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Jane Rice

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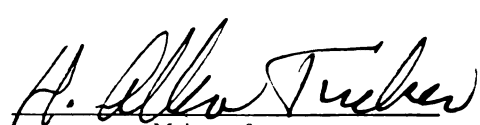

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EFFECT OF LIGHT EXPOSURE ON MELATONIN CONCENTRATIONS AND DEPRESSION SCORES IN SEASONAL AFFECTIVE DISORDER

By

Jane Rice

A DISSERTATION

Submitted to
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ABSTRACT

EFFECT OF LIGHT EXPOSURE ON MELATONIN CONCENTRATIONS AND DEPRESSION SCORES IN SEASONAL AFFECTIVE DISORDER

By

Jane Rice

Seasonal affective disorder (SAD) is a major depressive disorder in which depressive episodes recur in autumn and winter. Daily exposure to morning bright light is effective in reducing depressive symptoms in SAD. The mechanism through which light exerts an antidepressant effect is unknown, although it may involve entrainment of circadian rhythms to the light:dark cycle.

In all experiments, subjects were diagnosed with SAD, rated for severity of depressive symptoms, and assessed for safety during phototherapy. Subjects entered crossover designs consisting of two week-long trials of phototherapy separated by a 1-week withdrawal period. Phototherapy was administered daily (0600-0800 h) at an illuminance of 2500 lux.

Serial saliva samples were collected in the morning (0600-0900 h) or evening (1800-2400 or 2000-2300 h) before and after each phototherapy trial and assayed for melatonin to determine whether evening onset or morning decline of nocturnal secretion changed.

Depression scores were reduced following phototherapy, with complete remission in 40% of cases. Cool white and narrow spectrum green light decreased depression scores as well as full spectrum light. Exposure of facial skin to light did not increase the antidepressant effect of eye exposure alone. Expectations of subjects for treatment did not predict outcome, but subjects'

psychological experience during phototherapy did.

Following phototherapy, salivary melatonin concentrations were increased in the evening and decreased in the morning compared with pretreatment values. These results are consistent with an advance in the timing of the melatonin rhythm.

Narrow spectrum green light decreased concentrations of melatonin in the morning similar to full spectrum light. Blended green-red light decreased concentrations of melatonin in the morning and evening more than full spectrum or blended blue-yellow light. However, alterations in color vision limited the application of blended light as a treatment.

Clinical remission was not correlated with alterations in melatonin secretion. Morning and evening concentrations of melatonin were similar in subjects who achieved clinical remission and subjects who did not.

In conclusion, the antidepressant effect of light is not mediated through an advance in the timing of the melatonin rhythm. The action spectrum for the antidepressant effect may lie within the green waveband. However, subjective experience influences treatment results.

In memory of

my sister Maureen Ann Rice Norman

(1945-1992)

who, without ever mentioning the pineal,

told me as a child that people in the olden days

had an eye in the back of the head

and first inspired me to wonder how

the body knows without seeing

and

my aunt Geraldine Catherine McCartney

(1906-1992)

who was and still is

my hero, the wind beneath my feet

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Introduction

Epidemiological studies indicate that the life-time risk of major depressive disorder in the United States is between 3 and 9 percent (Gold et al., 1988). One type of major depressive disorder is seasonal affective disorder, or SAD. SAD is characterized by recurrent depressive episodes during the autumn and winter that remit spontaneously in spring. The seasonal pattern of depressive episodes in SAD suggests that seasonal changes in the environment, especially light, may be involved in precipitating and remitting episodes. Many have demonstrated the efficacy of bright, artificial light, or phototherapy, in reversing depressive symptoms in SAD (Rosenthal et al., 1984; Lewy et al., 1987; Terman et al., 1988). However, the mechanism through which light exerts an antidepressant effect is not clear, although it may be associated with two photosensitive processes in humans: secretion of the pineal hormone melatonin and entrainment of circadian rhythms to the light:dark cycle.

The specific focus of this thesis was to determine the waveband of light responsible for the antidepressant effect and whether light-induced changes in the circadian rhythm of melatonin secretion are associated with the antidepressant effect.

In human studies, a balance must be struck between ethical and technical considerations and sound scientific design and experimentation. Research in the field of psychiatry is especially complicated by high intersubject variability, uncontrolled secondary variables, expectations of the

subjects for treatment effects, nonspecific placebo responses to the therapeutic setting, safety issues, and ethical considerations of withholding treatment. My approach has been one of observing subjects and collecting samples under the natural light settings in which they become depressed and achieve remission, utilizing design and statistical controls (crossover studies with repeated measures) to maximize information from small groups of subjects, and interpreting data within a physiological and psychological framework.

Research findings on phototherapy for SAD are quickly put into clinical practice without, at this time, the oversight of the Food and Drug Administration. Patient safety must therefore be a priority in research trials. Furthermore, the efficacy of various treatment protocols must be interpreted in terms of clinical significance as well as statistical significance. For many individuals with SAD, the use of light to treat and prevent winter depressive episodes offers a safe, fast-acting, and effective alternative to pharmacological treatments. For many researchers in biological psychiatry, the predictable onset and offset of depressive episodes in SAD along with its moderate severity and quick responsiveness to an environmental intervention may make it a useful model for major depressive disorder in general.

Review of Literature

A. Seasonal Changes in Human Physiology

1. Seasonality of Affective Disorders

Annual variations in human physiology and behavior are common. Annual rhythms are observed in conception, birth, and mortality rates (Aschoff, 1981), weight, sleep, energy, and mood states (Kasper et al., 1989), affective disorders and suicide (Aschoff, 1981; Rosenthal et al., 1983), hormone secretion (Weitzman et al., 1975; Broadway and Arendt, 1985; Haus et al., 1980; Illnerova et al., 1985), metabolic rate (Yurigi et al., 1972), and immune function (Shifrine et al., 1982). Annual rhythms are classified as circannual, social, or seasonal in origin. Circannual rhythms are generated endogenously and persist without environmental input, although they are normally synchronized to the seasonal cycle (Gwinner, 1981). Circannual rhythms are documented in animals (Gwinner, 1981) and may exist in humans (Wirz-Justice et al., 1984). Annual rhythms that are social in origin include physiological and behavioral aspects of calendar events, such as weight gain associated with holiday celebrations. This review focuses on seasonal rhythms which are annual rhythms that depend upon periodic environmental input such as light and temperature (Zucker, 1988). Seasonal rhythms can be distinguished from social rhythms by their occurrence 6 months apart in the northern and southern hemispheres and by their dependence on latitude for the magnitude of the effect (Aschoff, 1981; Gwinner, 1981).

Recent reports of the influence of season on psychiatric illness might appear novel. However, the ancient humoral theory emphasized seasonal influences on these diseases. Aristotle (1953 translation) noted that "if it be cold beyond due measure, it produces groundless despondency." Hippocrates believed that the black humor, associated with autumn, induced fear when its darkness threw a shadow over the area of thought (Jackson, 1987). Seasonal patterns have recently been documented for several types of affective (mood) disorders (Wehr and Rosenthal, 1989) Most prominent of these is seasonal affective disorder (SAD), the periodic recurrence of major depression in autumn and winter with remission in spring and summer.

2. Animal Models for SAD

The seasonality and environmental sensitivity of SAD suggests that it may be a disorder of systems that mediate the organism's adaptation to changes in the physical environment. The literature on animal seasonality is helpful here. Many animals, in their normal adaptations to changes in the physical environment, exhibit behavioral and physiological adjustments that are similar to those exhibited by SAD patients. These include changes in food intake, body weight, energy level, sleep duration, and interaction with the physical and social environment (Gwinner, 1981). Seasonal changes in animals are often induced by changes in photoperiod and mediated physiologically by altered hormonal secretion, especially melatonin (Reiter, 1987). SAD easily lends itself to analogies with animal models of seasonality.

Hibernation may be a neurobiological model for SAD based on similar behavioral and physiological changes and the periodicity of

symptoms (Wirz-Justice et al., 1986). Both are characterized by increased food intake, weight gain, decreased activity, and increased sleep. Mrosovsky (1988), however, notes several flaws with this model. For example, hibernation is characterized by increased slow wave sleep while, in contrast, SAD patients spend a smaller proportion of sleep in the slow wave state (Rosenthal et al., 1984). Additionally, weight gain precedes torpor in hibernating animals while, in SAD, increased eating and weight gain appear coincidently with decreased activity.

Nonetheless, there are other seasonal strategies used by mammals that may be operative in SAD. Rosenthal et al. (1987a) suggest that the symptoms of SAD may be coordinated by neurophysiological systems that vary seasonally in an interrelated way. A growing literature on seasonal rhythms in human physiology and behavior, discussed below, supports this hypothesis. While human seasonality is the norm in some physiological variables, SAD may be an extreme on a seasonality continuum.

3. Human Seasonality

A review of the literature on seasonal variations in hypothalamic function, thermoregulatory variables, serotonergic function, and circadian rhythmicity follows. Some of these seasonal variations occur in physiological functions that are problematic in SAD and may have potential explanatory value for SAD. These are discussed in a separate section on biological studies of SAD.

Hypothalamic functions, such as sleep, appetite, mood, motivation, and autonomic nervous system activity, are prime candidates for seasonal variation due to their involvement in regulating physiological responses to environmental demands. Indeed, one quarter of the normal population

experiences increased appetite and sleep and decreased mood in winter (Terman 1988; Bartko and Kasper, 1989; Rosen and Roenthal, 1991). In addition to increased sleep duration, slow wave sleep is also increased in winter compared with summer in normal control subjects (Lacoste and Wirz-Justice, 1989). Plasma norepinephrine and dopamine beta hydroxylase, reflecting short and long term sympathetic neuronal activity, respectively, are increased in winter (Lacoste and Wirz-Justice, 1989). Not surprisingly, systemic blood pressure is also elevated in winter (Lacoste and Wirz-Justice, 1989).

Seasonal changes occur in thermoregulatory and hypothalamic-pituitary-thyroid variables, even in subjects not exposed to extreme temperature variations. Mean core temperature decreases in winter compared with summer or autumn (O'Malley et al., 1984; Buguet et al., 1989). Physiological responses to cold exposure vary seasonally with autumn being the time of the slowest rewarming rate and the greatest subjective sensitivity to cold (Lacoste and Wirz-Justice, 1989). Thyroid hormones and basal thyrotropin are increased in autumn and winter (Lacoste and Wirz-Justice, 1989). Resting metabolic rate is increased in winter (Yurigi et al., 1972). Additionally, there is seasonal variation in the thyrotropin response to exogenous stimulation with thyrotropin releasing hormone (Lacoste and Wirz-Justice, 1989).

The serotonergic system appears to be uniquely susceptible to seasonal influences as evidenced by high amplitude seasonal rhythms in several variables (Lacoste and Wirz-Justice 1989). The concentration of serotonin in postmortem hypothalamic tissue is highest in autumn and lowest in winter (Carlsson et al., 1980). Cerebrospinal fluid (CSF) 5-

hydroxyindole-acetic acid (5-HIAA), a serotonin metabolite, is highest in winter as is platelet uptake of serotonin (Wirz-Justice and Richter, 1979).

Seasonal changes occur in the timing of circadian rhythms (Pittendrigh, 1988). The timing of peak cortisol concentrations is delayed 90 minutes in winter compared with summer (Griffiths et al., 1986; Kennaway and Royles, 1986). The timing of peak core body temperature is delayed 45 minutes in winter compared with summer (Kloeppel, 1982). The morning decline (offset) in nocturnal melatonin secretion is delayed in winter compared with summer (Griffiths et al., 1986; Kennaway and Royles, 1986). The volume of the human suprachiasmatice nuclei and the number of vasopressin-immunoreactive neurons contained within it are twice as high in autumn as in summer (Hofman and Swaab, 1992). These physiological findings of delayed circadian rhythms parallel the delay in morning alertness reported in winter by healthy subjects (Lacoste and Wirz-Justice, 1989).

The limitations of seasonal studies need to be acknowledged. Variations in age, sex, methodology, latitude, and definition of season can influence results. Similarly, zeitgebers (light, temperature), weather modifications, and social cues (activity, eating) can confound results (Lacoste and Wirz-Justice, 1989). Nonetheless, the widespread capacity for seasonal change in mammalian physiology is unlikely to be absent in humans or unsusceptible to pathology (Mrosovsky, 1988). SAD may well be a case in point. Pathology may arise from a supersensitivity to environmental cues that allows seasonal rhythms to reach an extreme, or, conversely, from a subsensitivity to environmental signals that precludes the development of normal seasonal rhythms.

B. Seasonal Affective Disorder

1. Diagnostic Validity

While seasonal changes in mood and behavior are a normal part of human physiology, SAD represents an extreme in seasonal rhythms of mood and energy that interferes with daily activities. SAD was first described in the scientific literature in the early 1980's (Lewy et al., 1982), although there are many references to seasonal depression throughout medical history (Wehr and Rosenthal et al., 1989). The diagnostic validity of a psychiatric disorder is based on six areas of evidence: symptomatology, natural course of the disease, epidemiology, family history, laboratory tests, and response to a specific treatment (Spitzer and Williams, 1989). A discussion of the diagnostic validity of SAD follows.

Seasonal affective disorder is diagnosed by the presence of a depressive or bipolar (manic-depressive) disorder in which depressive episodes recur annually in the autumn and winter and remit spontaneously in the spring and summer. Initial diagnostic criteria, developed by the National Institute of Mental Health, required at least two depressive episodes that occurred in the autumn or winter and remitted in spring and summer (Rosenthal et al., 1984), one of which fulfilled Research Diagnostic Criteria for major depressive disorder (Spitzer et al., 1978). Depressive episodes for which an antecedent psychosocial stressor could be identified were excluded. The current diagnostic criteria is based on the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R; American Psychiatric Association, 1987). DSM-III-R contains a provision for the specification of a seasonal pattern to both recurrent major depression and bipolar disorder (manic-depression). DSM-III-R criteria stipulate that recurrent onsets of depressive episodes

must occur within the same 60-day window each autumn. Similarly, remission of depressive episodes must occur within the same 60-day window each spring. Additionally, all depressive episodes must meet criteria for major depression, with winter depressive episodes outnumbering other depressive episodes by a ratio of at least 3:1. There must be at least three winter episodes, two of which occur in consecutive years. Similar to the original criteria, diagnosis is precluded when seasonally related psychosocial stressors are in evidence.

2. Clinical and Demographic Features

The clinical symptoms of SAD include fatigue, hypersomnia (increased sleeping, often up to 15 h per day), increased appetite, especially for carbohydrates, weight gain, and depressed mood (Rosenthal et al., 1984). Hypersomnia and increased appetite with weight gain are considered atypical depressive symptoms, in contrast to the more common symptoms of insomnia and weight loss seen in major depressive disorders in general. However, a sizeable proportion of SAD patients experience insomnia, loss of appetite, and weight loss (Thase, 1989; Winton and Checkley, 1989). Depressed SAD patients consume carbohydrate-rich foods more often than normal control subjects and exhibit a seasonal rhythm of carbohydrate intake with a maximum value in winter (Krauchi and Wirz-Justice, 1988). The most frequent and intense symptom is a general lack of energy (Terman et al., 1989b). Moreover, diurnal variation in symptom severity (mood regularly worse upon awakening or before retiring) is present in 85% of SAD patients (Graw et al., 1990).

Little is known about the natural course of SAD. The age of onset of SAD is typically in the third decade of life (Hellekson, 1989). The onset of

depressive symptoms is usually in September, October, or November (Dilsaver et al., 1990; Mayor et al., 1991). Spontaneous remission usually occurs in March or April, with an average episode duration of 5.2 months (Hellekson, 1989). The summer mood state of SAD patients is normal (euthymic) or occasionally manic. While SAD is considered a chronic disorder with recurrent depressive episodes every winter, longitudinal studies have not yet been performed.

