

# THE USE OF LIGHT IN THE TREATMENT OF DEPRESSION

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## INTRODUCTION

Light has recently been reported to be a useful treatment in affective illness (1, 2, 3, 4, 5, 6). What type of patients respond to this type of treatment? What is the theoretical mechanism of action of light therapy and what are the implications of this research for the existing theories of affective illness? This review will seek answers to these questions by summarizing the recently reported studies of the effects of light on depression, by reviewing the pertinent contributions from neuroanatomy, endocrinology and circadian rhythm physiology, and, finally, by suggesting some points of integration of these recent findings with existing theories of depression.

## HISTORICAL ASPECTS OF SEASONAL MOOD CHANGES

Hippocrates wrote: "If any violent change has occurred in the air according to seasons, the brain becomes different from what it was" (7). Hellpach, in 1911, was the first in modern medical literature to notice the existence of seasonal mood changes in manic-depressive patients (1). Kraepelin, in 1921, agreed with Hellpach and further described such patients as follows: "Repeatedly I saw moodiness set in in the autumn and pass over in the spring, when the sap shoots in the trees to excitement, corresponding in a certain sense to the changes which come over even healthy individuals at the changes of the seasons" (8). Several recent epidemiological studies have shown seasonal variation in the preponderance of affective illness, with peak rates for depression (both unipolar and bipolar) in the spring and fall of the year, and peak rates for suicide in the summer months (1, 9, 10, 11).

The length of day, or photoperiod, is one variable that may be linked with seasonal variations of depression in susceptible individuals.

## USING LIGHT TO TREAT DEPRESSION

The first case of using artificial light in the treatment of affective illness was reported by Lewy, et al (2). The subject was a sixty-three-year-old male, diagnosed by

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Research Diagnostic Criteria (13) as having a bipolar-II major depressive disorder, who had not responded to a variety of antidepressant drugs due to intolerable side effects. The patient kept a diary for fourteen years documenting a history of: hypomanias beginning in January or February of each year, each lasting an average of 22 weeks; and of depressions beginning in July of each year, each lasting at least 29 weeks. During December 1980, sixteen weeks into a depressive episode, he was exposed to fluorescent light (Vitalite) of 2000 lux intensity between his time of awakening at 6:00 until 9:00 A.M. and again between 4:00 and 7:00 P.M., thus extending his photoperiod to thirteen hours (i.e., a spring photoperiod compared to a ten-hour December photoperiod with dawn at 7:00 A.M. and dusk at 5:00 P.M.). After four days of this regimen, the patient appeared markedly improved with Visual Analog Mood Scale self-ratings increasing from (+ - S.D.) 20(+ - 2) to 39(+ - 1) (50 = euthymia). Nurses' ratings of depression declined significantly and 24-hour activity counts increased from a mean of 4748 to 7003.

Rosenthal and colleagues reported a case of a twenty-nine-year-old woman who regularly suffered depressions every winter and hypomanias every spring since early adolescence (1). These cycles were strongly effected by the relative latitude of her residence, i.e., the further north she lived, the earlier her fall depressions began with more severe and long lasting symptoms. Early morning light therapy was reportedly used successfully beginning in August when her depressive cycle began, and this therapy reportedly continued to be beneficial during the fall and winter for four years of follow-up.

A more systematic study was subsequently done by Rosenthal et al (1). Eleven subjects were screened from 2000 applicants who responded to a news article describing the above patient. For inclusion in the study the patients had to have a history of major affective disorder according to RDC criteria (13), with onset in the fall or winter for at least two consecutive years and subsequent remissions in the following spring or summer. Patients were then followed with regular clinic visits until they began to feel depressed (assessed by self-report, clinical interview, and Hamilton and Beck Depression Rating Scales). When patients became moderately depressed for two weeks, they were offered experimental light treatment. Two kinds of light were used: a) bright full spectrum fluorescent light, approximately 2500 lux at 90 cm; and b) dim yellow fluorescent light of 100 lux intensity at 90 cm (used as a control). Patients were requested to sit in front of the lights doing some activity other than sleeping for three hours before dawn and three hours after dark. A crossover study was performed such that if clinical improvement was noted after two weeks of either bright or dim light therapy both lights were withdrawn for one week before the alternate light therapy was begun. Improvement was defined by psychiatric interview and a Hamilton Score of less than fifteen. If no improvement was noted after two weeks the second regimen was begun without delay.

