Seasonal Affective Disorders and Phototherapy

Report of a National Institute of Mental Health–Sponsored Workshop

Mary C. Blehar, PhD, Norman E. Rosenthal, MD

- This report summarizes presentations made at a National Institute of Mental Health–sponsored workshop dealing with recurrent winter depression, or seasonal affective disorder (SAD), and with phototherapy as its treatment. Workshop participants reviewed major issues in the following areas: (1) diagnosis, clinical characteristics, and epidemiology of the disorder; (2) critical issues in phototherapy research; (3) biologic effects of light and mechanism of action of phototherapy; (4) biologic abnormalities in SAD; and (5) animal models and their applicability to the study of SAD. Most research evidence to date supports the efficacy of phototherapy in the treatment of SAD. However, considerable controversy remains concerning its mechanism of action and the underlying pathophysiology of the disorder. These and other unresolved issues are reviewed, and areas of consensus in the field are identified.

Arch Gen Psychiatry 1989;46:469-474

In the past decade, there has been a rapid expansion of interest in the phenomenon of seasonally recurrent mood disorders, which have been termed winter depression or seasonal affective disorder (SAD). These terms will be used interchangeably throughout the report. Increased clinical and research acceptance of the syndrome is signaled by the recent inclusion in the DSM-III-R of “seasonal pattern” to describe recurrent major depression and bipolar disorder. Work on winter depression has led to a new type of effective therapy for the condition—an exciting development in psychiatry where major new therapies have not been freely forthcoming. The discovery that bright-light treatment alleviates depressive symptoms in SAD has led investigators to postulate a variety of theories, mainly involving the circadian system, to explain not only the therapeutic mechanism of the action of bright light but also the cause of the disorder. In this regard, SAD has lent itself readily to analogies with animal models of seasonality, for which a wealth of literature exists.

Despite these developments, a number of issues concerning the disorder remain as yet unsettled. Broad agreement exists concerning its diagnostic criteria and clinical features, but some aspects remain debated, for example, whether a majority of patients with SAD are unipolar or bipolar. Sparse epidemiologic data exist to establish the prevalence of SAD or to address its public health significance.

To date, animal models have not proved directly applicable to understanding the pathophysiology of SAD, although a growing literature on seasonal rhythms in normal human physiology and behavior suggests that SAD represents an extreme on that continuum. Attempts to identify biologic markers have as yet produced few definitive findings, although a number of provocative findings have been reported.

Perhaps the most currently controversial area in SAD research involves studies of phototherapy. That phototherapy works seems clear. What is unclear is whether its effect is mediated primarily via the circadian system or some other mechanism and what the nature of these mechanisms might be. Other unresolved questions concern the importance of the timing of light treatment and the extent of the placebo effect in response.

It was with such issues in mind that in May 1987 the Affective and Anxiety Disorders Research Branch, Division of Clinical Research, National Institute of Mental Health (NIMH), Rockville, Md, in collaboration with the Clinical Psychobiology Branch, NIMH, Bethesda, Md, convened a workshop of clinical and basic scientists to present their most recent findings and thinking in the area. Our report will present the major themes of that meeting, with emphasis on areas of controversy, consensus, and future directions for research. For more detail on aspects of SAD, the reader is referred to several published reviews and to papers prepared for the workshop by participants and abstracted herein.

The NIMH Intramural Research Program was the first to publish criteria for SAD, and most investigators at the workshop had used these in their studies. By these criteria, at least two depressions must have occurred in the fall or winter and have remitted in the spring and summer. Furthermore, at least one episode must have met research diagnostic criteria (RDC) for major depressive disorder. No other Axis I diagnoses were permitted, and depressions for which an antecedent psychosocial stressor could be identified were excluded.