The incidence of SAD appears to be dependent on latitude (Potkin et al., 1986; Rosen et al., 1990). Rosen et al. (1990) estimated the prevalence of SAD over a range of latitudes from Florida (1.4%) to New York (9.7%). Depue (1989b) suggests that the overall prevalence of SAD is 3% while Thase (1989) estimates the population prevalence to be 4-6%. In addition to many North American and European reports, SAD is reported in Asia (Nagayama et al., 1991) and Australia (Boyce and Parker, 1988; McIntyre et al., 1989a). The female to male ratio of SAD is usually given as 4:1 (Hellekson, 1989). A positive family history for depression in first degree relatives of SAD patients is reported (Hellekson, 1989).

Phototherapy is the treatment of choice for SAD, being effective in 50-80% of cases (Terman et al., 1989b). Clinical remission usually occurs within 4-7 days (Rosenthal et al., 1984). Maintenance of the antidepressant response depends upon daily phototherapy, with relapse occurring within 4-7 days after withdrawal from treatment. Other types of major depression do not respond to phototherapy (Blehar and Lewy, 1990), suggesting that SAD is a distinct psychiatric disorder (Stewart et al., 1990). Little is known about the response of SAD patients to antidepressant medications. Initial reports suggest that SAD can be treated with imipramine, a noradrenergic

reuptake blocker (Thase, 1989), and tranylcypromine, a monoamine oxidase inhibitor (Dilsaver et al., 1990).

3. Biological Studies

While the validity of SAD receives support from epidemiologic and therapeutic studies (Blehar and Rosenthal, 1989; Rosen et al., 1990), laboratory studies do not reveal a consistent profile of biological abnormalities (Skwerer et al., 1988). Moreover, no biologic marker discriminates unequivocally between SAD patients and either non-seasonal depressed patients or healthy persons. Interestingly, none of the biological abnormalities commonly seen in major depression, such as non-suppression of cortisol with dexamethasone, decreased thyroid stimulating hormone response to exogenous protirelin, and early onset of REM sleep, are present in SAD (Rosenthal et al., 1984; James et al., 1986; Skwerer et al., 1988).

However, numerous differences are noted between SAD patients and normal control subjects, often in physiological variables that exhibit seasonal rhythms. For example, SAD patients spend less time in slow wave sleep in winter than in summer (Rosenthal et al., 1984), a pattern which is opposite to that described in normal control subjects (Lacoste and Wirz-Justice, 1989). Plasma norepinephrine concentrations, which normally increase in winter, are decreased in SAD patients compared with control subjects (Rosenthal et al., 1987b). Depressed SAD patients report feeling energized 1 h after carbohydrate ingestion, whereas normal control subjects report sedation (Rosenthal et al., 1989). A disturbance in the medial hypothalamic satiety system is proposed to explain the presence of

these hypothalamic-mediated symptoms in SAD (Krauchi and Wirz-Justice, 1988).

Thermoregulatory and hypothalamic-pituitary-thyroid axis variables often differ between SAD patients and normal control subjects. The rate of heat loss following an endogenous heat challenge induced by exercise is decreased in depressed SAD patients compared with normal control subjects (Arbisi et al., 1989). SAD patients also exhibit a higher resting metabolic rate compared to control subjects (Gaist et al., 1990). Lacoste and Wirz-Justice (1989) suggest that the response of the hypothalamic-pituitary-thyroid axis to long term changes in environmental temperature may be involved in the etiology of SAD. However, thyroid hormones, thyrotropin, and mean core body temperature do not differ between SAD patients and healthy control subjects (Jacobsen et al., 1987a; Skwerer et al., 1988; Rosenthal et al., 1990).

The serotonergic system which displays seasonal variation in normal control subjects shows some abnormalities in SAD patients. The binding of ^{3}H-imipramine to the serotonin transporter on platelet membrane is decreased in SAD patients compared to normal control subjects (Szadoczky et al., 1989;1991). Additionally, stimulation with m-chlorophenylpiperazine, a serotonin post-synaptic agonist, increases cortisol and prolactin secretion more in SAD patients than in normal control subjects (Jacobsen et al., 1989). Wurtman and Wurtman (1989) suggests that a deficiency in serotonin, perhaps related to dietary intake of the precursor tryptophan, may be involved in triggering winter depressive episodes. Treatment with either tryptophan (McGrath et al., 1990) or serotonergic drugs (O'Rourke et al., 1989) has met with initial success.

Circadian rhythm function may differ between SAD patients and normal control subjects in terms of phase position (Lewy et al., 1987) and amplitude (Czeisler et al., 1987). These findings are the basis of a current hypothesis for the etiology of SAD and are discussed fully in a separate section.

The retinal response to light is of interest since it is the first step in the regulation of circadian rhythms. However, data are controversial in this area. Electrooculographic (EOG) ratios which reflect the activity of the retinal pigmented epithelium are lower in depressed SAD patients than in normal control subjects (Lam et al., 1991). Decreased EOG ratios may thus reflect a deficiency in photoreceptor disk renewal and, consequently, a subsensitivity to light (Reme et al., 1990).

On the other hand, some evidence suggests that SAD patients are supersensitive to light (Beersma, 1990). For example, depressed SAD patients are more sensitive to detecting very dim light than normal control subjects (Oren et al., 1991b). Additionally, SAD patients are more sensitive to the effect of light on melatonin suppression (McIntyre et al., 1990; Thompson et al., 1990). For example, depressed SAD patients suppress melatonin to a greater extent than normal control subjects (40% versus 87% of baseline values) following exposure to bright light (2000 lux for 1 hour; Thompson et al., 1990). Interestingly, this supersensitivity to light in terms of melatonin suppression (Thompson et al., 1990) and dim light detection (Terman and Terman, 1991) is not present in SAD patients in the summer, suggesting a seasonal variation in light sensitivity.

In summary, SAD appears to be a distinct psychiatric disorder in which depressive episodes are associated with the seasonal decrease in photoperiod. At present, the diagnosis of SAD is based on symptomatology

and history of seasonally occurring depressive episodes. The development of a biological marker for SAD would increase diagnostic specificity and have implications for future research.

C. Phototherapy of SAD

The general concensus within psychiatry is that phototherapy is an effective treatment for SAD (Blehar and Rosenthal, 1989). Despite its efficacy, the important parameters of phototherapy such as dose, spectrum, and timing, are incompletely characterized (Lewy et al., 1986; Rosenthal et al., 1988). Furthermore, neither the pathophysiological mechanism underlying SAD nor the mechanism of action of the antidepressant effect of light are known. A discussion of the important aspects of phototherapy follows, including protocol, efficacy, dosage, and design and methodological issues. Biological effects of phototherapy, both positive and negative, are also discussed.

1. Protocol

The current trend of treating SAD with light began with a case study by Lewy and colleagues (1982). In this study, phototherapy was based on the idea of imitating the natural light of a summer day in length, intensity, and spectrum. The subject gazed at a bright light source for 3 h in the morning and 3 h in the evening. A therapeutic effect occurred within 1 week, but relapse occurred within 1 week of withdrawal from treatment. Controlled group studies soon replicated this finding (Rosenthal et al., 1984; 1985). Subsequent studies revealed that imitating natural light in terms of intensity (Wirz-Justice et al., 1986) and photoperiod (Wehr et al., 1986) is unnecessary. The current protocol of phototherapy is 2 h daily during the

months of winter depression. Moreover, phototherapy administered prior to onset of symptoms can prevent subsequent episodes (Meesters et al., 1992).

2. Efficacy

The efficacy of phototherapy is measured by the magnitude of the decrease in depressive symptoms. The Hamilton Rating Scale for Depression (HRSD; Hamilton, 1961) is commonly used to measure changes in depressive symptoms. However, this scale is not entirely appropriate for SAD since it underestimates severity when atypical depressive symptoms (hypersomnia, increased appetite, weight gain) are present. The Seasonal Affective Disorder Rating Scale was developed to measure these symptoms and serve as a supplement to the HRSD (Rosenthal and Heffernan, 1986). The most reliable conclusions on treatment efficacy are derived from those studies using remission criteria incorporating both absolute (HRSD score within the normal range, i.e., <8) and relative (50% reduction of HRSD score) improvement. Applying these criteria to pooled results of individual studies, phototherapy is successful in 53% of patients (Terman et al., 1989b).

Individual responsiveness to phototherapy may be predicted by clinical symptoms. Hypersomnia is associated with a superior response to morning light (Avery et al., 1991). Pretreatment severity of atypical depressive symptoms (hypersomnia, increased appetite, weight gain) correlates highly with treatment success (Nagayama et al., 1991) while pretreament severity of the typical symptoms of depression (insomnia, decreased appetite, weight loss) predicts a poor response to phototherapy (Stinson and Thompson, 1990). Terman et al. (1992) suggest that the ratio of atypical symptoms to total depressive symptoms is the best predictor of clinical success, with a ratio above .29 associated with a positive response.

The dose of light in phototherapy, defined as the amount of light falling on the subject, is conventionally set at 2500 lux. This dose, termed bright light, appears to be more effective than a dose of 300 lux light, or dim light (Rosenthal et al., 1984; 1985; James et al., 1985; Terman et al., 1989b; Kasper et al. 1990). However, some studies report equal efficacy of bright and dim light (Wirz-Justice et al., 1986).

The efficacy of a therapeutic agent often depends upon the time at which it is administered (Reinberg, 1983). Phototherapy is no exception. The efficacy of a given dose of light may depend upon the time at which it is delivered relative to a critical photosensitive period (Kripke, 1984) or to the timing of circadian rhythms (Lewy et al., 1987; Terman et al., 1989b). In some studies, morning light has a superior antidepressant effect to that of evening light (Lewy et al., 1987; Avery et al. 1990b; 1991; Terman et al., 1988; Sack et al., 1990). However, other studies fail to find a treatment difference between morning and evening phototherapy (James et al., 1985; Hellekson et al., 1986; Yerevenian et al., 1986; Wirz-Justice et al., 1989) or morning and afternoon phototherapy (Jacobsen et al., 1987b). Small sample sizes and different methodologies, especially in the definition of treatment success, may account for these conflicting results. The pooled results of individual morning versus evening crossover studies support the superiority of morning phototherapy, with 37% of subjects responding exclusively to morning light, 25% responding at both times of day, 3% responding exclusively to evening light, and 35% to neither (Terman et al., 1989b).

In addition to influencing treatment efficacy, the timing of phototherapy may influence the dose of light required to produce an antidepressant response. For example, dim light (300 lux) is effective when

administered just before and during awakening (Terman et al., 1989a), even though it is ineffective when administered after awakening (Rosenthal et al., 1984). Furthermore, twilight transitions may be more effective than abrupt dark-light transitions. Phototherapy delivered with graded increases of light intensity just before and during awakening (dawn simulation) is an effective antidepressant treatment (Terman et al., 1989a; Terman and Schlager, 1990; Avery et al., 1990a).

3. Design and Methodological Issues

Design and methodologic issues play an important role in the interpretation of results from SAD studies. The widespread publicity about phototherapy generates high patient expectations for treatment success which is often associated with nonspecific placebo responses to the therapeutic setting. The lack of a convincing placebo control further exacerbates the problem of distinguishing a true response between various treatment protocols.

A placebo control, indistinguishable from the active treatment, is technically difficult to develop for light since subjects are not blind to the treatment. A low intensity light (dim light) is often used as a placebo control, but with questionable credibility (Eastman, 1990). Even with an adequate placebo control, the magnitude of placebo response to phototherapy needs to be estimated. Dim light controls achieve only 11% remissions, much lower than the typical placebo response in studies of other depressive disorders (Terman et al., 1989b).

Experimental design issues are likewise controversial. A crossover design with subjects serving as their own controls is often used as a means to decrease the variability of subject response and the number of subjects

required. However, crossover designs often give rise to carryover and order effects (Terman et al., 1990). While parallel designs avoid these disadvantages, they require more subjects and have increased inter-subject variability. Both types of designs often yield equivocal results due to the low power to detect treatment differences (type II error) resulting from small sample sizes.

Methodological differences among studies may also lead to disparate results. Differences in entry criteria, pretreatment severity, and remission criteria may account for some of the conflicting results. Incidental variables, such as the changing photoperiod over the course of a study, variability in the amount of naturally occurring sunlight, and changes in the duration and timing of sleep, may confound results and obscure treatment effects.

4. Biological Effects

Phototherapy induces multiple physiological effects, but it is unclear which of these are mechanistically important or mere epiphenomena of treatment. Moreover, it is unclear whether there are negative effects of phototherapy in addition to the therapeutic antidepressant effect. For example, while phototherapy is safe for short term use (Rosenthal et al., 1984), it is unknown whether there are hazards of chronic use.

Numerous physiological effects of clinical importance are observed with phototherapy. Phototherapy increases slow wave sleep (Skwerer et al., 1988), decreases sleep duration (Rosenthal et al., 1984) and carbohydrate intake (Krauchi and Wirz-Justice, 1988) and normalizes mood (Terman et al., 1989b). Phototherapy increases plasma norepinephrine concentrations (Skwerer et al., 1988) and the density of ^{3}H-imipramine binding sites on

platelet membranes (Szadoczky et al., 1989; 1991). Phototherapy reduces resting metabolic rate (Gaist et al., 1990). Additionally, phototherapy normalizes temperature recovery from an endogenous heat challenge (Arbisi et al., 1989).

Phototherapy also suppresses nocturnal melatonin secretion (Winton et al., 1989) and affects circadian rhythms (Lewy et al., 1987). These physiological effects are the basis of two current hypotheses of the therapeutic effect of light in SAD and are discussed in following sections.

Safety with phototherapy focuses on the type of light source and the health status of the individual (Weale, 1988; Terman et al., 1990b). Potential harmful effects of ultraviolet B (UVB), ultraviolet A (UVA), and visible radiation are a concern. A person staring directly at a phototherapy unit for 2 h per day for 90 days receives an annual UVB dosage of 1.7 J/cm^2 (Oren et al., 1990) which is higher than the dosage associated with an increased risk (5-10%) of developing cortical cataracts. UVA radiation may present a similar, yet less serious risk. Visible radiation, especially within the violet and blue wavebands, may have deleterious effects on the retina (Paramore and King, 1989). While emissions from phototherapy units do not exceed phototoxic levels by any current national standard (Sliney and Wolbarscht, 1980), there are no standards outlining safe exposure limits for long term phototherapy.

In some situations, even short term exposure may be associated with adverse effects. For example, subjects with compromised ocular status may be at risk. Aphakia (loss of the ocular lens), glaucoma (increased intraocular pressure), retinal diseases, inflammatory diseases of the eye, and optic nerve disease may all be exacerbated by exposure to bright light (Terman et al., 1990b). SAD patients taking photosensitizing drugs (tricyclic

antidepressants, phenothiazines, psoralens, porphyrins, tetracycline) during phototherapy may be at risk for erythema (sunburn; Terman et al., 1990b). Side effects have been noted in unmedicated patients with normal ocular status undergoing phototherapy, including headache, eye irritation, agitation, and mania (Schwitzer et al., 1990).

In summary, phototherapy is considered the treatment of choice for SAD with clinical remission achieved by over 50% of patients within 1 week. Well-controlled studies of phototherapy are difficult to achieve due to the lack of a suitable placebo control for light. The development of a placebo control depends, in part, on an understanding of the interaction of light and human physiology and psychology.

D. Photobiology of SAD

1. Photobiological Effects in Humans

Phototherapy falls within the realm of photobiology and therefore requires an understanding of the terms and principles of photobiology (Parrish, 1981). The science of photobiology is concerned primarily with absorption of radiation by photosensitive compounds within the human body. The energy of the absorbed photon may be dissipated as heat or harnessed in a photochemical reaction which induces biochemical and cellular changes and, ultimately, an observable biological effect.

Photobiologic effects are initiated in the skin and eye. Dermally-mediated photobiologic effects are common due to the large surface area and blood volume of the skin which allow the irradiation of many photosensitive compounds (Anderson and Parrish, 1981). For example, absorption of visible radiation by circulating bilirubin is the basis of skin phototherapy for neonatal hyperbilirubinemia (Sisson, 1976).

