough to require hospitalization, their illness can precipitate catastrophic life events. In this case, we believe that seasonal affective disorder led to the loss of the patient's job, her husband, and finally her home.

2. Seasonal affective disorder is underdiagnosed. Despite describing a classic history for seasonal affective disorder and attending several hospital-based psychiatric clinics, our patient was diagnosed with nonseasonal major depression and was treated with antidepressants rather than light therapy. This resulted in a poor response to treatment; it is generally

recognized that light therapy is a more effective treatment than medication for winter depression.

3. Medicaid's policy is clinically and economically wrong for not covering light therapy. A light box costs approximately $200 and will provide treatment for many years. Our patient could not afford the $200 and would not have received the treatment had we not loaned her our light box. New York State Medicaid did pay for her antidepressants—fluoxetine and venlafaxine—which gave minimal relief and cost Medicaid approximately $200 per month ($164 per month for fluoxetine, 40 mg/day, and $212 per month for venlafaxine, 375 mg/day). Thus, Medicaid spent approximately $200 a month to provide an inferior treatment when this same $200 could have provided a light box for a universally accepted preferred treatment modality that would have assisted our patient not just for 1 month but for many years. Medicaid needs to finally "see the light" by including light therapy in its treatment formulary.

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Glucose Dysregulation and Mirtazapine-Induced Weight Gain

TO THE EDITOR: Weight gain, a common side effect of psychotropic medications, may cause diabetes, hyperlipidemia, coronary heart disease, and hypertension (1, 2) and is an important factor in medication noncompliance (3).

Mirtazapine is an atypical antidepressant with noradrenergic and serotonergic activity that blocks alpha 2 autoreceptors and selectively antagonizes serotonin 5-HT_2 and 5-HT_3 receptors. It also blocks histaminergic (H_1) and muscarinic receptors (4). Weight gain associated with mirtazapine treatment has been reported (3, 4) and may be accounted for by its effects on 5-HT_{2c} and H_1 receptors. To our knowledge, this is the first report of glucose dysregulation secondary to mirtazapine-induced weight gain.

Ms. A was 32 years old and had a history of depression and substance abuse. Her episodes of depression induced her to abuse cocaine, marijuana, and alcohol periodically. She took carbamazepine for seizures. Her mother was diabetic. On her first hospital admission for depression, her weight was 70.5 kg (body mass index=26.7 kg/mm^2), a random glucose measurement was 148 mg/dl, and a urine screening was positive for cocaine. At her discharge, mirtazapine, 15 mg at bedtime, was added, and she was referred to an outpatient chemical dependence program. She missed appointments and continued abusing cocaine. Although her mood improved, she experienced headaches, increased appetite, sluggishness, and weight gain.

Ms. A developed blurry vision, fatigue, and nausea, and 5 months after her first admission she was readmitted with severe hyperglycemia (1042 mg/dl) that paralleled her weight gain (to 86.4 kg). Ketoacidosis and other complications were absent. Her hemoglobin A_{1c} level was 10.9%, and the result of testing for antiglutamic acid decarboxylase antibodies was negative. Her insulin, proinsulin, and C-peptide levels were not measured.

She continued taking carbamazepine, she started taking citalopram, and she discontinued mirtazapine therapy. Her glucose levels were controlled with insulin and a diabetic diet. After discharge, metformin was added, as she required less insulin; her mood was stable, and she abstained from cocaine. Her glucose levels were normal, and she gradually lost weight.

Ms. A then discontinued her medications, and 6 months after her second admission, she was readmitted because of cocaine abuse and depression. Her weight was 83.0 kg, and her glucose level was below 160 mg/dl. Carbamazepine, citalopram, and a diabetic diet were resumed. Her fasting glucose level was 119 mg/dl, her insulin level was 23 mU/ml, and her hemoglobin A_{1c} level was 5.9%. Six months later, her weight was 79.2 kg, and a random glucose measurement was 123 mg/dl.

Our patient gained 16 kg in 5 months, severely aggravating her premorbid hyperglycemia, suggesting that obesity was an important risk factor for her glucose dysregulation. Controlled studies should follow, and diabetic patients and those at high risk of developing diabetes should be closely monitored.

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Psychoanalytic Prison

TO THE EDITOR: In his discussion of Franz Alexander in Images in Psychiatry, Judd Marmor, M.D. (1), wrote, "Alexander was a rare psychoanalytic pioneer who, despite a thorough grounding in classical Freudian theory, had the courage, vision, and flexibility to modify his thinking in the light of newer knowledge." This presumably indicates how stifling the intellectual orthodoxy associated with psychoanalysis was, at least at the time that Alexander practiced, rather than constituting faint praise for him.

Reference

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Dr. Marmor Replies

TO THE EDITOR: Dr. Bernadt's presumption is correct. It is difficult in today's more enlightened psychoanalytic atmosphere to realize how stifling and controlling the intellectual psychoanalytic orthodoxy was at the time Alexander began to pub-