In the recent edition of DSM-III-R, provision was made for the specification of the seasonal pattern of recurrent major depression and bipolar disorder. Criteria provided go beyond those formulated originally in stipulating that recurrent onsets and offsets must occur within a 60-day window from year to year; that the depressive episode must meet criteria for major depression; that there must be at least three seasonal episodes, two of which occur in consecutive years; and that the ratio of seasonal to nonseasonal depressive episodes must be more than 3:1. Like the original criteria, the DSM-III-R criteria preclude the diagnosis when “obvious seasonally related” psychosocial stressors are in evidence.

At the workshop, there was agreement that the increased specificity of the DSM-III-R criteria was a desirable feature, especially for future work on validation of the diagnosis and epidemiologic investigations. Workshop participants were generally in agreement that the new criteria should be used in an exploratory way, however, and should remain provisional until further research had been done to address a number of issues concerning the characteristics of patients with SAD. In particular, the following issues were raised.
Since the season of the depressive episode was left unspecified in *DSM-III-R*, it was noted that other forms of seasonal depression, such as recurrent summer depression reported by Wehr et al., would be classified with winter depression. While Spitzer and Williams said that this lack of specificity was deliberate, some participants expressed a concern that it might result in etiologically different forms of disorder being assigned the same diagnosis.

Virtually all participants at the workshop, including the NIMH Intramural Research group that originally framed the criteria, regarded as unhelpful the exclusion from seasonal classification of recurrent depression with antecedent psychosocial stressors. The criterion had rarely been applied by any of the participants, and there was consensus that it be dropped.

### Clinical Issues

Among workshop participants with clinical experience, there was considerable agreement on the chief clinical characteristics typically found in winter depression. In a review of this area, Hellekson noted strong female predominance of 4:1, and a mean age of onset in the early to mid-20s. An atypical depressive picture is frequently found, consisting of fatigue, overeating, carbohydrate craving, weight gain, and oversleeping, although specific features may vary from patient series to series, and patients with endogenous or melancholic symptom patterns have also been noted to have a seasonal pattern to their affective disorders.

A point of disagreement at the meeting was whether patients with SAD were mainly hypomanic or euthymic during the summer months. As reviewed by Hellekson, workshop participants Lewy, Teran, Thase, and Wirz-Justice typically found a majority of patients with SAD to be unipolar. By contrast, Rosenthal and Hellekson most commonly assigned bipolar II diagnoses. It was noted that this difference might be due partly to differences in the definition of hypomania, particularly the extent to which impairment in functioning is required for the diagnosis to be assigned. Rosenthal suggested that the RDC are “lenient” in their criteria of hypomania, while *DSM-III* criteria are stricter. Depue provided criteria for hypomania, a term he suggested be applied to states of increased energy and mood that do not impair functioning and, therefore, do not meet strict criteria for hypomania.

It was also noted that differences among researchers in diagnosis assigned may stem in part from clinical interpretation of the patient's mood. Although patients with SAD report exuberance, energy, and reduced need for sleep during the spring and summer relative to their winter depression, it is not clear how often their affect is indeed in excess of normal. There was consensus that hypomania or hyperthyemia is not an essential feature of SAD, but rather that seasonality is the sole invariant defining characteristic of the syndrome.

Although the majority of clinical presentations dealt with winter depression in adults, Sonis presented a clinical picture of the syndrome in children. Hypersomnia and hyperphagia were not central features, but anergia was. As in adults, children were found to respond favorably to phototherapy.

Wehr et al. described a syndrome of recurrent summer depression based on their study of 33 patients. Summer depressed patients report sensitivity to environmental temperature changes, feeling worse when the weather is hot and humid and best when cool. (This contrasts with reports of winter depressed patients who often report sensitivity to changes in ambient light.) As in winter depression, the majority of patients with summer depression are women, but in other respects the clinical picture of the syndromes is quite different. Summer depressed patients report weight gain, hypersomnia, and hyperphagia less frequently. In fact, they tend to report decreased appetite, weight loss, and insomnia. Wehr et al speculated that the pathophysiology of winter and summer depression is different, and their experimental approaches to the treatment of summer depression have involved manipulations of ambient temperature and humidity as well as of ambient light.