Retinal photobiologic effects, whether visual or non-visual, are mediated by the photosensitive rods and cones. Phototherapy is believed to exert its antidepressant effect through eye exposure (Wehr et al., 1987). Two retinal, yet non-visual, photobiologic effects, the suppression of melatonin secretion (Lewy et al., 1980) and the entrainment of circadian rhythms (Wever, 1986), are the focus of much SAD research and are discussed in the following sections.

2. Dosage

Photobiologic effects depend upon three variables of light exposure: intensity, duration, and spectrum (Thorington, 1985). Intensity, or dose, refers to the amount of light being delivered per second. Dosage is the total amount of light delivered (intensity x duration). Photobiologic effects are dosage dependent. The standard dose of phototherapy (2500 lux) given for 2 h yields a radiometric dosage of 4.86 Joule/cm^2. While a complete dosage-response curve has not been elucidated, preliminary data are available. With a constant dose of 2500 lux, .5 h of phototherapy is less effective than 1.0 or 2.0 h (Hellekson et al., 1986; Wirz-Justice et al., 1987; Terman et al., 1989c). The reciprocal relationship between dose and duration suggests that an increase in dose (10,000 lux) may allow a proportional decrease in duration (.5 h). Preliminary results support this prediction (Terman et al., 1990a). Unfortunately, potential risks of phototherapy increase with higher intensities of light.

3. Action Spectrum

In addition to intensity and duration (dosage), photobiological effects are wavelength dependent (Anderson and Parrish, 1981). The wavelength range that produces a specific biologic effect is termed its action spectrum

and is determined by the photosensitive compound underlying the effect. Preliminary data are inconclusive regarding the action spectrum for the antidepressant effect of light. Brainard et al. (1990) notes that neither blue (430-465nm) nor red (615-655nm) light is as effective as broad spectrum white light in treating SAD. Green light (505-555nm) is superior to red light (Oren et al., 1991a), but inferior to that of white light (Stewart et al., 1991). Methodological differences, primarily in the quantification of light, may account for the lack of progress in determining the optimal action spectrum for the antidepressant effect of light.

4. Quantification of Light

Since both dosage and spectrum influence the antidepressant effect of light, a quantity that combines both parameters is needed in phototherapy trials. However, this has not been the case in most previous studies of SAD. Photometric quantities are used extensively in phototherapy. Photometric units are based on the spectral sensitivity of the human eye and describe light in terms of its ability to evoke a visual response in humans. The amount of light falling on a subject is termed illuminance in the photometric system. Illuminance, measured in lux, is the most commonly reported quantity in phototherapy trials (Rosenthal et al., 1984; 1985; Terman et al., 1989b).

The use of photometric quantities in phototherapy implies a dependence on visual perception which may be unfounded given the positive effect of phototherapy administered during sleep (Avery et al., 1990a). Radiometric quantities, which measure the absolute amount of radiant energy without regard for its ability to evoke a visual sensation, may be a more appropriate quantity to measure (Indyck, 1976). In the

radiometric system, the radiant power falling on a unit area of irradiated surface (i.e., human subject) is termed irradiance. Irradiance, measured in Watts per square centimeter (W/cm^2), is the basis of dose in photobiology (Yerevanian et al., 1986).

A more specific and precise measure of dose is spectral irradiance since it encompasses both dose and action spectrum (W/cm^2 within a specific waveband). Photon density is a similar measure of dose within the action spectrum, but it is based on the number of photons delivered ($photons/cm^2$), rather than the total power delivered. Photon density may be the best quantity for dose calculations of phototherapy because photochemical reactions ultimately depend upon the number of photons absorbed (Brainard et al., 1990).

In summary, phototherapy of SAD may achieve its effect according to established principles of photobiology. However, the critical variables of photobiologic effects, dosage and action spectrum, are unknown at this time. Both dosage and action spectrum are involved in the quantification of light.

E. Melatonin Hypothesis of SAD

Two main hypotheses have been proposed to explain the antidepressant effect of light, both of which are based upon physiological processes that are photosensitive in humans. The first hypothesis which is discussed in this section is based upon the suppressant effect of light on melatonin secretion (Rosenthal et al., 1984). The second hypothesis, which is discussed in the following section, is based upon the effect of light on circadian rhythms (Lewy et al., 1987).

According to the melatonin hypothesis, SAD resembles the behavioral and physiological changes of some animals during winter which are induced by the seasonal change in photoperiod and mediated physiologically through alterations in melatonin secretion (Gwinner, 1981). Therefore, decreased daylength may induce increased melatonin secretion in humans which, in turn, may precipitate the seasonal change in mood and behavior in SAD patients (Rosenthal et al., 1985). Since bright light can suppress melatonin secretion (Lewy et al., 1980), extending the winter photoperiod with bright artificial light may alleviate depressive symptoms (Rosenthal et al., 1985). Critical analysis of the melatonin hypothesis requires an understanding of the physiological regulation of melatonin secretion.

1. Pineal Gland

Melatonin is produced by the pineal gland, a small structure located at the base of the pineal recess of the third ventricle, superior to the tectum, and covered by the occipital lobe of the cerebrum. The pineal gland has been the subject of inquiry since ancient times. Three thousand years ago, yoga practitioners described the vertex of the skull, corresponding anatomically with the pineal, as a distribution center through which solar radiation energized the body (Leskowitz, 1990). Ancient Greeks considered the pineal to be the seat of the soul, a concept extended by Descartes in the seventeenth century. The pineal was often thought of as a vestigial parietal eye, giving rise to folklore about an eye in the back of the head. Modern inquiry into pineal gland function began with the discovery of the biologically active hormone melatonin (Lerner, 1958). The pineal has direct

photosensory capabilities in lower vertebrates. In mammals the pineal is neurosecretory in function.

2. Synthesis and Secretion of Melatonin

The pinealocyte is the primary site of melatonin synthesis containing all the necessary enzymatic machinery for hormone biosynthesis. Melatonin, or N-acetyl-5-methoxytryptamine, is synthesized from the amino acid tryptophan. The first two steps in the biosynthetic pathway produce serotonin, or 5-hydroxytryptamine (5-HT), through hydroxylation and decarboxylation (Axelrod, 1974). Subsequently, 5-HT is acetylated by N-acetyltransferase (NAT). NAT is the rate limiting enzyme for the conversion of 5-HT to melatonin (Klein, 1970). The final step in the synthesis of melatonin is catalyzed by the enzyme hydroxyindole-O-methyltransferase (HIOMT).

Melatonin synthesis is under sympathetic control from the superior cervical ganglia (Klein, 1979). Synthesis is increased at night due to a large and sustained increase in norepinephrine release from prejunctional sympathetic nerve endings (Axelrod, 1974). Binding of norepinephrine to $beta_1$ adrenergic receptors on the pinealocytes activates the cAMP second messenger system (Axelrod, 1974; Cowen et al., 1983), resulting in increased 5-HT uptake and HIOMT activity. Newly synthesized melatonin diffuses out of pinealocytes into the great cerebral vein and CSF (Reppert, 1980).

The systemic circulation is the major route for delivery of melatonin to target sites (Rollag et al., 1978). Approximately 70% of circulating melatonin is bound to plasma albumin (Cardinali, 1972). Melatonin can be detected in saliva in amounts equal to one third the plasma concentration

(Miles et al., 1985). The half-life of melatonin in blood is estimated at 20 to 40 minutes (Cardinali et al., 1983; Terman and Schlager, 1990). Systemic melatonin is degraded by hepatic 6-hydroxylation to 6-hydroxymelatonin which is subsequently conjugated with sulfate or glucuronate for urinary excretion (Cardinali, 1981; Kopin et al., 1961). Binding sites for melatonin are found in the human brain and ovary (Cohen et al., 1978). Brain binding sites include the hippocampus and frontal cortex (Brown et al., 1981) as well as the suprachiasmatic nuclei (Reppert et al., 1988).

Melatonin secretion decreases with age in humans. Mean 24-h melatonin secretion in adults over age 65 is about half of that of young adults (19-25 years; Sharma et al., 1989). Similarly, peak melatonin concentrations in older adults is 50% that of young adults (Sharma et al., 1989). Melatonin concentrations may rise during the luteal phase of the menstrual cycle (Webley and Leidenberger, 1986; Brun et al., 1987), although there is some disagreement on this point (Brzezinski et al., 1988). The circadian rhythm of melatonin secretion is abolished by destruction of afferent sympathetic fibers to the pineal gland (Li et al., 1989), pinealectomy (Neuwelt and Lewy, 1983), or peripheral beta adrenergic blockade by pharmacologic agents such as atenolol (Cowen et al., 1983) and propanolol (Hanssen, 1977).

3. Circadian Rhythm of Melatonin

Melatonin secretion exhibits one of the most stable and high amplitude circadian rhythms in humans. Negligible concentrations are present in the blood during the day with a sharp rise observed after the onset of darkness (Waldhauser and Dietzel, 1985). Maximum values (100-200 pg/ml) are reached between 0000 and 0600 h, with peak concentrations

generally reached at 0200 h (Waldhauser and Dietzel, 1985). The concentration of melatonin at 0200 h correlates highly with total 24-h melatonin secretion (Arendt et al., 1982; r=0.97). The melatonin rhythm is stable within an individual, but between individuals, there is often great variability in mean and peak concentrations as well as total amount secreted (Waldhauser and Dietzel, 1985). However, duration of nocturnal secretion is stable between individuals at a given time (Waldhauser and Dietzel, 1985). Duration of nocturnal melatonin secretion varies with season, being longer in winter than in summer (Illnerova et al., 1985; Kauppila et al., 1987). A delay in the morning decline (offset) of nocturnal melatonin secretion may be responsible for the increased duration in winter (Broadway and Arendt, 1985).

Melatonin secretion is photosensitive (Wurtman, 1963; Lewy et al. 1980). Light has a suppressant effect on melatonin secretion. For example, exposure to bright light (2500 lux) in the night decreases plasma melatonin concentrations by 50 to 70% (Lewy et al., 1980; Boyce and Kennaway, 1987). The effect of light on melatonin secretion follows the principles of photobiology. First, suppression is intensity dependent (McIntyre et al., 1989b). Second, the degree of suppression depends upon the wavelength of light. Maximal suppression occurs with light at 509 nm (Brainard et al., 1985). Photic information is transmitted from the eye to the pineal through a multisynaptic pathway beginning with the retinohypothalamic tract to the suprachiasmatic nuclei (SCN; Sadun et al., 1984). Fibers of the SCN project to the paraventricular nuclei which send axons through the medial forebrain bundle to preganglionic cells in the intermediolateral cell column of the spinal cord. Preganglionic fibers project from the superior cervical ganglia to the pineal. Exposure to light ultimately decreases

norepinephrine release from sympathetic terminals and subsequently reduces melatonin production (Wurtman et al., 1963).

4. Melatonin in SAD

The melatonin hypothesis of SAD is based on lengthening the winter photoperiod in order to induce a summer pattern of melatonin secretion. However, subsequent studies show that this hypothesis is inadequate to explain the therapeutic response of light (Mrosovsky, 1988). For example, extending the winter photoperiod with 6 h of light is unnecessary for a positive therapeutic effect (Wehr et al., 1986). Inhibition of melatonin secretion with a beta adrenergic antagonist rather than light is not effective in treating SAD (Rosenthal et al., 1988a). Conversely, administration of exogenous melatonin does not cause a relapse in remitted patients undergoing phototherapy (Rosenthal et al., 1986). Furthermore, SAD patients do not secrete more melatonin in winter than normal control subjects (Rosenthal et al., 1987b; Thompson et al., 1990). Moreover, suppression of nocturnal melatonin secretion is unnecessary for an antidepressant effect (Wehr et al., 1986; Rosenthal et al., 1988b; Winton et al., 1989). Therefore, inducing a summer pattern of melatonin secretion by the acute suppression of nocturnal secretion is not associated with the antidepressant effect of light. However, other aspects of melatonin physiology, discussed in the next section, may be involved in SAD.

F. Circadian Rhythms in SAD

1. Circadian Rhythms and Light

The second hypothesis for the antidepressant effect of light is based upon a putative delay in the timing of circadian rhythms in SAD patients and the ability of light to influence circadian timing (Lewy et al., 1987).

Human physiology is characterized by daily rhythms. Many of these rhythms, termed circadian, are innate and have a period (cycle length) of about 24 h. For example, the daily rhythm of melatonin secretion is maintained even in constant low level illumination (Wever, 1986). However, under normal conditions, circadian rhythms are entrained, or synchronized, to the environmental 24-h day by various time cues, or zeitgebers (Wever, 1986). A circadian rhythm can be characterized by its period, amplitude (peak to mean), and phase position (timing relative to clock time). While human circadian rhythms appear to be remarkably stable (Wirz-Justice and Wehr, 1983), disturbances in circadian rhythm function may be involved in some depressive disorders, including SAD.

Recent evidence increasingly points to light as a chronoactive agent, one which can affect circadian rhythms (Wever, 1986; Czeisler et al., 1989). For example, the environmental light-dark cycle synchronizes the endogenous rhythm of melatonin to the 24-h day. Additionally, repeated exposure to bright light for several days shifts the timing of circadian rhythms (Czeisler et al., 1989). The direction of the shift depends upon the timing of light exposure. For example, morning light exposure shifts the timing of circadian rhythms to an earlier, or advanced, phase position. Evening light exposure shifts the timing of circadian rhythms to a later, or delayed, phase position. The human phase-response curve expresses this relationship between the timing of light exposure and the subsequent response in terms of phase shifting (Czeisler et al., 1989).

2. Timing of Circadian Rhythms in SAD

Depressed SAD patients exhibit evidence of delayed timing of circadian rhythms. The melatonin rhythm is delayed about 90 minutes in

depressed SAD patients compared with normal control subjects as assessed by the onset time of nocturnal secretion (Lewy et al., 1987; Terman et al., 1988; Sack et al., 1990). The core temperature rhythm may be also be phase delayed (Avery et al., 1987; 1990b). For example, the timing of peak core temperature occurs about 90 minutes later in SAD patients than control subjects (Avery et al., 1987). However, some studies do not show phase delayed rhythms in SAD patients (Rosenthal et al., 1987b; 1990). This discrepancy may be accounted for by the presence of both phase-delayed and phase-advanced rhythms within the SAD population (Rosenthal et al., 1990).

The phase shifting effect of light is evident after several days of repeated timed light exposure. For example, following 1 week of morning phototherapy, the onset time of evening melatonin secretion is advanced by 60-90 minutes compared with pretreatment values (Lewy et al., 1987; Terman et al., 1988, 1989a; Sack et al., 1990). The timing of the circadian rhythm of core temperature is also advanced following 1 week of morning phototherapy (Avery et al., 1987; Rosenthal et al., 1990). Following 1 week of evening phototherapy, the onset time of nocturnal melatonin secretion is delayed. (Lewy et al., 1987). The light-induced advance in the timing of the melatonin rhythm and core temperature rhythm correlates with an antidepressant effect (Avery et al., 1987; Lewy et al., 1987; Sack et al., 1990; Rosenthal et al., 1990). Based upon the differential effect of morning versus evening light and the delay in circadian rhythms in SAD, Lewy et al. (1987) propose that light exerts an antidepressant effect in SAD because of its ability to correct an underlying circadian rhythm disturbance.

3. Amplitude of Circadian Rhythms in SAD

In addition to shifting the timing of circadian rhythms, light also enhances the amplitude of circadian rhythms (Czeisler et al., 1989). The amplitude-enhancing effect of light is more pronounced in circadian rhythms characterized by a low amplitude. Low amplitude circadian rhythms are believed to be relatively unstable and susceptible to manipulation by chronoactive agents (Wever, 1986). Low amplitude circadian rhythms may reflect an abnormality in the responsiveness of the human biological clock (Czeisler et al., 1987).