Results showed that those patients treated with bright white light showed significant antidepressant effects with a mean Hamilton Rating Scale (HRS) pretreatment score of 17.7 + - 3.7 and a posttreatment score of 6.7 + - 5.1 ( $p < .001$ ). Those patients exposed to dim light (control) showed a nonsignificant change in mean HRS

score from a pretreatment baseline of  $15.41 + -4.6$  to  $13 + -7.1$ . There was a statistical difference in the change in HRS score induced by bright white light versus dim yellow light ( $p < .01$ ) when a paired t test was performed. Seven patients requested to be restarted on the bright light regimen at the end of the crossover study, and first and second responses to light treatment were similar in all cases. Mood improvement with bright light was noted within three to seven days of therapy, and relapse occurred to a significant degree ( $t = 3.29$ ;  $p < .01$ ; two tailed paired t test) after withdrawal of the light within three to four days on the average.

### **CHARACTERISTICS OF RESPONDERS TO LIGHT THERAPY**

Seventy-six percent of Rosenthal's patients were diagnosed as bipolar-II and seventeen percent as bipolar-I, though mania was not a selection criterion. One-third of the patients had never received psychiatric treatment and only three had been previously hospitalized suggesting that Seasonal Affective Disorder (SAD) may be a mild variant of manic-depression as Kraeplin had originally stated (7). Rosenthal further points out that SAD seems to be a bipolar variant of so-called "atypical" depression with frequent symptoms of hypersomnia, hyperphagia, carbohydrate craving, and weight gain.

The outstanding clinical feature of SAD, noted by Rosenthal and colleagues, was a sensitivity to changes in season or latitude that corresponded to the approximate annual occurrence of affective episodes. Of Rosenthal's patients, 83% described their moods as worsening with northward travel and symptom amelioration after traveling south (within the northern hemisphere). The prevalence of seasonal exacerbations in manic-depressive patients was noted by Kraeplin to be four or five percent (7). Rosenthal suggests that the disorder may be more frequent than the literature shows, pointing out that a rhythm with a period of one year is difficult for both patient and doctor to perceive. This, together with the findings that these patients have relatively milder hyperphagic, hypersomnic, and anergic symptoms, may contribute to these patients being misdiagnosed or never treated.

### **POTENTIAL RESEARCH PROBLEMS USING LIGHT THERAPY**

In their discussion, Rosenthal and colleagues point out possible problems with the interpretation of their results. These are: a) that the news article may have screened for suggestable subjects who expected a similar result to that described; b) that the dim (control) light could not be "blind" to the subjects; c) that sleep deprivation in the second half of the night is known to have antidepressant effects (21) and since subjects were sometimes awakened in the morning for light therapy, this effect must be controlled for; and, finally, d) that a search should be made for psychosocial variables, such as anniversary reactions and holiday depression.

In a recently reported study (5), Rosenthal and colleagues further studied the effects of light treatment in SAD, using a similarly designed study with some notable exceptions: a) seven outpatients were studied as well as six additional inpatients, and b)

sleep was monitored polysomnographically during the study. Pertinent highlights will be presented here. (The reader is referred to the original article for further details.) Using more rigorous statistical analysis than in their earlier study, Rosenthal and colleagues closely replicated their earlier findings of the antidepressant action of bright white light in SAD compared to dim light controls. No significant differences were noted comparing the response of outpatients versus inpatients, nor were there any significant differences in the mean sleep time in subjects getting bright versus dim light treatment during either baseline, treatment, or withdrawal conditions. Rosenthal admits that some phase advance of the sleep cycle (referred to in depth later in this review) occurred when subjects were awakened at 5:00 A.M. for light therapy; but argues that sleep deprivation or phase advancement cannot be sufficient to explain the noted antidepressant response since the sleep effects were present in both bright and dim light treatment settings, but only those subjects exposed to bright light treatment showed a significant antidepressant response. On the issue of patient expectations in the "nonblind" crossover aspect of the study, Rosenthal argues against a placebo explanation of the study findings by emphasizing the similarity of first and second responses to bright light, the latency of the response and relapse (a few days), and the successful use of maintenance light therapy in four subjects throughout the winter (5). Rosenthal reports that although his group has successfully maintained an antidepressant response using bright white light therapy in ten patients diagnosed with SAD, regular exposure is critical for maintenance with relapse occurring in a few days if light therapy is omitted.