Several presentations examined the evidence for the syndromal validity of SAD. Mrosovsky approached the evidence from his perspective not as a clinician but as a researcher in animal seasonality. He argued the necessity of first establishing that recurrent depression is nonrandomly distributed before the seasonal nature of SAD could be accepted unequivocally as evidence of a syndrome. Because most patients with SAD have been recruited by advertisement and are therefore self-selected, it is difficult to use their own reports of seasonality to establish a diagnosis. Selective presentation of suicide rates and hospital admissions are not consistent in showing a seasonal pattern that coincides with the typical seasonal pattern found in SAD (eg, suicide peaks in April when one might expect remissions to be occurring in SAD). By this line of reasoning, symptom clustering reported in SAD might also be an artifact of methods of recruitment rather than a reflection of a syndrome, since symptoms might coexist by chance in individuals responding to advertisements in which the symptoms were described.

However, as Mrosovsky himself noted, reports of frequent winter recurrences of depression within individuals make it unlikely that such patterns are occurring solely by chance. Likewise, the clinical experience of workshop participants, with both physician-referred and self-referred patients with SAD, was that the symptom cluster occurs too often to be explained by chance.

The report of Thase partly addressed the issue of self-selection of patients. He evaluated 115 patients for seasonality being treated and followed up for recurrent depressions at a clinic. Sixteen percent of these patients, who were not initially selected for their reports of seasonality, met the NIMH criteria for SAD. Furthermore, they appeared less "endogenous" (melancholic) on a number of measures than did nonseasonal depressed patients from the same setting. The seasonal depressed patients reported more hypersomnia, hyperphagia, and weight gain—a pattern typical of SAD. Thase noted that this high frequency of "reverse vegetative" symptoms would tend to support the validity of SAD as a separate syndrome. However, he also noted that reverse vegetative symptoms have been reported in bipolar and atypical depressed patients of undetermined seasonality.

An analysis by Thase of recurrent depressions occurring in his clinic setting suggested the possibility that seasonality may characterize episodes not meeting strict criteria for SAD. Retrospective reports of patients with three or more episodes of depression (including 15 who met criteria for SAD) indicated clear seasonality with respect for time of year, with more depressions occurring in September through November.

Workshop discussion of evidence for validity from two other important sources—namely, biologic markers and treatment response—was extensive. These topics are covered in subsequent sections of this report. Several biologic markers, including circadian phase, hormonal, neurotransmitter, immunologic, attentional, and sleep functioning, have been studied in patients with SAD. Although previ-
ously no biologic measures have been shown to discriminate unequivocally between patients with SAD and either non-seasonal depressed patients or healthy persons, evidence for a number of candidate markers was presented by several participants. This research area is characterized by both a high level of interest and a high level of controversy.

Treatment response provides stronger evidence for the validity of SAD as a syndrome. As discussed below, the majority of studies of light therapy find it efficacious in alleviating depressive symptoms. On the other hand, the majority of research protocols that have attempted to use light in the treatment of nonseasonal depressed patients (e.g., Kripke et al29) and reviewed by Thase24 have not found similar evidence of efficacy, although at the meeting, Kripke et al11 presented evidence for an antidepressant effect of light in such patients. Conversely, Thase noted that imipramine hydrochloride was effective in treating subjects with SAD from his clinic sample. A conservative conclusion is that bright-light treatment works well with patients with SAD and that its therapeutic value in the treatment of other forms of depression is as yet an open issue.

In a summary discussion of the clinical presentations, Spitzer and Williams70 concluded that in terms of traditional validation criteria, there is more evidence for the validity of SAD as a syndrome than for commonly assigned and clinically important diagnoses such as melancholia and dysthymia. The inclusion in DSM-III-R of the dimension of seasonality was meant both to reflect the strength of this evidence and to serve the heuristic function of stimulating further research into diagnostic and clinical issues.