SAD patients may display low amplitude or unstable circadian rhythms (Czeisler et al., 1987; Rosenthal et al., 1990). For example, SAD patients advance the timing of the melatonin rhythm to a greater extent than healthy subjects in response to a controlled light-dark cycle or to bright light exposure in the morning (Lewy et al., 1987; Sack et al., 1990). Additionally, combined morning and evening light schedule shifts both the melatonin rhythm and the core temperature rhythm in some SAD patients, but not in normal control subjects (Rosenthal et al., 1987b). Czeisler et al. (1987) propose that phototherapy may exert its antidepressant effect by increasing the amplitude of circadian rhythms (Czeisler et al., 1987), thus rendering them less susceptible to manipulation by chronoactive agents (Mrosovsky, 1988). The amplitude of the core temperature rhythm in SAD patients is increased following phototherapy (Rosenthal et al., 1990).

In summary, both the phase position and amplitude of circadian rhythms, most notably melatonin, differ between depressed SAD patients and normal control subjects. Bright light exposure in the morning increases amplitude and advances circadian phase position. Bright light exposure in the morning is also associated with an antidepressant effect in

SAD patients. It is unknown whether these changes in circadian rhythms are essential for the therapeutic effect of light in SAD.

Objectives

The overall objective of the following series of experiments was to study the effect of different types of light exposure on depressive symptomatology and melatonin concentrations in patients with SAD. The same general crossover design was used in all experiments. The design consisted of 1 week of daily phototherapy followed by a 1-week withdrawal period which was then followed by the crossover to an alternate type of phototherapy for 1 week. Measurements were obtained at pretreatment and the end of treatment in both the first trial of phototherapy and in the second trial.

Chapter 1. Effect of Full Spectrum versus Cool White Phototherapy on Melatonin Concentrations and Depression Scores in SAD Patients

Introduction

Morning (0600-0800 h) phototherapy utilizing a light source with a spectral distribution similar to sunlight (full spectrum) reduces depression scores, sleep duration, appetite, and fatigue in SAD patients (Rosenthal et al., 1984; Avery et al., 1987; Lewy et al., 1987; Terman et al., 1988). Moreover, morning phototherapy has both an acute and a cumulative effect on melatonin concentrations in blood. The acute effect is a suppression of melatonin secretion. Melatonin concentrations in blood decrease toward daytime concentrations within 1 h of morning bright light exposure (Wehr et al., 1986; Terman and Schlager, 1990). However, acute suppression of melatonin is not necessary for the antidepressant effect of light (Wehr et al., 1986; Winton et al., 1989). The cumulative effect of phototherapy on melatonin secretion is observed in changes in the timing of the circadian rhythm. One week of morning phototherapy advances the onset of nocturnal melatonin secretion to an earlier time of day (Lewy et al., 1987). Clinical improvement in SAD patients undergoing phototherapy is correlated with an advance in the timing of nocturnal melatonin secretion (Lewy et al., 1987; Terman et al., 1988; Lewy and Sack, 1989: Sack et al., 1990). Whether an advance in the timing of the melatonin rhythm is necessary or sufficient for the therapeutic effect is unknown.

Measurement of nocturnal melatonin secretion is accomplished with serial blood sampling in the evening under dim (<50 lux) illumination in order to avoid the acute suppressant effect of light (Lewy et al., 1987). Onset time of nocturnal melatonin secretion is defined as the time at which melatonin concentrations rise above a set criterion (Lewy et al., 1987; Sack et al., 1990). Melatonin can also be detected in saliva (Miles et al., 1985b). Salivary melatonin exhibits a circadian rhythm which mirrors that of

plasma (Miles et al., 1985a). Whether serial saliva samples can be used to detect light-induced changes in the onset of nocturnal melatonin secretion is unknown.

At the present time, it is unclear whether improvement in depression scores and modulation of the melatonin rhythm with phototherapy depends upon full spectrum sunlight-simulating light. Whether other types of white light, such as cool white, produce similar results in depression scores and melatonin secretion is unknown.

Therefore, an experiment was conducted to quantify changes in depressive symptoms and salivary melatonin concentrations in SAD patients with full spectrum and cool white phototherapy. The purpose of the experiment was threefold: 1) to determine whether saliva samples can be used to measure light-induced changes in the onset of nocturnal melatonin secretion; 2) to determine whether full spectrum light is necessary for the antidepressant effect; and 3) to determine whether an advance in the onset time of nocturnal melatonin secretion is sufficient to induce clinical remission.

Materials and Methods

Subjects. Human subjects, aged 18-59, were recruited through newspaper articles and referrals from local clinicians. The admission criteria for the study included 1) a DSM-III-R diagnosis of recurrent major depression, seasonal pattern (American Psychiatric Association, 1987), 2) a history of depressive episodes that occurred in the fall and winter and remitted by the following spring for the two previous years, and 3) a score of at least 18 on the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967). Exclusion criteria included pregnancy, concomitant treatment with antidepressant medications or beta adrenergic antagonists,

and suicidal behavior. Subjects were free of psychopharmacologic medications for at least 12 days prior to entering the study and remained so for the duration of the study.

Subjects who met the admission criteria underwent medical assessment to ensure safety during phototherapy. A medical history was obtained with emphasis on ophthalmic and dermal status. Current health status was determined for use as a baseline in monitoring the development of adverse effects. A sleep history was obtained to assess hypersomnia and the stability of the sleep-wake cycle. Subjects entered the study at least 5 weeks before spontaneous remission was expected based on recall of previous episodes. A written informed consent was obtained from each subject. The experiment was performed with the approval of the University Committee for Research Involving Human Subjects (UCRIHS; IRB#88-349).

Experimental Design. The design of the experiment was a 2 x 2 (2 treatments in 2 stages) crossover design consisting of two stages of phototherapy separated by a 1-week withdrawal period (Jones and Kenward, 1989). Subjects were assigned by a balanced procedure to either full spectrum or cool white phototherapy in stage 1 and then crossed over to the alternate treatment in stage 2 of the crossover. Both treatment periods were 7 days. The duration of the study for an individual subject was 3 weeks, but subjects did not all begin on the same day.

Stage 1 of the crossover consisted of pretreatment and treatment measures associated with the first treatment assignment. Pretreatment measures of depression and melatonin were obtained on the evening before day 1 of the treatment week. Treatment measures of depression and melatonin were obtained on the evening of day 7 of the treatment week.

Stage 2 likewise consisted of pretreatment and treatment measures obtained at the same time relative to the treatment week (Figure 1).

Phototherapy Equipment. The two treatment conditions were full spectrum (FS; Vita-Lite F40T12; Duro-Test Corporation) and cool white (CW; Sylvania F40T12CWSS) phototherapy. Phototherapy in each treatment consisted of daily exposure (0600-0800 h) to a bank of eight fluorescent tubes at a distance of 90 cm (Rosenthal et al., 1984). An acrylic diffusing lens (Lithonia) with an absorption cut-off at 325 nm was used to prevent transmission of UVB radiation.

Subjects were seated in front of the light source, but at a right angle to the light source so that the direction of their gaze was 90^{o} to the plane of light. Subjects were instructed to stay awake and glance at the light source for a minimum of 1 second every minute. Subjects were monitored for development of adverse effects and to ensure compliance with the phototherapy protocol. Subject reports were collected daily on sleep timing and duration, mood and energy states, and health status.

Illuminance (Gossen Panlux photometer) for FS light was 2690 lux and 3013 lux for CW light. Irradiance (Kettering; 250-33000 nm range) was 675 uW/cm^2 for FS light and 600 uW/cm^2 for CW light, yielding a calculated dose of 4.86 J/cm^2 and 4.32 J/cm^2 for FS and CW light, respectively. The spectral power distribution of visible radiation (ISCO spectrophotometer) for FS and CW light is shown in Figures 2 and 3, respectively.

Depression Ratings. The response to phototherapy was measured with the HRSD and the SAD Supplementary Items scale (Rosenthal and Heffernan, 1986; Appendix A). Depression ratings were obtained on four occasions: pretreatment of stage 1, last day of treatment in stage 1, pretreatment of stage 2, and last day of treatment in stage 2. Pretreatment

Crossover Design

Stage	Stage 1		Stage 2	
Period	Pretreatment	Treatment	Pretreatment	Treatment

Figure 1. Experimental protocol for two stage crossover design with two treatments.

Figure 2. Spectral power distribution of visible radiation of full spectrum (Vita-Lite F40T12) light.

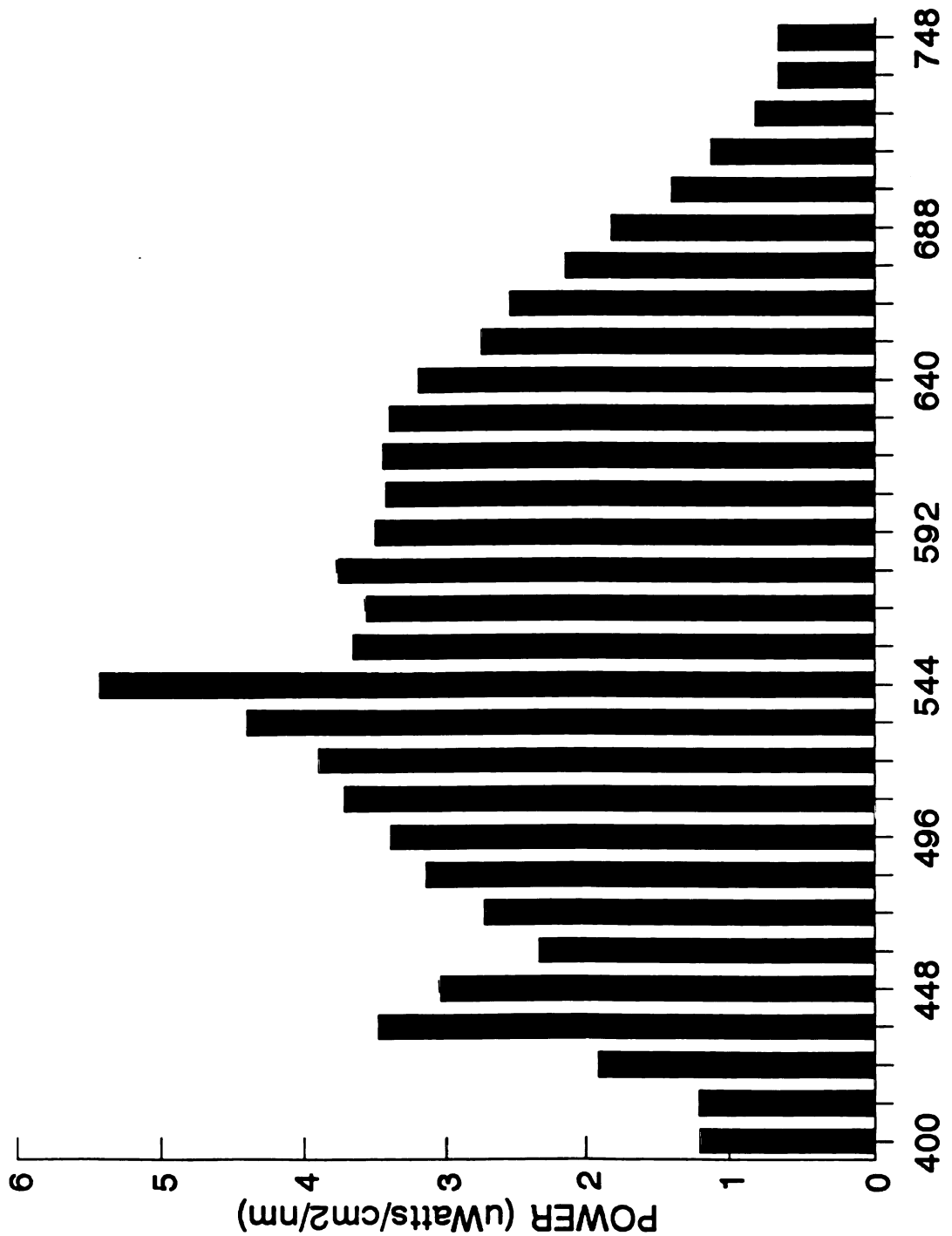
POWER (uWatts/cm2/nm)
0
1
2
3
4
5
6
400
448
496
544
592
640
688
748
WAVELENGTH (nm)

Figure 2

Figure 3. Spectral power distribution of visible radiation of cool white (F40T12CWSS) light.

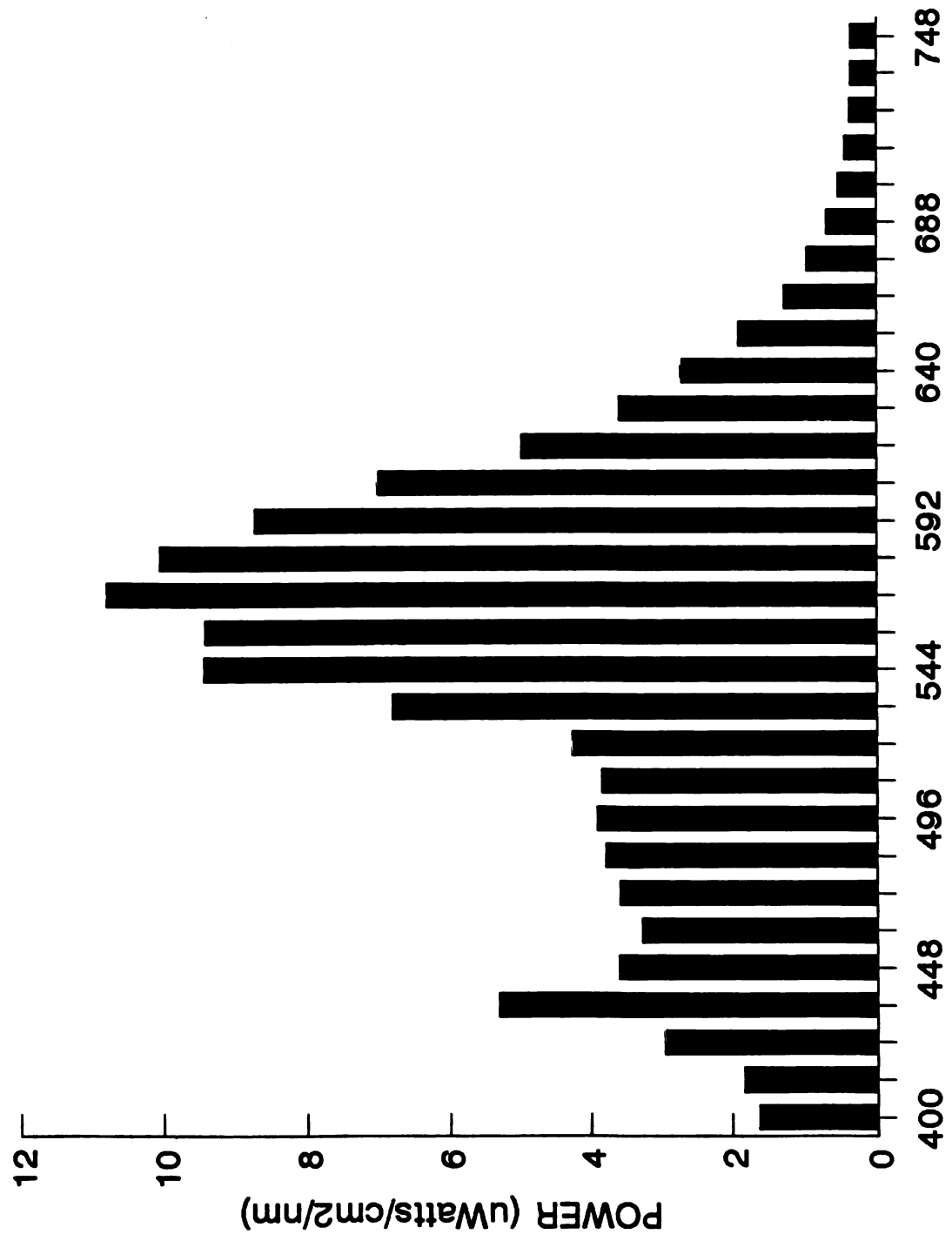
POWER (uWatts/cm2/nm)
0
2
4
6
8
10
12
400
448
496
544
592
640
688
748
WAVELENGTH (nm)

Figure 3

of stage 2 corresponded to the last day of the 1-week withdrawal period. Ratings were performed by a nurse trained in psychiatric evaluation and blind to treatment assignments. Ratings were obtained between 1800 and 2000 h to eliminate the effect of diurnal mood variation on depression scores. Subjects were required to have a pretreatment HRSD score of at least 18 at stage 1 and at least 16 in stage 2. Subjects who did not have a HRSD score of at least 16 at the time of the crossover were rated weekly and were only allowed to crossover to the second stage when they met this criterion.