Rosenthal concludes that a) Seasonal Affective Disorder is a subgroup of affective illness wherein susceptible patients show apparent reactivity to environmental factors, b) that preliminary evidence suggests that artificially manipulating environmental light may be clinically useful in treating these patients, and c) that further work is required to validate SAD as a distinct clinical syndrome.

## **A THEORETICAL MECHANISM OF ACTION OF LIGHT THERAPY**

Understanding how light could effect depression involves related research in neuroanatomy, endocrinology, and in the physiology of biological rhythms as they relate to affective illness.

Many animal species show seasonal or circannual rhythms that are known to control such phenomena as migration, breeding patterns, and hibernation (12). The control of these rhythms have been shown to be endogenous in origin, i.e., that they continue to manifest themselves in the absence of environmental stimuli, although environmental stimuli are known to influence or regulate the timing of these rhythms. Of these environmental stimuli, the photoperiod seems to be the most influential (2).

## **THE NEUROANATOMY OF BIOLOGICAL RHYTHMS**

Circadian rhythms (meaning: of about 24 hours) have been studied in many animal species, including man, and are known to occur in such physiological parame-

ters as cortisol secretion, fluctuations in body temperature, REM sleep propensity, and melatonin secretion (12, 14, 15). Ablative experiments have shown these rhythms to be controlled by an endogenous brain pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus (15, 16, 17). This brain center receives neural input from the retina via several neural tracts, of which the retinohypothalamic tract has been shown to mediate the effects of light on biological rhythms (12, 17). Further neural pathways have been shown connecting the SCN to the thoracic spinal cord nuclei and, subsequently, the pineal gland via noradrenergic neurons traversing the superior cervical ganglion (17). Hence, the effects of light impinging on the retina are relayed via neural pathways to the CNS pacemaker for biological rhythms and subsequently to the pineal gland.

Embryologically the pinealocytes are known to have evolved from photoreceptor cells in lower animals similar to those found in the lateral eyes of certain animals (16, 17). In higher animals the pineal is no longer directly sensitive to light; its effects require the above neural pathways to relay information about environmental light (17). The blinding of experimental animals, as well as ablation of the SCN, pineal gland, or any of the neural connections between them, have been shown to prevent the regulatory effects of light on certain biological rhythms (12).

## THE PINEAL GLAND AND MELATONIN IN BIOLOGICAL RHYTHMS

The function of the pineal gland is a subject of continuing intensive study, particularly in relation to biological rhythms. The pineal gland is known to secrete indolamine hormones and certain peptides (14, 15, 16, 17, 18). Melatonin, an indoleamine hormone synthesized from serotonin, is secreted by the pineal gland in a diurnal rhythm. Peak levels occur during the nighttime sleep of humans and during the nighttime active period of nocturnal animals (in the absence of environmental light) (17). Light impinging upon the retina is known to immediately suppress the secretion of melatonin (16, 17, 18). Interestingly, humans seem to require light of considerably higher intensity than animals to suppress melatonin, perhaps due to man's adaptation to an artificially lit environment (20). The function of melatonin is a subject of great speculation and few known facts. Whether melatonin is an endocrine messenger linking the light/dark cycle with biological rhythms in humans remains a question under intensive study. Some studies do, however, demonstrate such effects in animals.

Seasonal reproductive cycles in animals are attributed to antigonadal properties of melatonin. At least one mechanism involves melatonin changing the sensitivity of gonadatropin control centers to negative feedback by steroid sex hormones (12). Thus, seasonal changes in the length of the photoperiod modulate blood levels of melatonin, which in turn controls seasonal reproductive cycles through its effects on gonadatropic function.