**Epidemiologic Evidence**

Although Kraepelin22 observed in 1921 that 5% of the manic-depressive patients he studied showed a seasonal pattern in their disorder, until recently epidemiologic information on the prevalence of SAD has been sparse. A number of workshop participants brought data to the meeting to bear on this issue. Using rates obtained in his clinic group, Thase24 estimated the population prevalence of SAD to be 4% to 6%. Terman20 reported preliminary results of a population survey in New York City in which a Seasonal Pattern Assessment Questionnaire was sent out to individuals selected at random from the Manhattan telephone directory. Over half of the 400 questionnaires sent out were returned. Of the responders, 31% to 50% (the figure varied depending on symptom) noted changes in sleep, social activity, weight, and energy in the same direction as the changes seen in SAD, and 14% considered the changes a personal problem in their lives. Terman noted that if these statistics are generalizable to the population of the New York metropolitan area, as many as 1.5 million people there may suffer from marked seasonal behavior changes.

Using a Seasonal Pattern Assessment Questionnaire, Kasper et al10 recruited a sample of subjects who were as equally seasonal as the winter “complainers” in Terman’s sample. Characterizing the group as “subsyndromal SAD,” Kasper et al found this to respond favorably to a trial of phototherapy. Depue26 et al used the Intensity of Seasonal Variation to survey a college sample. Three percent of the sample reported seasonal changes similar in magnitude to those found in patients with severe SAD. Although the population prevalence of SAD is not known from these data, they suggest that if the full range of intensity of SAD was examined, prevalence would likely exceed 3%.

Sons18 surveyed a Minnesota school sample using the Seasonal Symptom Checklist for Children. Since scores were skewed toward low values of the checklist, for purposes of analysis individuals in the third quartile or higher were defined as highly seasonal. With this definition, 6.5% of the sample fell into the highly seasonal range; and of these, 29% also scored in the severely depressed range on the Beck Inventory Scale. One percent of the total sample fell into the highly seasonally–highly depressed category.

Lacoste and Wirz-Justice22 summarized the vast literature on seasonal variations in biologic measurements in healthy individuals, including neurotransmitter functioning, neuroendocrine responses, feeding and metabolism, sleep, and thermoregulation. This literature indicates that many biologic substrates vary seasonally in humans, raising the possibility that patients with SAD might fall at the extremes of both behavioral and biologic spectra.

**CRITICAL ISSUES IN THE USE OF PHOTOTHERAPY**

The treatment of the first patient with SAD with light2 was inspired by the finding that humans required bright light for suppression of melatonin.29 This implied that humans, like animals, could have seasonal rhythms cues to the natural photoperiod as it changed throughout the year, unperturbed by the use of indoor light, and that bright light could be used to manipulate experimentally and perhaps therapeutically these rhythms in humans.

Since the first controlled trial, the use of phototherapy has burgeoned. As Rosenthal et al30 noted in their review, by mid-1987 at least 24 controlled phototherapy trials comparing two different types of light treatment had been carried out by 11 centers. The majority of studies reported statistically significant differences between control and active treatments and, therefore, the preponderance of scientific evidence supports an antidepressant effect for light.

Rosenthal et al also reviewed parameters of light treatment that have been systematically studied. Most studies indicate that bright light (2500 lux) is more of an antidepressant than dim light (<400 lux), which is frequently used as a control.

Terman20 presented some preliminary data demonstrating the efficacy of intense light (10,000 lux) in having an antidepressant effect with shorter exposures (in this case 30 minutes) rather than the two to four hours commonly used in studies of phototherapy.

As reviewed by Rosenthal et al34 a number of workshop participants (Lewy, Terman, Wirz-Justice, and Hellekson) had conducted studies comparing the efficacy of varying periods of light, namely, two hours vs 30 minutes of morning light. Wirz-Justice, Terman, and Hellekson found the longer period to be significantly more effective than the shorter one, whereas the Portland group failed to find a significant difference, although the longer duration appeared to be slightly more effective. In general, however, there seems to be evidence of duration-response relationships between phototherapy and antidepressant effect.