Saliva Samples and Assay. Serial saliva samples were collected on four occasions that coincided with the timing of depression ratings: pretreatment of stage 1, last day of treatment in stage 1, pretreatment of stage 2, and last day of treatment in stage 2. Saliva samples (2 ml) were collected without stimulation of salivary flow every 30 minutes from 1800 to 2400 h. Subjects were kept in dim light (<50 lux) during the procedure and refrained from eating, drinking, and smoking. Water was allowed immediately after each sample collection, but not closer than 15 minutes prior to the next collection. Samples were stored at -20° C until the time of assay.

Saliva samples met the classification criteria for a biosafety level 2 hazard and were assayed in accordance with the Universal Blood and Bodily Fluids regulations of the Center for Disease Control (USPHS, 1988). Immediately before assay, samples were thawed, refrozen, and thawed for 24 h to reduce viscosity. Samples were then centrifuged at 2500 x g for 30 minutes to remove food particles. Saliva was assayed for melatonin by radioimmunoassay (Fraser et al., 1983) with a double antibody separation

method (Webley et al., 1986) using tritiated melatonin tracer (New England Nuclear) and antiserum G/S/704-6483 (Guildhay Antisera).

Statistical Analysis. The effect of phototherapy on HRSD scores was modeled with a split plot crossover design (Gill, 1978). Two-way analysis of variance with treatment (FS v. CW) and stage (1 v. 2) as between subjects factors and period (pretreatment v. treatment) as the repeated factor was used. Comparisons of means within periods were tested with the Bonferroni t-test. The effect of phototherapy on SAD scores was analyzed similarly. Clinical remission was defined as at least a 50% reduction in HRSD score to a value less than eight, adapted from the recommendation for the 21-item HRSD (Terman et al., 1989). The frequency of clinical remission between treatments was analyzed with a X^2 test. All data are reported as mean$\pm$SD.

The effect of phototherapy on melatonin concentrations was modeled with a double split plot crossover design (Gill, 1978). Analysis of variance with treatment and stage as main plot effects, period as the sub-plot effect, and sampling time (1800-2400 h) as the sub-sub plot effect was used. Differences in melatonin concentrations between 2000 and 2200 h (the usual time of onset of nocturnal secretion) were compared between periods with the Bonferroni t-test. Hormone values were then averaged over each 6-h sampling period to obtain a representative mean. Bonferroni t-test was used to test for differences between means of treatments within periods. Subjects were divided (post-hoc) into two groups on the basis of their clinical status on day 7 of phototherapy: responders were those who met clincial remission criterion and non-responders were those who did not meet clinical remission criterion. Mean concentration of melatonin at

pretreatment and at treatment was compared between responders and non-responders with Student's t-test.

Results

One hundred and three potential subjects were initally interviewed for eligibility and 30 of these underwent medical assessment at the Psychiatry Clinic. Twenty-seven (90%) of these subjects met the diagnostic criteria for SAD. Twelve subjects (nine women and three men) met the admission criteria for the study and agreed to participate. Six subjects received FS light first and six received CW light first. The two light treatments were indistinguishable to subjects. Eleven subjects completed the crossover (one male in the FS-CW sequence group failed to relapse during the withdrawal period). The mean age of the subjects was 36.6±12.3 years (range: 20-59), with a mean age of SAD onset of 23.4±10.3 years. All subjects reported hypersomnia, hyperphagia, and carbohydrate craving.

Analysis of variance of the effect of phototherapy on HRSD and SAD scores and melatonin concentrations is in Appendix B. In order to balance the design, data from one subject were randomly discarded from the CW-FS sequence group to match the subject in the FS-CW sequence group who failed to complete the crossover. HRSD scores were similar ($p>.25$) before FS and CW phototherapy (23.5±4.9 v. 22.6±4.6). HRSD scores were also similar ($p>.25$) after FS and CW phototherapy (9.5±6.8 v. 8.9±5.1). Thus, treatment results were pooled within periods. HRSD scores were reduced ($p<.0001$) on day 7 of treatment compared with pretreatment (Figure 4). Stage of the crossover did not influence ($p>.2$) HRSD scores. SAD scores were similar ($p>.1$) before FS and CW light (17.2±2.9 v. 15.3±3.9). SAD scores were also similar ($p>.25$) after 1 week of FS and CW phototherapy (5.0±3.5 v. 6.1±5.1) Thus, treatment results were pooled within periods.

Figure 4. Pretreatment and treatment HRSD scores for FS and CW light. Treatment consisted of 1 week of daily phototherapy (0600-0800). Pretreatment scores were obtained in the evening before treatment began; treatment scores were obtained in the evening of day 7 of treatment. Both treatments decreased ($p<.05$) HRSD scores.

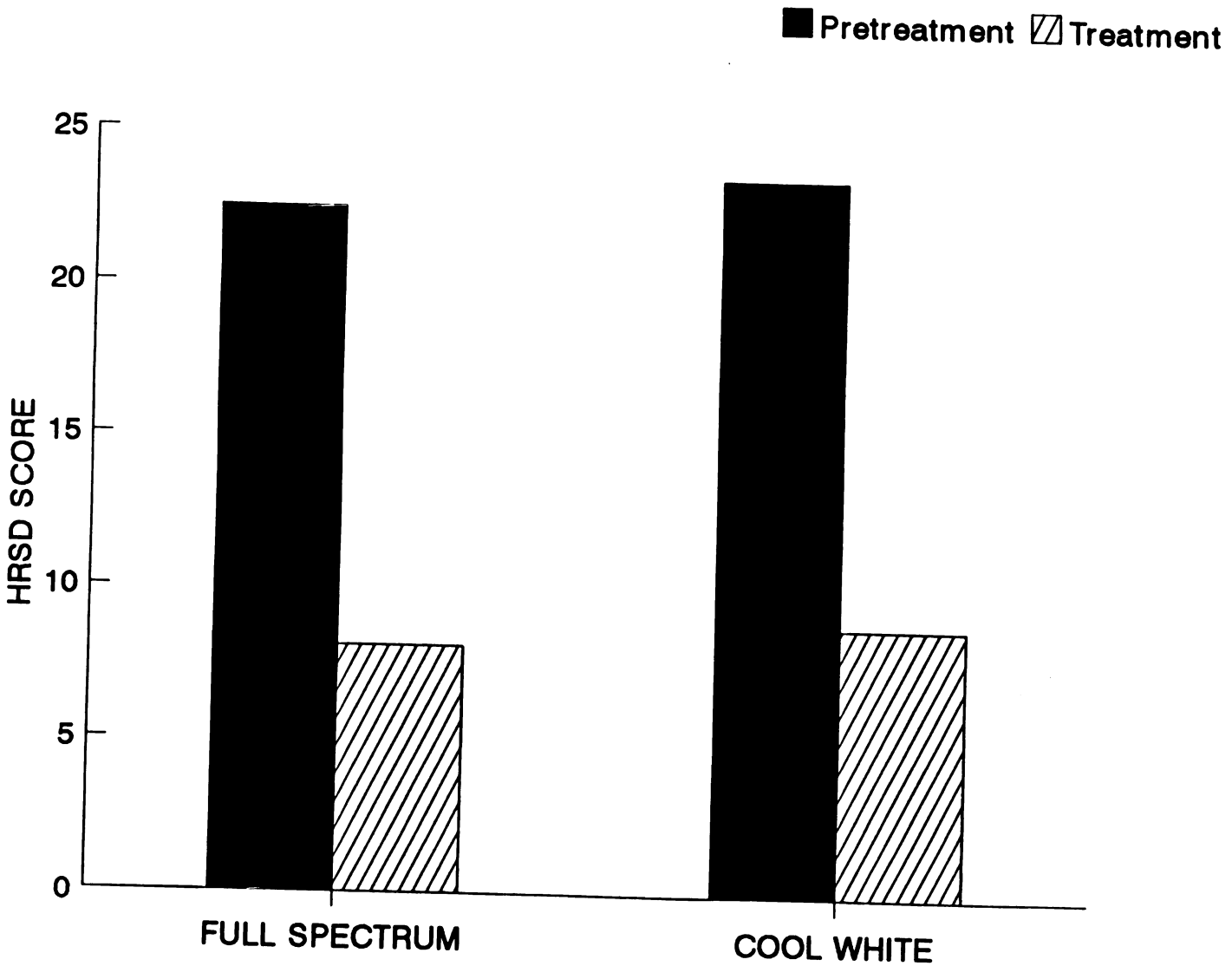
Pretreatment
Treatment
25
20
15
10
5
0
HRSD SCORE
FULL SPECTRUM
COOL WHITE

Figure 4

SAD scores were reduced ($p<.0001$) after 1 week of phototherapy compared with pretreatment. Stage of the crossover did not influence ($p>.8$) SAD scores, but there was an interaction between the effect of stage and period ($p<.06$) such that SAD scores decreased more in stage 1 than in stage 2.

Both treatments were similarly effective in inducing clinical remission (50% for FS vs. 40% for CW light; $X^2=.18$, $p=.67$, $df=1$). Individually, two subjects responded to both FS and CW light, three subjects responded only to FS light, two subjects responded only to CW light, and three subjects responded to neither light. Subjects (except one) were unable to maintain the antidepressant effect of light during the withdrawal week and relapsed into a depressive state. One subject maintained a partial antidepressant effect for 3 weeks before relapsing and entering stage 2 of the crossover. FS phototherapy triggered a hypomanic episode in one patient and CW phototherapy was associated with transient agitation (n=1), headache (n=2) and eye irritation (n=1).

Melatonin concentrations varied between subjects ($p<.03$) and sampling times ($p<.0001$). High melatonin concentrations (range: 40 to 125 pg/ml) were observed at 1800 and 1830 h on each of the four sampling days. Melatonin concentrations then plummeted in the next hour before beginning a steady rise over the remainder of the evening. Mean melatonin concentrations were similar ($p>.2$) before FS and CW phototherapy (26.6 ± 17.5 v. 34.3 ± 26.7 pg/ml). Mean melatonin concentrations were similar ($p>.25$) between the two light treatments on day 7 of treatment (FS: 37.5 ± 20.5; CW: 41.2 ± 24.0 pg/ml). Thus, treatment results were pooled within periods. Stage of the crossover did not influence ($p>.9$) melatonin concentrations. Mean concentrations of melatonin in saliva increased ($p<.03$) between pretreatment and day 7 of treatment (Figure 5). There was

Figure 5. Pretreatment and treatment melatonin profiles. Treatment consisted of 1 week of daily phototherapy (0600-0800 h) with either FS or CW light. Concentrations of melatonin in saliva were measured every 30 minutes from 1800 to 2400 h under constant dim (<50 lux) illumination. Pretreatment melatonin profiles were obtained on the evening before treatment began; treatment profiles were obtained on day 7 of treatment. Treatment results were pooled for FS and CW light. Each data point represents the mean of 20 observations. Mean melatonin concentrations increased ($p<.03$) following phototherapy compared with pretreatment.

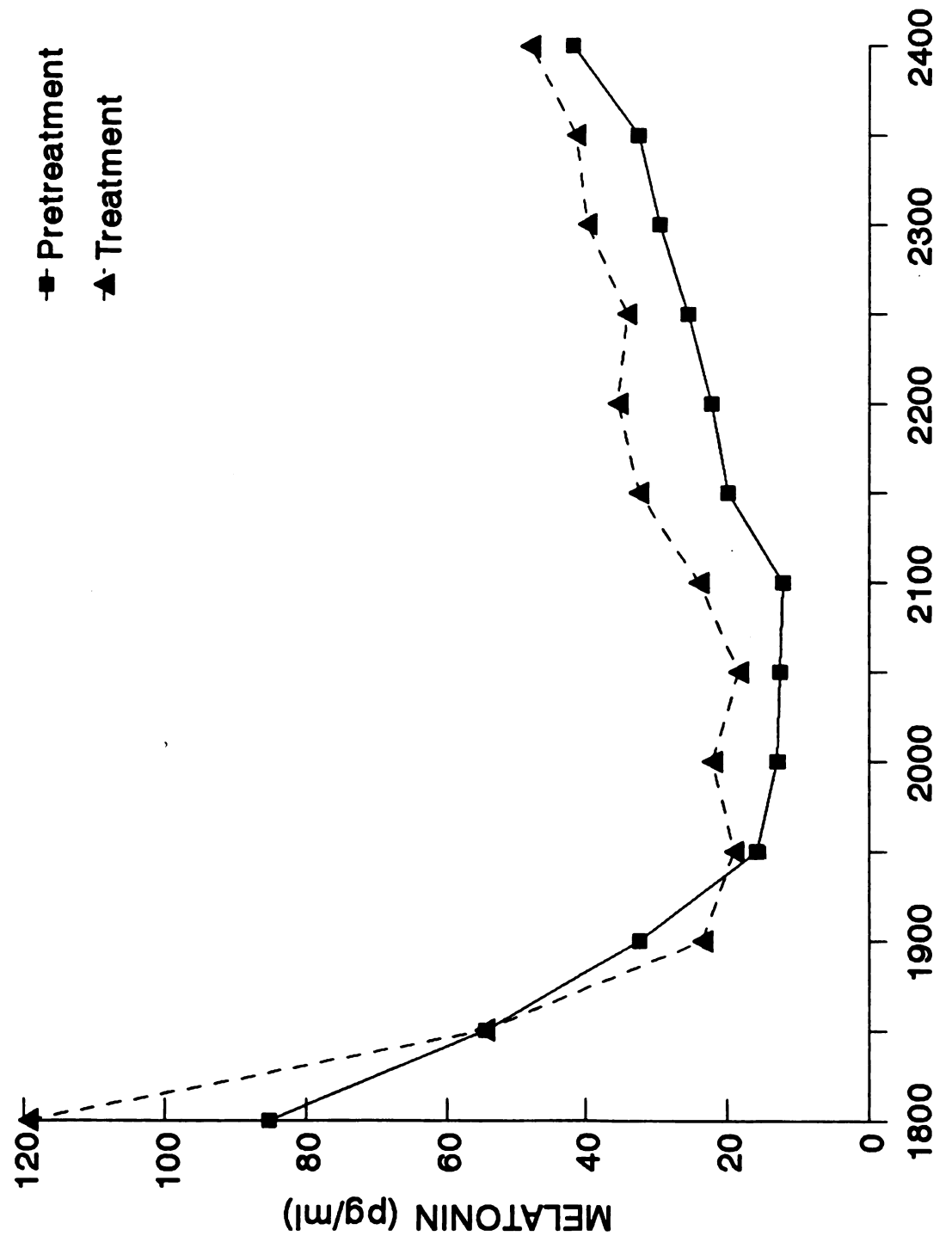
Pretreatment
Treatment
MELATONIN (pg/ml)
120
100
80
60
40
20
0
1800
1900
2000
2100
2200
2300
2400
TIME OF DAY (h)

Figure 5

no increase in melatonin concentrations between 2000 and 2200 h in pretreatment profiles. However, treatment profiles showed a rise ($p<.05$) in melatonin concentrations between 2000 and 2200 h.