Comparatively less is known about the function of melatonin in man. A few small studies have reported giving exogenous melatonin to humans to test its effects on Parkinson's Disease and depression. Using doses up to six grams per day, no beneficial effect was noted in Parkinson's Disease (21) and increased dysphoria was noted in a

study of eight depressed patients given melatonin (22). The most frequent effects noted were sedation and somnolence (21, 22).

In summary, light has been proven to regulate the biological rhythm of seasonal reproductive cycles in animals. Information about fluctuations in environmental light is relayed from the eye to the circadian pacemaker (SCN) and pineal gland. Thus, light indirectly regulates pineal melatonin secretion which in turn alters the gonadotropic control of reproductive cycles. Whether an analogous mechanism affects those biological rhythms relevant to depression remains speculative at this time.

## **BIOLOGICAL RHYTHMS IN DEPRESSION**

The hypothesis that circadian rhythm disturbance could be involved in affective illness originally evolved from consideration of four clinical features of depression: early morning awakening, diurnal variation of symptom severity, seasonality, and cyclicity of the illness (14).

When the sleep architecture of normal subjects is sampled during short naps around the clock, REM sleep also exhibits a circadian rhythm with a REM sleep peak in the midmorning and a minimum in the late afternoon. Thus REM sleep in normal subjects predominates in the later half of the sleep cycle.

The sleep EEGs of depressed patients show that REM sleep occurs earlier in the sleep period than in nondepressed controls (23). The sleep disturbances seen in depression with shortened REM latency, short total sleep time, and early morning awakening can be mimicked in normal subjects by shifting the onset of sleep from 10 P.M. to 10 A.M. Wehr and colleagues thus speculated that the circadian rhythm peak of REM sleep may occur abnormally early in depression, that is, phase advanced, relative to the sleep period. Wehr states: "If this inference is relevant to the etiology of affective illness, advancing a patient's sleep period by several hours should alter the internal phase relationship between the circadian sleep-wake cycle and other circadian rhythms (such as temperature or the probability of REM sleep) so as to normalize both sleep architecture and mood" (23). This observation led Wehr and colleagues to experimentally phase advance a depressed patient's sleep cycle by six hours, that is, from the conventional 11:00 P.M. to 7:00 A.M. sleep period to a 5:00 P.M. to 1:00 A.M. sleep period. These investigators reported a complete remission of depressive symptoms followed by a slight hypomanic state. Two weeks later the patient relapsed and a second six-hour phase shift produced a similar remission. Wehr, et al, reported similarly successful results with three additional patients using phase advance therapy (19).

Thus, a particular imbalance in the temporal relationship of REM sleep to the total sleep cycle is postulated to cause depression.

## **ENVIRONMENTAL LIGHT ENTRAINS BIOLOGICAL RHYTHMS IN MAN**

Several investigators have shown that if human subjects are kept in artificially controlled constant light or dark environments, the circadian rhythms controlling body

temperature, cortisol secretion, and REM sleep propensity continue to show endogenous (or free-running) cycles which are slightly longer than the expected 24-hours, e.g., 25–28 hours (12, 14, 24). This suggests that human, as well as animal circadian rhythms, are continually adjusted to maintain a 24-hour periodicity by the prevailing light/dark cycle.

### **DESYNCHRONIZED CIRCADIAN PACEMAKERS IN DEPRESSION**

Goodwin and colleagues postulate a more complex model consisting of two pacemakers or oscillators; a strong one controlling body temperature, REM sleep propensity and cortisol secretion; and a weak one controlling the sleep cycle and sleep related neuroendocrine activity (14).

Goodwin states that: "Light acting on circadian oscillators is the basis of seasonal and annual biological rhythms. Phase shift experiments and rapid transmeridian travel can temporarily disturb the normal phase relationships between the two circadian oscillators and their overt rhythms. It is reasonable to assume that such a system of oscillators may be altered by disease or by treatment interventions. The intrinsic period of the oscillators could be altered or changes could occur in the coupling to the external day/night cycle" (14).