As noted above, there is some evidence that the antidepressant effects of light are specific for SAD vs other forms of depression. However, the range of applications of light is not limited to the affective disorders. As reviewed by Terman, other applications in the literature include treatment of jet lag, delayed sleep syndrome, and chronobiologic disorders in shift workers. In these disorders, the basis for phototherapy and method of treatment may differ from those typically associated with SAD. The possible applications of light treatment to a variety of disorders involving biologic rhythms need to be explored further.

Other issues raised at the meeting but considered unresolved concerned which part of the light spectrum is necessary or optimal for producing antidepressant effects of light. This latter issue is of practical importance, since
full-spectrum light containing ultraviolet rays has a potentially toxic effect on both the eyes and skin.

Several workshop participants noted that a remaining major impediment to progress in phototherapy research was the lack of systematic standards for research protocols. There was considerable interest expressed in cooperative working mechanisms to promote more uniformity in some aspects of design that may account for discrepancies found among investigators.

**BIOLOGIC EFFECTS OF LIGHT AND MECHANISMS OF ACTION OF PHOTOTHERAPY**

Perhaps the most controversial issue in phototherapy research pertains to its mechanism of action. The first phototherapy studies in SAD were influenced by findings that seasonal rhythms in animals depend on changes in day length or photoperiod. For light to switch an animal from a winter condition to a summer condition, it must impinge on the photosensitive phase of the day-night cycle. Many photoperiodic effects in animals have been shown to be mediated by the influence of changing photoperiod on the pattern of melatonin secretion. By analogy, light treatment was initially administered in research paradigms by extending the photoperiod to which the subject was exposed.

Other studies of animals have established that pulses of light have different effects, depending on the time of day at which they are administered. Relationships between light timing and its effect on circadian rhythms are typically portrayed by a phase-response curve. A phase-response curve is thought to characterize all circadian systems entrained by light, and, although it has as yet not been completely characterized in humans, serious investigators in the field do not question its existence. A light pulse in the later part of the subjective night will move circadian rhythms earlier (advancing their phase); a light pulse in the early part of the subjective night will move them later (delaying their phase). There is a period, during the subjective day, during which light has little or no effect on circadian rhythms.

Lewy et al.\(^{13}\) have hypothesized that phototherapy exerts its antidepressant effect, at least in part, by phase advancing patients with SAD, most of whom are, according to this theoretical framework, phase delayed. As a corollary of this theory, early morning light will be most efficacious in treating SAD. Conversely, evening light administered in the early part of the subjective night should be ineffective or even worsen symptoms, since it will produce further phase delays. Light at midday would not be expected to shift the circadian phase according to this theory. The circadian phase-shift theory is perhaps the most currently actively studied theory of the mechanism of action of phototherapy. As yet, it has been neither confirmed nor refuted conclusively. The published literature, as reviewed by Rosenthal et al.\(^{14}\) and Terman,\(^{20}\) contains findings of the efficacy of morning, evening, and even of midday light depending on sample sizes and in methods that may have affected results. However, a review of such issues will not be undertaken here. (For fuller discussion of this controversy, the reader is referred to workshop papers.\(^{15,16,20}\))

Partly to address this controversy, Terman\(^{20}\) presented a cross-center analysis of published phototherapy research. He evaluated the response to phototherapy by determining the percentage of responders, defined as those individuals whose posttreatment Hamilton ratings were at least 50% lower than baseline scores and were reduced to less than 8 points. Using this stringent criterion, he noted that while 25% of the light responders in morning-evening crossover studies responded at both times of day, 37% responded exclusively to morning light, 3% exclusively to evening light, and 53% to neither. Fifty-three percent of the subjects showed Hamilton ratings of less than 8 with morning light, and 51% of subjects with morning and evening light showed this response; only 40% showed such decreased ratings with evening light and 32% with midday light. The dim-light controls, by contrast, achieved only 11% remissions, an unusually low rate of response, even for placebo. In short, morning light appears to be superior but not uniquely antidepressant.