On the basis of clinical status on day 7 of phototherapy (remission: a 50% decrease in HRSD score to a value less than eight v. depressed: HRSD score greater than or equal to eight), there was no difference ($p>.25$) in mean melatonin concentrations at pretreatment between subjects who eventually achieved clinical remission (9 observations) and subjects who did not (11 observations). Additionally, there was no difference ($p>.25$) in mean melatonin concentrations on day 7 between the two groups (Figure 6).

Discussion

The symptomatology, demographic characteristics, and response to phototherapy in this sample of SAD patients is consistent with previous reports (Wirz-Justice et al., 1986; Rosenthal et al., 1988). The decrease in HRSD and SAD scores following 1 week of morning phototherapy confirms previous observations using similar protocols (Rosenthal et al., 1984). Pretreatment HRSD scores were comparable before both stages of the crossover, indicating that the 1 week withdrawal period was sufficient to prevent carryover effects of light on depression scores. This observation is consistent with previous reports (Rosenthal et al., 1984; Wehr et al., 1986). Other studies which failed to use a 1-week withdrawal period have reported carryover effects of light (Salinas et al., 1992). The equal efficacy of FS and CW light to decrease HRSD and SAD scores indicates that a spectral distribution similar to natural light is not critical for an antidepressant response. Furthermore, the positive response to phototherapy in the absence of UVB radiation indicates that the action spectrum for the antidepressant response is not within this waveband (290-320 nm).

Figure 6. Melatonin profiles on day 7 of treatment in subjects who achieved clinical remission (9 observations) and subjects who did not (depressed; 11 observations). Treaatment consisted of 1 week of daily phototherapy (0600-0800 h) with either FS or CW light. Salivary samples were collected under dim (<50 lux) illumination. Treatment results were pooled for FS and CW light. Mean melatonin concentrations were similar ($p>.25$) between the two groups following 1 week of phototherapy.

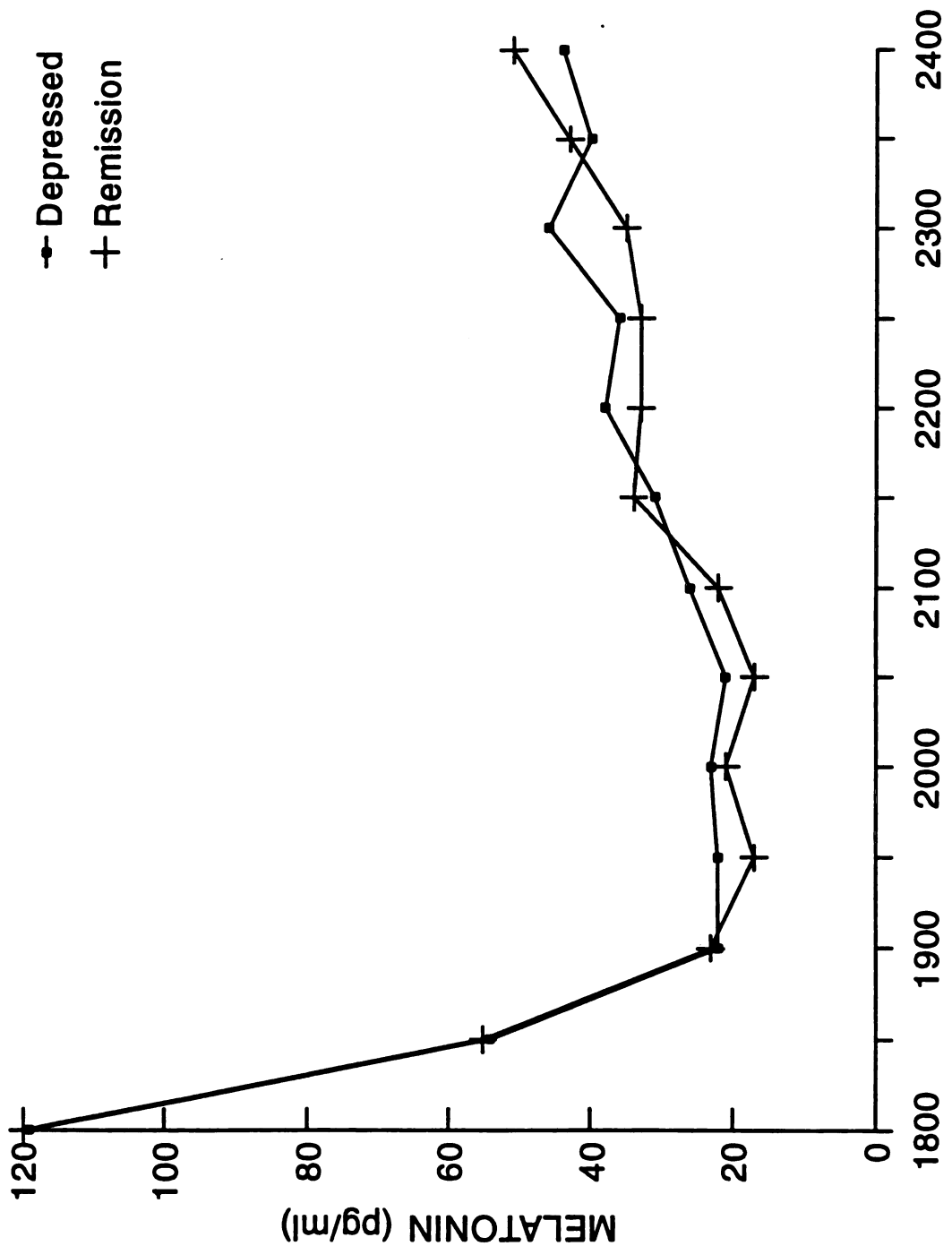
Depressed
Remission
MELATONIN (pg/ml)
120
100
80
60
40
20
0
1800
1900
2000
2100
2200
2300
2400
TIME OF DAY (h)

Figure 6

Subjects found saliva sampling relatively easy to perform and preferable to blood sampling. Melatonin concentrations in saliva showed high interindividual and low intraindividual variability, a finding that is consistent with reports based on plasma melatonin (Waldhauser et al., 1985; Laasko et al., 1990). In the present experiment, melatonin concentrations increased steadily between 2000 and 2400 h, reflecting thenocturnal rise in pineal uptake of serotonin (Axelrod, 1974), pineal NAT activity (Klein and Weller, 1970), and plasma melatonin concentrations (Waldhauser et al., 1985). The data in the present experiment are consistent with previous reports of circadian rhythmicity in salivary melatonin (Miles et al., 1985a, 1985b, 1989; McIntyre et al., 1987). The light-induced increase in salivary melatonin concentrations in this experiment parallels that reported for plasma melatonin following a similar phototherapy protocol (Hansen et al., 1987). Melatonin concentrations in saliva are generally 30% of plasma concentrations (Miles et al., 1985a). Approximately 70% of circulating melatonin is bound to plasma albumin (Cardinali et al., 1972) and cannot diffuse into acinar cells of the salivary glands. Thus, salivary melatonin concentrations may reflect the biologically active free fraction of circulating melatonin (Miles et al., 1985b).

The finding of very high melatonin concentrations in saliva early in evening is not readily explainable. Others have also noted it (Miles et al., 1989; Nickelson et al., 1991). One possibility is that salivary flow rate may have varied throughout the 6-h profile. Salivary flow rate exhibits a circadian rhythm with flow rate higher early in the evening (1800 h) compared with later in the evening (2400 h; Dawes, 1972). However, Miles et al. (1989) reported that changes in salivary flow rate do not affect the concentration of melatonin in saliva. Another possibility is that entry into

the dim light environment removed the suppressant effect of light on melatonin. However, this possibility appears unlikely since melatonin concentrations at this time were often twice as high as midnight concentrations. Furthermore, this effect has not been observed in plasma samples obtained under similar protocols (Lewy et al., 1987). More likely the effect is related to the salivary assay. In the present experiment as well as in the two previous reports (Miles et al., 1989; Nickelson et al., 1991), high concentrations of melatonin in saliva were observed at sampling times closely associated with food ingestion. Miles et al. (1989) suggests that the presence of certain kinds of food in saliva may contaminate the radioimmunoassay system. Thus, high concentrations of melatonin in saliva early in the evening are most likely an artefact of the assay rather than a measure of circulating melatonin.

The similar response in melatonin concentrations to FS and CW light indicates that a spectral distribution similar to sunlight is not necessary to modulate melatonin secretion. This observation is consistent with other photobiologic effects in which the full spectral range of light is unnecessary to elicit a response (Anderson and Parrish, 1981). The observation of similar melatonin concentrations before both stages of the crossover indicates that there is no carryover effect of light on melatonin concentrations following the 1-week withdrawal period. Others have reported carryover effects of light persisting beyond 1 week (Rosenthal et al., 1990). This inconsistency may be due to differences in the duration of daily phototherapy between experiments (2 vs. 6 h).

Sleep deprivation does not account for the antidepressant effect of morning phototherapy. In a study of hospitalized SAD patients, Rosenthal et al. (1985) reported that awakening patients at 0500 h and administering 3

h of dim (<5 or <300 lux) light was not effective in reducing depression scores.

Studies of light-induced changes in the circadian rhythm of melatonin usually employ 24-h profiles. However, for practical reasons (subject compliance and availability of subjects), studies of SAD patients frequently employ shorter time periods such as overnight (Terman and Schlager, 1990) or evening (Lewy et al., 1987; Sack et al., 1990) profiles. Determination of onset time of nocturnal melatonin secretion within these profiles is often based upon visual inspection of the raw data (Terman and Schlager, 1990) or the time at which melatonin concentrations rise above a set criterion, such as 15 or 20 pg/ml (Lewy et al., 1987; Sack et al., 1990). In the present experiment, high variability between subjects and high concentrations of melatonin early in the evening precluded the use of a set criterion in determining onset time. Visual inspection was deemed unreliable. Another approach is to determine whether a significant increase in melatonin concentration occurs within the usual timeframe (2000-2200 h) of onset of nocturnal secretion (Lewy et al., 1987). In the present experiment, melatonin concentrations remained low between 2000 and 2200 h before treatment, suggesting that the onset of nocturnal secretion had not yet occurred. In contrast, on day 7 of treatment, melatonin concentrations increased significantly between 2000 and 2200 h, suggesting that the onset of nocturnal secretion had occurred. These observations are consistent with previous reports of advanced onset of nocturnal melatonin secretion in SAD patients following 1 week of phototherapy compared with pretreatment (Lewy et al., 1987; Terman et al., 1988; Sack et al., 1990).

Others have used mean hormone concentrations within a specified time period to monitor light-induced changes in the timing of circadian rhythms (Hansen et al., 1987; Wirz-Justice et al., 1990). For example, an increase, relative to pretreatment, in the mean concentration of melatonin between 2200 and 2400 h following 7 days of phototherapy may be indicative of a phase advance of the rhythm such that more melatonin is secreted earlier in the evening (Hansen et al., 1987). In the present experiment, comparison of mean melatonin concentrations before and after phototherapy revealed an increase in evening melatonin secretion following phototherapy. This finding may be due to an advance in the timing of the melatonin rhythm or to a general increase in 24-h melatonin secretion. Skwerer et al. (1988) compared 24-h profiles of melatonin secretion in SAD patients before and after 1 week of phototherapy and found no evidence of an overall increase in 24-h melatonin secretion. The result of the Skwerer study suggests that an increase in evening melatonin concentrations following phototherapy as occurred in the present experiment may be specific to that timeframe and may reflect an advance in the timing of the circadian rhythm. Assessment of the morning decline (offset) of nocturnal melatonin secretion will strengthen this interpretation if morning melatonin concentrations are decreased following phototherapy.

In the present experiment, the increase in evening melatonin concentrations and possible advance in the melatonin rhythm following 1 week of phototherapy was associated with clinical remission. Others have reported the same association of clinical remission and a circadian advance in the melatonin rhythm (Lewy et al., 1987; Terman et al., 1988; Sack et al., 1990). However, these studies have utilized a morning versus evening crossover design which leads to circadian phase shifts in opposing

directions with each week of phototherapy (advance with morning light and delay with evening light). Since a therapeutic effect occurs only with morning light, the circadian phase advance is confounded with the therapeutic result. Nonetheless, several investigators have proposed that the antidepressant effect of light is mediated by the phase advance in the melatonin rhythm (Lewy et al., 1987; Sack et al., 1990). In the present study, only morning light was used and a possible circadian advance was observed in the onset of nocturnal melatonin secretion. However, when subjects were divided on the basis of clinical status on day 7 of phototherapy (subjects who achieved clinical remission versus subjects who remained depressed), it was observed that both groups showed a similar increase in evening melatonin concentrations. This observation suggests that there is a dissociation between an advance in nocturnal melatonin secretion and clinical remission. Others have noted the same dissociation in individual case studies (Terman et al., 1990; Allen et al., 1992). While both clinical remission and an advance in the onset of nocturnal melatonin secretion are the result of cumulative exposure to morning bright light, the two effects are not directly related. However, it cannot be ruled out that a circadian phase advance in the melatonin rhythm may be necessary for an antidepressant effect, although it is not sufficient in itself to cause clinical remission.

In conclusion, measurement of melatonin in saliva offers a non-invasive technique for assessing the effect of phototherapy in SAD patients. FS light is not essential to decrease depression scores or modulate the circadian rhythm of melatonin. Both FS and CW light contain the necessary waveband of light with a sufficient intensity to induce clinical remission and increase nocturnal melatonin concentrations. The results

of this study indicate that there is a dissociation between the effect of light on depression scores and evening melatonin concentrations following 1 week of morning phototherapy in SAD.

Chapter 2. Effect of Full Spectrum versus Narrow Spectrum Green Light on Melatonin Concentrations and Depression Scores in SAD Patients

Introduction

Daily phototherapy for 2 h with full spectrum light decreases depression scores (Rosenthal et al., 1984) and advances the timing of the nocturnal onset of melatonin secretion (Lewy et al., 1987). The effect of narrow spectrum light on depression scores and melatonin secretion is not fully known. In other areas of photomedicine, narrow spectrum light is often as effective in producing the desired result as the full spectrum of visible light. For example, neonatal hyperbilirubinemia is effectively treated with narrow spectrum blue or green light (Ennever, 1990).

Narrow spectrum blue and narrow spectrum red light are not as effective as full spectrum light in reducing depression scores in SAD patients (Brainard et al., 1990). Whether the loss of efficacy with blue and red light is due to the absence of white light or the lack of a critical waveband of light is unknown. In addition, it is not known whether white light is required to modulate the circadian rhythm of melatonin. The timing of the circadian rhythm of melatonin can be assessed from the time of onset of the nocturnal rise, the time of peak concentration, or the time of the morning decline (offset) of nocturnal secretion. In Chapter 1, it was shown that increasing evening melatonin concentrations (consistent with advancing the timing of nocturnal secretion) was insufficient to induce an antidepressant response. However, it is not known whether decreasing melatonin concentrations in the morning (also consistent with advancing the timing of nocturnal secretion) may be important in inducing clinical remission in SAD patients. Therefore, an experiment was conducted to determine the effect of white light versus green light on morning melatonin concentrations and depression scores in SAD patients. The purpose of the experiment was threefold: to determine 1) whether green light can

decrease depression scores, 2) whether green light can modulate the circadian rhythm of melatonin, and 3) whether clinical remission is associated with a decrease in melatonin concentrations in the morning.

Materials and Methods

Subjects. Subjects were recruited through an advertisement in the Lansing State Journal newspaper as well as through the methods described in Chapter 1. The admission criteria for the study were identical to that described in Chapter 1, with the exception that the criterion for the HRSD score was decreased to 14. Exclusion criteria were expanded to include previous photosensitizing reactions and cataract surgery based upon the advice of a dermatologist and optometrist. Lactation was also added to the exclusion criteria due to the possibility of stimulating vitamin D synthesis (Adams et al., 1982). The medical assessment was identical to that described in chapter 1. Subjects did not maintain sleep logs during this experiment. The experiment was performed with the approval of UCRIHS (IRB#89-506).