### **SUMMARIZING THE PROPOSED ANTIDEPRESSANT ACTION OF LIGHT THERAPY**

Individuals with SAD are postulated to have some impairment in the coupling of their biological rhythms with the day/night cycle such that the shorter days of winter cause the biological rhythm for REM sleep to peak abnormally early in the sleep cycle, producing depression according to the model proposed by Wehr, et al (23). If such a mechanism is correct, then artificially extending the photoperiod to one "seen" by the biological rhythm control system as a spring day could normalize the REM sleep abnormality, thus relieving depression in SAD. A mechanism similar to the retina-SCN-pineal-melatonin axis outlined in the control of mammalian seasonal reproductive cycles may underlie the manner in which shorter photoperiods alter biological rhythms and hence mood. Presenting the retina with light of a desired intensity and duration could then be potentially used to normalize the biological rhythms altered in SAD.

### **INTEGRATING BIOLOGICAL RHYTHMS WITH OTHER THEORIES OF DEPRESSION**

Goodwin noted in animal studies that the number of various brain receptors (alpha and beta adrenergic, cholinergic, dopaminergic, opiate, and benzodiazepine receptors) also show circadian rhythm fluctuations and that chronically administering imipramine (a tricyclic) or chorgyline (an MAOI inhibitor) phase delayed the diurnal variation in all receptors to various degrees, e.g., peak alpha adrenergic receptor

binding occurred twelve hours later in drug treated patients than in untreated controls (other wave characteristics were also changed) (14, 25). Lithium has also been shown to slow circadian rhythms in animals (25). These studies suggest that antidepressant drugs may alleviate depression by phase delaying the depressed patient's already phase advanced circadian rhythms, restoring them to a more homeostatic state.

Lingjaerde, in 1983, reviewed the biochemistry of depression (26), citing the well known biogenic amine theories, the more recent neuroendocrine findings in depression that underlie the use of the dexamethasone suppression test (DST) and the thyrotropin releasing hormone (TRH) test. He also includes the question of biological rhythms, suggesting that they not be viewed separately, but integrated with existing theories. Lingjaerde states: "It is not unreasonable to assume that the function of the hypothalamic nucleus is dependent on monoaminergic mechanisms. If so, general hypofunction, or inherent lability in noradrenergic or serotonergic functions may well predispose to disturbances in the regulation of circadian rhythms. Thus it is clear that disturbed biological rhythms are to be regarded . . . as a disturbance that is most intimately connected with disturbances in monoaminergic and neuroendocrinological functions" (26).

## DISCUSSION

Treating depression in properly diagnosed patients with light therapy is an exciting concept to potentially add to the psychiatrist's armamentarium. Much research remains to be done to confirm previous work with larger numbers of subjects in controlled studies, selecting subjects with seasonal symptoms from larger groups of depressed patients, and devising reliable ways to select out those patients with seasonally dependent psychosocial determinants of depression.

Perhaps even more significant are the implications of the theoretical mechanism of action of light therapy in the etiology of depression. Circadian rhythm research in affective illness offers, in the author's opinion, the most novel conceptualization of affective illness since the biogenic amine hypothesis. The level of knowledge, at this time, of even the most fundamental aspects of the etiology of depression is by no means clear. Current biological research seems focused on neurotransmitter altering drugs and receptor physiology. Could some of this research explain more of the complete picture if data were also viewed from the perspective of altered biological rhythms? Anna Wirz-Justice points out that biochemical determinations such as platelet serotonin concentrations reveal new dimensions when analyzed with circadian (as well as circannual) variability in mind as opposed to single point determinations (7). Could, for example, the lag time in the onset of action of tricyclic antidepressants be explained by the time required for these drugs to normalize the biological rhythm disturbances of depression?

Do antidepressant drugs work by acting on the aminergic neural systems that are known to control biological rhythms, as Lingjaerde suggests? The facts that a) the SCN has the highest concentration of serotonergic neurons in the hypothalamus, b) that the control of melatonin secretion is a noradrenergic system, and c) that the



number of monoaminergic receptors themselves show circadian rhythm periodicity that is altered by antidepressant drugs (including lithium in rats) all suggest some points of potential integration between biogenic amines, receptor physiology, and biological rhythms.

Future depression research will undoubtedly show new perspectives in the design of studies that more fully integrate the tenets of biological rhythm research with the more prevalent research based on theories of synaptic physiology.

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