At the workshop, Lewy et al.\(^{13}\) argued that the superiority of morning light was consistent with a phase-shift theory. Rosenthal et al.\(^{14}\) argued that findings of efficacy of evening and midday light argue against phase-shifting circadian explanations.

To account for the therapeutic effect of light in the evening, Lewy et al.\(^{13}\) hypothesized that light also has an "energizing effect." The typical evening-light protocol involves treatment from 6 PM to 8 PM, a period that may not coincide with the subjective night in some phase-delayed persons. Therefore, early evening light could be antidepressant if it did not impinge on the beginning of the subjective night, and induce phase delays.

Rosenthal et al.\(^{14}\) argued that the superiority of morning light over evening light does not necessarily mean that phototherapy was working through phase-advancing circadian rhythms; they suggested that there may be a differential sensitivity to light depending on the time of day when it is administered, which implies involvement of a diurnal rhythm but not necessarily a circadian phase-shifting mechanism.

Lewy et al.\(^{13}\) also reported findings of phase delays in dim light melatonin onset, a marker for circadian phase, in patients with SAD compared with healthy subjects. In addition, the more extensively circadian rhythms were advanced by light treatment, the more antidepressant the effects of light were found to be. This finding of a phase advance (also seen by Terman\(^{20}\)) in a biologic marker for circadian phase was not replicated in other studies from the NIMH as reported on by Skwerer et al.\(^{17}\) In that research, melatonin onset was not measured in dim light as was done in the research by Lewy et al, and therefore the methods are not comparable. No phase advance was noted in the rhythms of prolactin, cortisol, and melatonin and core body temperature in subjects treated successfully with morning plus evening light.

**OTHER BIOLOGIC FINDINGS IN SAD**

Information about biologic abnormalities in SAD and the biologic effects of light has accumulated rapidly over the past five years. Many aspects of the data were presented and discussed at the workshop. In addition to the information presented by Lewy et al, Skwerer et al.\(^{17}\) discussed the findings of the NIMH group on biologic abnormalities in SAD and the effects of bright light as well as the group's "melatonin hypothesis" of SAD. Deupue et al.\(^{17}\) O'Rourke et al.\(^{18}\) Beth Buckwald and Ronald E. McGrath, PhD (unpublished observation, 1987), and Jacobsen et al.\(^{18}\) presented data suggesting abnormalities of neurotransmitter regulation in SAD.

Skwerer et al reviewed the evidence for and against a melatonin hypothesis, originally advanced by the NIMH group.\(^{20}\) Changes in melatonin secretory patterns in many species occur in response to changes in day length or photoperiod. These altered melatonin patterns in turn mediate seasonal changes that occur in a number of behavioral and physiologic systems. (See below for a detailed discussion of animal models.) The NIMH group had originally proposed that antidepressant responses to
phototherapy were similarly mediated by melatonin. However, their subsequent studies appear to go against this hypothesis. Reports of the efficacy of midday light (Wehr et al23) were considered by Skwerer et al to argue strongly against the involvement of melatonin. In another study by Rosenthal et al,22 orally administered melatonin did not completely reverse the effects of phototherapy nor did the \( \beta \)-adrenergic blocker, atenolol, which suppresses melatonin secretion, reproduce the antidepressant effects of light in SAD, although some patients seemed to benefit from it.

Skwerer et al also reported on results of some recent biologic measurements made at the NIMH on subjects with SAD. Preliminary results from their patient series indicate that plasma norepinephrine levels are inversely related to the level of depression, as measured by the Hamilton Rating Scale. Increases occur following phototherapy, and the degree of increase is proportional to the antidepressant response. Increased in vitro response of peripheral blood lymphocytes to mitogen stimulation was also found in patients with SAD, and this response normalized after phototherapy. The P500 component of visual event-related potentials in response to visual but not auditory stimuli was also enhanced in these patients following phototherapy. Antidepressant effect was in direct proportion to improvement in P500, and changes were noted as early as 48 hours after initiation of phototherapy.