Experimental Design. The experimental design was that described in Chapter 1 with the following modifications. The treatment period lasted 6 days. Day 7 of the treatment week was reserved for morning saliva sampling. In order to differentiate the circadian effects of light from the direct suppressing effect on melatonin secretion, phototherapy was not administered on the morning of saliva collection (Lewy et al., 1980). Pretreatment and treatment values were obtained for both stage 1 and stage 2 of the crossover. Pretreatment scores for depression were obtained 2 days before the start of treatment. Pretreatment melatonin profiles were obtained 1 day before the start of treatment. Treatment depression scores

were obtained on day 6 of the treatment week and treatment melatonin profiles were obtained on the following morning (day 7).

Phototherapy. Phototherapy was administered daily at the Psychiatry Clinic between 0600-0800 h. The two treatments were full spectrum light (FS; Vita-Lite F40T12, Duro-Test Corp.) and narrow spectrum green light (Sylvania F40T12G) with a half-peak bandwidth between 505 and 555 nm. Illuminance for FS phototherapy was 2690 lux and 4500 lux for green phototherapy. Irradiance was 675 uW/cm^2 for FS light and 600 uW/cm^2 for green light. These measured irradiances yielded a calculated dose of 4.86 and 4.32 Joules/cm^2 for FS and green light, respectively. The spectral power distribution for FS and green light is shown in Figures 2 and 7, respectively.

Depression Ratings. Depression ratings (HRSD and SAD) were obtained between 0900-1200 h on four occasions: pretreatment and treatment in stage 1 of the crossover and pretreatment and treatment in stage 2 of the crossover. Additionally, a SIGH-SAD (Structured Interview Guide for the Hamilton - Seasonal Affective Disorder) score, which is a composite of the HRSD score and SAD score, was calculated on each of the four occasions (Williams et al., 1988). Subjects were required to have a HRSD score of at least 13 to crossover to stage 2.

Saliva Handling and Assay. Serial saliva samples were collected on four occasions: pretreatment and treatment in stage 1 of the crossover and pretreatment and treatment in stage 2 of the crossover. Samples were collected every 30 minutes from 0600-0900 h. Subjects were allowed to eat and drink briefly between sample collections, but not within 15 minutes of the next sample collection. Sample collection was performed at each

Figure 7. Spectral power distribution of green light (Sylvania F40T12G).

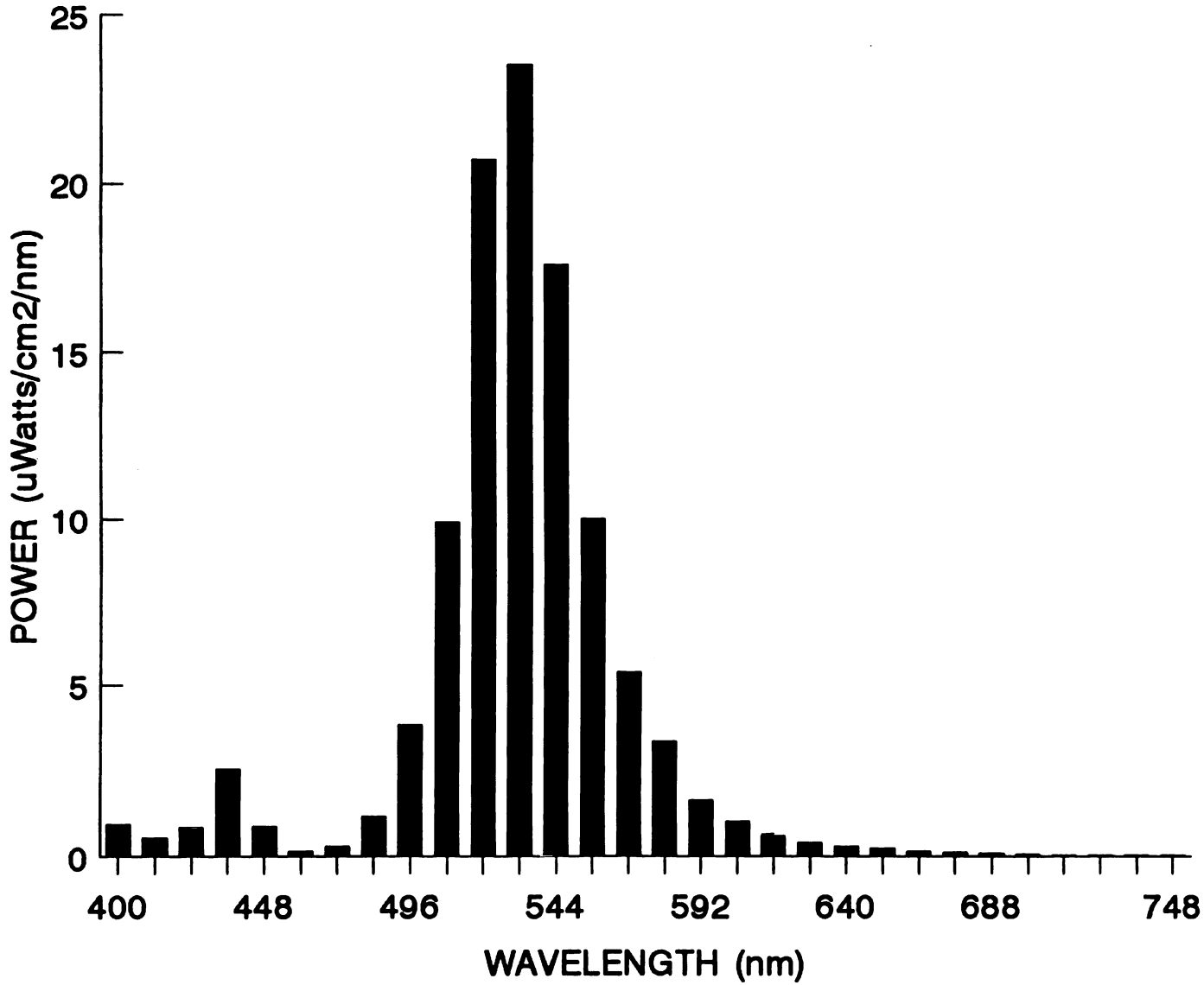
25
20
15
10
5
0
POWER (uWatts/cm2/nm)
400
448
496
544
592
640
688
748
WAVELENGTH (nm)

Figure 7

subject's home under the natural and artificial lighting (<300 lux) to which they were normally exposed (below the threshold for melatonin suppression; Lewy et al., 1980). Samples were stored in home freezers (approximately -10 to -20° C until returned to the clinic and then stored at -20°C until time of assay. Saliva samples were assayed for melatonin as described in the previous chapter.

Statistical Analysis. As described in Chapter 1, a split plot crossover design was used to model the effect of phototherapy on depression scores. In brief, treatment (FS v. green) and stage (1 v. 2) were the main plot (between subjects) effects and period (pretreatment v. treatment) was the repeated factor of the sub-plot. Separate analyses of variance were performed on HRSD, SAD, and SIGH-SAD scores. Bonferroni t-test was used to determine whether pretreatment scores were comparable before light treatments (or stages) and whether treatment scores were comparable after light treatments (or stages). Change in depression score (pretreatment score minus treatment score) within treatments (or stages) was calculated and tested with Bonferroni t-test. The criterion for clinical remission was a 50% decrease in HRSD score to a value less than eight. The effect of phototherapy on melatonin concentration was modeled as a double split plot as described in Chapter 1 with sampling time (0600-0900 h) as a sub-sub-plot effect. Hormone values were averaged over each 3-h sampling period to obtain a representative mean. Bonferroni t-test was used to test for differences between means of treatments (or stages) within periods. All data are reported as mean±SD.

Results

One hundred fourteen potential subjects were assessed to determine study eligibility over the course of two winter seasons. Forty-five

underwent medical assessment at the Psychiatry Clinic and forty-one (91%) met the diagnostic criteria for SAD. Twenty-two subjects (17 women, 5 men) met the study criteria and agreed to participate. Eighteen subjects completed the crossover. One female and one male subject failed to relapse during the withdrawal period from FS light, one female subject developed hypomania with FS light, and one female subject attempted suicide during the withdrawal period from green light. Data from these subjects were not included in the analyses. The mean age of study subjects was 43.8±8.5 (range:28-60) with an average age of onset of SAD of 30.7±10.2 (range:10-51). Subjects had not previously participated in a phototherapy study.

Analysis of variance for the effect of phototherapy on HRSD, SAD, and SIGH-SAD scores and melatonin concentrations is in Appendix C. There was no difference in HRSD ($p>.1$), SAD ($p>.1$), or SIGH-SAD ($p>.05$) scores between green and FS light. Thus, results were pooled for green and FS light. Phototherapy reduced HRSD scores (19.3±3.2 v. 10.3±6.8; $p<.0001$), SAD scores (12.7±4.9 v. 7.1±5.5; $p<.0001$), and SIGH-SAD scores (32.0±5.6 v. 17.3±11.2; $p<.0001$). However, there was an interaction ($p<.05$) between the effect of stage (1 v. 2) and period (pretreatment v. treatment) on depression scores on all three rating scales (Figure 8). Depression scores were comparable at pretreatment between the stages, but treatment scores were lower ($p<.005$) in stage 1 of the crossover than in stage 2. The change in depression scores (pretreatment score - treatment score) was greater in stage 1 of the crossover than in stage 2 for all depression rating scales (HRSD change score: 13.8 v. 4.3, $p<.005$; SAD change score: 8.8 v. 2.5, $p<.01$; SIGH-SAD change score: 22.6 v. 6.8, $p<.005$).

Based on clinical remission criterion, one subject responded to both green and FS light, seven responded only to FS light, five responded only to

Figure 8. SIGH-SAD, HRSD, and SAD scores at pretreatment in stage 1 (St1-Pretrt), treatment in stage 1 (St1-Pretrt), pretreatment in stage 2 (St2-Pretrt), and in stage 2 (St2-Trt). Treatment consisted of 6 days of daily phototherapy (0600-0800 h) with either green or FS light.

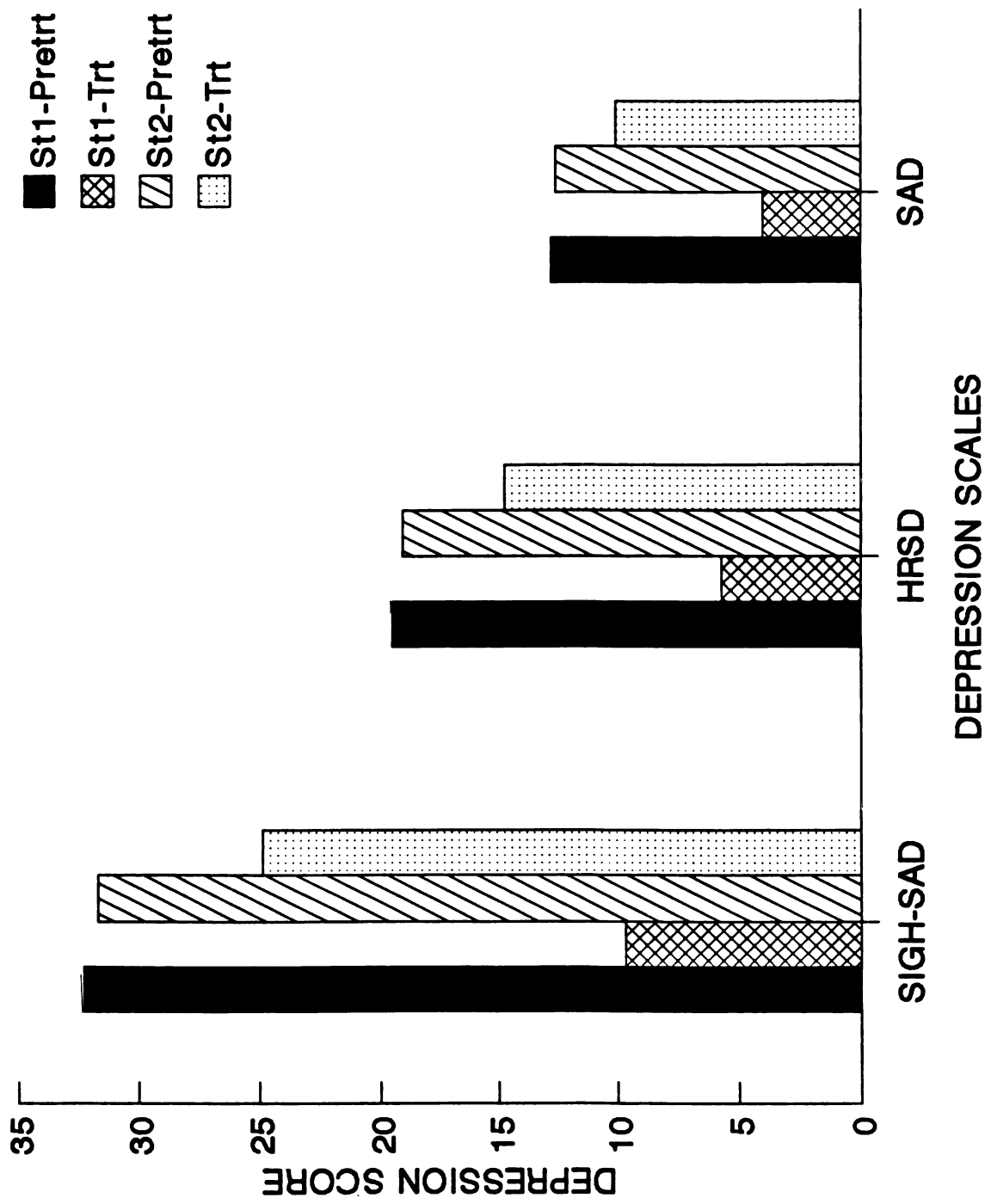
St1-Pretrt
St1-Trt
St2-Pretrt
St2-Trt
DEPRESSION SCORE
35
30
25
20
15
10
5
0
SIGH-SAD
HRSD
SAD
DEPRESSION SCALES

Figure 8

green light, and five did not respond to either light treatment. The frequency of clinical remission did not differ between light treatments (X^2=.28, p>.9). However, the frequency of clinical remission was higher (X^2=7.14; p<.01) in stage 1 (12 out of 18 subjects) than in stage 2 (2 out of 18 subjects). All subjects relapsed during the withdrawal week and immediately entered stage 2 of the crossover.

A substantial proportion of subjects reported difficulty with phototherapy during stage 2. Six out of nine subjects who received green light in stage 2 and seven out of nine subjects who received FS light in stage 2 reported a strong dislike for the light and discomfort (nausea, headache) during the 2-h sessions. Three of these subjects experienced a worsening of depressive symptoms (insomnia, loss of appetite, psychomotor retardation) during stage 2. One subject experienced discomfort in both stages of the crossover. Following 1 week of phototherapy, HRSD scores for subjects (15 observations) who reported a dislike for and discomfort with phototherapy averaged 16.2±4.8 compared with 8.8±4.3 for subjects (8 observations) who reported no preference for one light over the other and 4.4±3.2 for subjects (13 observations) who reported a positive experience with phototherapy.

The mean concentration of melatonin in saliva was similar between FS and green light at pretreatment (36.6±7.9 v. 39.6±8.6 pg/ml; p>.1) and treatment (29.9±6.8 v. 28.1±5 pg/ml; p>.1). Thus, results were pooled for green and FS light. Melatonin concentrations were reduced between pretreatment and treatment (38.2±8.5 v. 29.0±6.2 pg/ml; p<.001; Figure 9). Pretreatment concentrations of melatonin were 35.7±5.8 and 40.7±10.4 pg/ml (p>.1) in stage 1 and 2, respectively. Concentrations of melatonin following 6 days of phototherapy were 31.5±6 and 26.5±5.8 pg/ml (p>.1) in stage 1 and 2 of the crossover, respectively. Melatonin concentrations

Figure 9. Salivary melatonin concentrations between 0600 and 0900 h at pretreatment and treatment. Treatment consisted of 6 days of daily phototherapy (0600-0800 h) with either green or FS light. Treatment results were pooled for green and FS light. Samples were collected under indoor lighting (<300 lux). Mean concentrations of melatonin were reduced ($p<.001$) following 1 week of phototherapy compared with pretreatment.