Depue et al reported on some work to test their hypothesis that dopamine functioning may be impaired in SAD. Patients were assessed both in summer remission and during winter episodes on a number of measures strongly influenced by dopaminergic functioning. While measures of response to thermal challenge and eye blink response differed between symptomatic patients with SAD and controls and normalized in the former following successful phototherapy, basal serum prolactin values did not change as a function of season or after phototherapy. Values in patients with SAD remained significantly lower than in controls. They suggested that basal prolactin may serve as a trait marker for SAD, and they noted that reports of low prolactin levels have not occurred consistently in other psychiatric disorders, including nonseasonal major unipolar depression. Although the measures were chosen to index dopaminergic activity, and although Depue et al found their results consistent with a theory implicating the dopaminergic system in SAD, they did not exclude the possible involvement of the serotonergic system, since decreased secretion of the prolactin may result from reduced serotonin stimulation.

In this regard, a number of participants gave brief reports of preliminary work implicating the serotonergic system in SAD. Beth Buckwald and Robert E. McGrath, PhD (unpublished findings, 1987), reported a preliminary finding of favorable response in patients with SAD to dietary \( \gamma \)-tryptophan, the precursor of serotonin. O'Rourke et al20 reported that n-flufluoramine, an indirect serotonin agonist, was superior to placebo in the treatment of 18 patients with SAD. Jacobsen et al24 reported euphoric and abnormally energized responses of ten patients with SAD to infusion of a direct serotonin agonist, \( M \)-chlorophenylpiperazine, that were normalized by light treatment, whereas controls reported increased lethargy and drowsiness. They also noted increased plasma cortisol levels and rises in prolactin levels following \( M \)-chlorophenylpiperazine infusions in patients with SAD as compared with controls. These responses were not normalized by phototherapy.

In their review of seasonal variations in biologic parameters, Lacoste and Wirz-Justice26 noted substantial evidence for seasonal rhythms in serotonin levels in healthy persons, with winter values being significantly lower than summer values. This pattern and the above reports with clinical samples indicate that it may be productive to pursue serotonergic hypotheses with regard to SAD.

In general, theories to explain the mechanism of action of phototherapy and the biologic basis of SAD are very closely related. The field is currently actively researched but results are as yet incomplete and at times conflicting.

**THE VALUE OF ANIMAL MODELS IN THE STUDY OF SAD**

In the popular press, analogies have been drawn between hibernating bears and patients with SAD. However appealing these analogies may seem, researchers on animal seasonality who were present at the workshop urged caution in extrapolating from animal behavior and physiology to a clinical condition in humans.

Mrosovsky28 pointed out that hibernation is not typically found in large mammals since they are able to store fat faster than it is metabolized, and he described a number of dissimilarities between SAD and hibernation.

Wade29 reviewed the literature on seasonal fluctuations in body weight and metabolism in a number of small mammals to determine if there are any appropriate animal models for SAD in terms of body weight change. Across species, such change is typically mediated by the pineal and its hormone melatonin.

Wade, Mrosovsky, as well as Zucker,24 who served as a discussant for this section of the workshop, all emphasized that there are no animal seasonal rhythms that can be adopted in their totality as models for SAD. Rather, as Mrosovsky stated, different seasonal strategies are adopted by different species to cope with the changing seasons. Comparisons between humans and animals are more likely to be fruitful if they are made in terms of discrete components rather than globally in terms of overall strategy. Furthermore, Zucker pointed out that different members of the same species may use different physiologic strategies to accomplish the same type of seasonal behavioral change. Different circannual behaviors may be mediated by different mechanisms.

Pittendrigh,30 who discussed basic photoperiodic mechanisms, noted that three different circadian pacemakers within a single species of fruitfly are present, each encoded by genomes of different species of that species. He summarized the marked functional similarities between species (plants as well as animals) in their photoperiodic behavior. In all cases, the crucial issue in photoperiod control is the extent to which light coincides with specific phases (of the so-called subjective night) of the organism's circadian cycles. Thus, the time of day at which light treatment is effective is crucial if the underlying basis of phototherapy is indeed circadian-photoperiodic. Pittendrigh pointed out that photoperiodic variation is mediated by the circadian system and should not be construed as an independent process. He suggested that the evidence against photoperiodic mechanisms (eg, studies reporting that midday light has an antidepressant effect in SAD) should be replicated before this analogy to the bulk of light-responsive seasonal rhythms in animals is discarded.

Pittendrigh also emphasized the need for caution before assuming that all photoperiodic phenomena are controlled by the same concrete physiologic mechanism—as seems to be assumed in the so-called melatonin hypothesis. He noted that different individuals in the same species commonly differ in the day length necessary to elicit a given response, such as gonadal growth; and the day length necessary in the same individual to elicit two different responses, such as temperature tolerance and gonadal growth, may differ widely.
Such observations serve as appropriate warnings to clinical researchers who might hope to explain all the phenomena involved in SAD and phototherapy in terms of a single biologic mechanism. Despite the limitations of attempting to find animal models for SAD, lessons derived from animal seasonal rhythms can serve as inspiration for clinical researchers. Indeed, they already have, although it is ironic that the photoperiodic, melatonin-mediated rhythms that originally inspired clinical researchers may have little in common with the mechanisms underlying SAD and phototherapy.

**GENERAL CONCLUSIONS AND RECOMMENDATIONS**

1. The evidence to date for the syndromal validity of SAD is fairly strong, stronger perhaps for more established diagnoses such as melancholia and dysthymia.

2. The preponderance of scientific evidence to date supports phototherapy as an effective treatment for SAD; but, as yet, the mechanism by which its antidepressant effect is achieved is not understood.

3. Circadian hypotheses have been frequently entertained and examined by researchers in their efforts to explain the mechanism of action of phototherapy and the pathophysiology of SAD. Nevertheless, results are as yet inconclusive. Animal models have served as theoretical inspirations for SAD researchers but have not been shown to be directly applicable to the disorder.

4. Pooling of data from different centers for purposes of analysis has proved useful in achieving some consensus in the field concerning interpretation of findings to date. To facilitate scientific progress, there is a need to establish some mechanism whereby interested investigators could meet to discuss methodologic differences that may lead to differences in results and to consider common protocols and parallel analyses to reduce controversy in interpretation of cross-center findings.

These observations represent the judgment of the authors as the workshop transactions and presentations, and we alone are responsible for any inadvertent error in reportage.

Participants at the workshop were as follows: Mary C. Blehar, PhD, National Institutes of Mental Health (NIMH) Affective and Anxiety Disorders Research Branch, Division of Clinical Research, Rockville, MD; Siegfried Kasper, MD, Frederick M. Jacobsen, MD, Robert E. Skwerek, MD, Norman M. Rosenthal, MD, Thomas A. Wehr, MD, NIMH Clinical Psychopharmacology Branch, Intramural Research Program, Bethesda, MD; Carla Hellekson, MD, Fairbanks (Alaska) Psychiatric and Neurological Clinic; Daniel F. Kripke, MD, University of California, San Diego; Alfred J. Lewy, MD, PhD, Oregon Health Sciences University, Portland; Robert E. McCann, MD, Faith Tryon Quality Care, Inc., NJ; Nicholas Mrosovsky, MD, University of Toronto; D. O’Rourke, MD, Massachusetts Institute of Technology, Cambridge; Colin Pittendrigh, PhD, Patagonia, Arizona; William A. Sonis, MD, Philadelphia Child Guidance Clinic; Robert L. Spitzer, MD, Michael Perelman, PhD, Janet H. J. Williams, DSW New York State Psychiatric Institute, New York; Michael E. Thase, MD, University of Pittsburgh; George N. Wade, PhD, University of Massachusetts, Amherst; Anna Wire-Juxtie, PhD, Psychiatrische Universitätsklinik Basel; Irving Zucker, PhD, University of California, Berkeley.

**References**