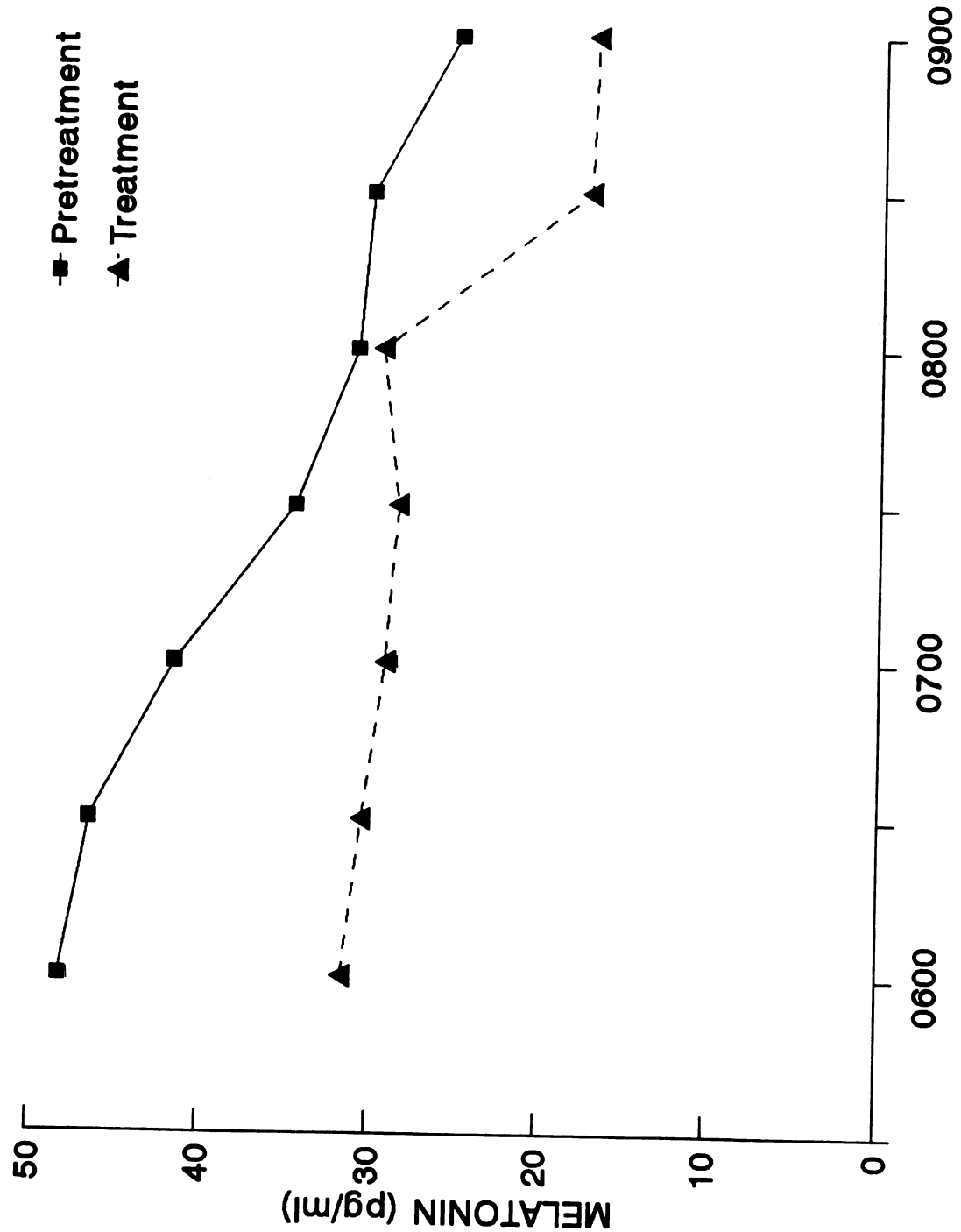
Pretreatment
Treatment
MELATONIN (pg/ml)
50
40
30
20
10
0
0600
0700
0800
0900
TIME OF DAY (h)

Figure 9

decreased ($p<.005$) more in stage 2 of the crossover than in stage 1. The concentration of melatonin was similar in subjects who achieved clinical remission (14 observations) and subjects who did not (22 observations) at pretreatment ($p>.2$) and following 6 days of phototherapy ($p>.05$; Figure 10).

Discussion

The monochromatic green light used in this study was intensely colored light. Thus, subjects were not blind to differences in the treatments. However, subjects did not know which treatment was considered the active treatment. Upon initial exposure, some subjects perceived green light as pleasant, while others perceived it as unpleasant. However, a person's first impression was transient and did not affect compliance with the phototherapy protocol or treatment results.

The finding that there was no difference between FS and green light in decreasing depression scores and inducing clinical remission would seem to indicate that the action spectrum for the antidepressant effect of light lies within the green waveband. This observation is inconsistent with a previous study (Stewart et al., 1991) which found green light not as effective as FS light in reducing HRSD scores. The decreased efficacy of green light in the study of Stewart et al. (1991) may have been due to the lower intensity (2367 lux) compared with the intensity (4500 lux) used in the present study. The results of the present experiment are consistent with a previous study (Oren et al., 1991a) which found green light capable of inducing clinical remission in SAD patients and more effective than red light in reducing HRSD scores. The intensity of green light (4680 lux) in the study of Oren et al. (1991a) was similar to that used in the present study. Therefore, green light may decrease depression scores and induce clinical remission when administered at a sufficient dose.

Figure 10. Melatonin profiles on the morning following 6 days of phototherapy (0600-0800 h) in subjects who achieved clinical remission (14 observations) and subjects who did not (depressed; 22 observations). Salivary samples were collected under indoor (<300 lux) lighting. Treatment results were pooled for FS and green light. Mean melatonin concentrations were similar ($p>.05$) between the two groups.

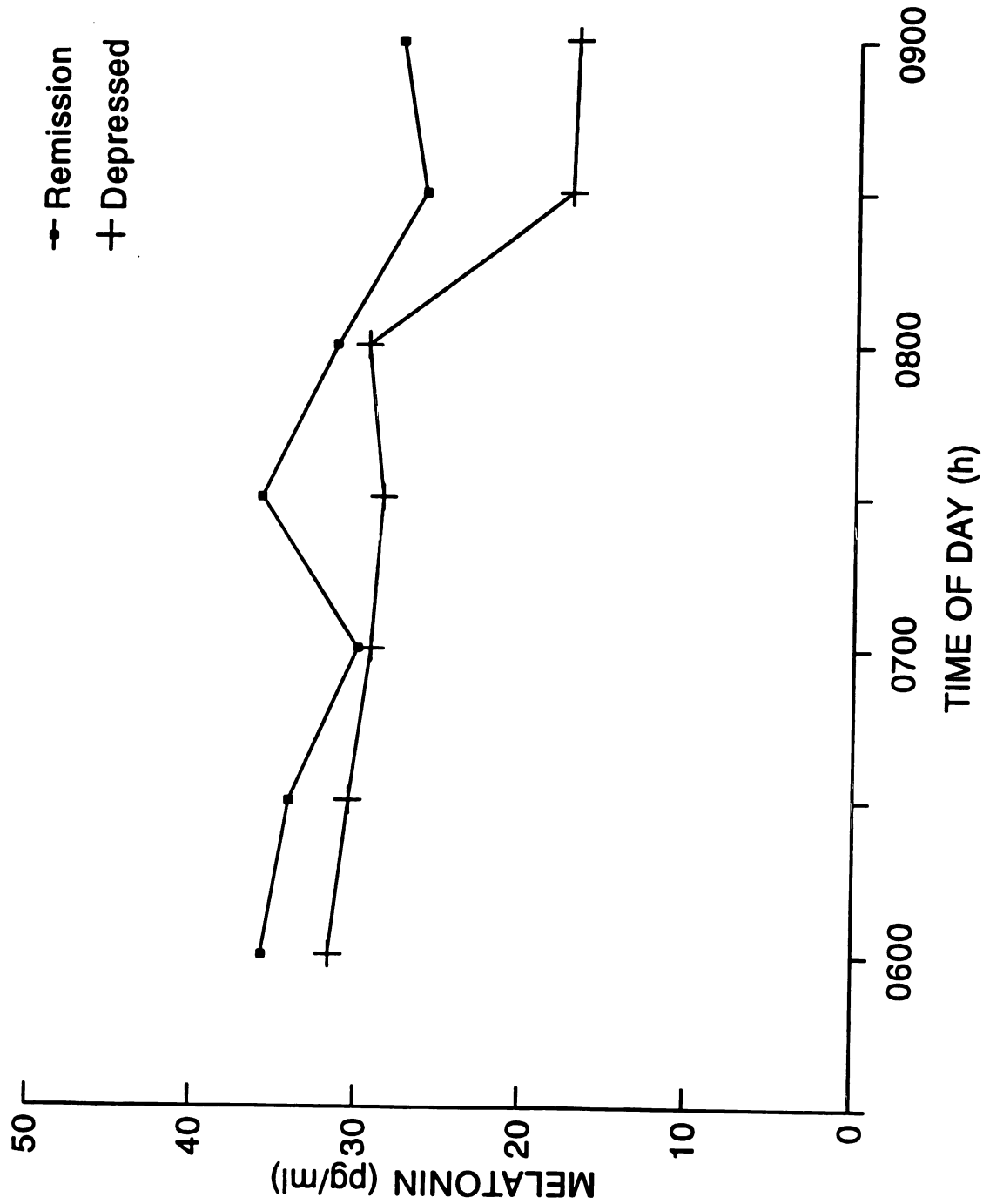
Remission
Depressed
MELATONIN (pg/ml)
50
40
30
20
10
0
0600
0700
0800
0900
TIME OF DAY (h)

Figure 10

However, the pronounced stage effect in the present study complicates the conclusion that the action spectrum for the antidepressant effect of light lies within the green waveband. Green light was as effective as FS light in inducing clinical remission in stage 1 of the crossover (5 out of 9 subjects with green light and 7 out of 9 with FS light). In contrast, green light and FS light were similarly ineffective in inducing clinical remission in stage 2 (1 out of 9 subjects both green and FS light). The stage effect on depression scores is not readily explainable, although it has been noted previously (Rafferty et al., 1990). Others have reported that expectations for treatment often predict treatment response (Evans, 1985; Wehr et al., 1987). For example, positive expectations may affect a subject's response by producing an emotional state which heightens the physiological effect (Uhlenhuth et al., 1959; Eastmen, 1990). Various physiological mechanisms, such as secretion of endorphins and steroids, have been proposed to explain the effect of positive expectations on treatment results (Ross and Olson, 1981; Grunbaum et al., 1986). Terman et al. (1990) suggest that positive expectations for treatment may be higher in the first stage than in subsequent stages of a crossover study and thus may give rise to a stage effect. The finding of the present experiment is consistent with this explanation. However, in the experiment described in Chapter 1, treatment results were similar in both stages of the crossover, indicating that initial expectations for treatment do not always cause a stage effect.

I speculate that expectations for treatment influence treatment response only if subjects can distinguish treatments and one treatment is positively or negatively experienced during the course of the trial. In the preceding study, two indistinguishable white light sources (FS and CW)

were used, subjects reported similar experiences during the course of each treatment, and no stage effect was observed. In contrast, in the present experiment, subjects were exposed to physically different types of light. Since many subjects (12 out of 18) responded positively to light treatment in stage 1 (whether the treatment was FS or green light), treatment with a different type of light in stage 2 may have been perceived as withdrawal from the active treatment. While expectations for treatment were not measured prior to beginning the study, subjects' experience during phototherapy was recorded. A positive experience during phototherapy enhanced the effect of light. Depression scores were 50% lower in subjects who reported a positive experience during phototherapy compared with subjects who reported a neutral experience.

On the other hand, a negative experience during treatment may inhibit a positive response to treatment. Physiological mechanisms may also mediate the effect of a negative psychological experience (Brier, 1989). For example, a negative experience of phototherapy in stage 2 may have induced a stress response in some subjects which ultimately influenced both depression scores and melatonin concentrations. HRSD scores were twice as high in subjects who reported a negative experience compared with subjects who reported a neutral experience. Stress is associated with increased melatonin secretion in some animal species (Khan et al., 1990). Human melatonin secretion appears to be unaffected by physical stress (Vaughan et al., 1979), yet may be influenced by psychological stress associated with increased plasma concentrations of cortisol. Many reports indicate that increased cortisol secretion is associated with decreased melatonin concentrations (Claustrat et al., 1984; Brismar et al., 1985). In the present experiment, melatonin concentrations decreased the most in

subjects who disliked treatment. Moreover, some of the adverse effects reported by subjects during stage 2, such as insomnia and loss of appetite, are commonly seen in other types of major depression in association with hypercortisolemia (Gold et al., 1988). However, since cortisol was not measured in the present experiment, it is impossible to draw a firm conclusion regarding the relationship of cortisol and melatonin.

If a person's physiological and psychological experience during treatment explains the stage effect, two possibilities exist. One possibility is that since green light parallels the effect of FS light in both stages, the antidepressant effect of light lies within the green waveband. However, the effect of green light (or white light containing the green waveband) can be modulated by subjective experience during treatment. The second possibility is that subjective experience during treatment determines the antidepressant effect, regardless of treatment. Analysis of treatment results from subjects who reported a neutral experience with both treatments may provide insight into the true effect of green versus FS light on depression scores. In these subjects, phototherapy decreased depression scores equally with both types of light, lending further credence to the hypothesis that the action spectrum for the antidepressant effect lies within the green waveband.

Unexpectedly high melatonin concentrations were observed only intermittently in saliva samples as opposed to the consistent pattern observed in Chapter 1. This difference is most likely due to a greater variability in food intake in subjects in the present study as compared to the previous study. In the present study, some subjects did not eat before or during the 3-h sample collection while in the previous study, all subjects ate prior to the 6-h sample collection.

In the present experiment, phototherapy was not administered during sample collection so the acute suppressant effect of bright light on melatonin secretion was avoided. Subjects collected samples under similar lighting conditions at pretreatment and treatment. Thus, changes in morning melatonin concentrations before and after phototherapy reflect the cumulative effect of 6 days of early morning light exposure. Others have reported changes in the melatonin rhythm induced by cumulative exposure to morning light (Lewy and Sack, 1989; Terman et al., 1988; Czeisler and Shanahan, 1991). The decrease observed in melatonin concentrations between pretreatment and treatment is consistent with a phase advance in the morning decline in nocturnal melatonin secretion. In Chapter 1 it was shown that melatonin concentrations increased between 1800-2400 h following 1 week of morning phototherapy compared with pretreatment. Together, these results suggest that a phase advance in nocturnal melatonin secretion occurs with morning phototherapy such that more melatonin is secreted in the evening (1800-2400 h) and less in the morning (0600-0900 h).

However, in the present experiment, concentrations of melatonin were similar following phototherapy in subjects who responded positively to phototherapy and those who did not. This finding is consistent with the results of Chapter 1 in which evening melatonin concentrations were similar in subjects who achieved clinical remission and those who did not. Taken together, these results indicate that changes in the timing of the melatonin rhythm as measured by evening onset and morning decline of nocturnal secretion are not associated with clinical outcome. Moreover, concentrations of melatonin were similar at pretreatment between subjects who eventually achieved clinical remission and those who did not. This

finding is also consistent with the results of Chapter 1. Therefore, mean melatonin concentrations measured in the morning or evening are not good predictors of clinical response.

It may be important that mean melatonin concentrations in the morning were reduced by morning phototherapy, regardless of any effect on the timing of the melatonin rhythm. High concentrations of melatonin are associated with drowsiness and decreased performance (Arendt et al., 1984; Wright et al., 1986). Rosenthal et al. (1984) proposed that high circulating melatonin may be implicated in the hypersomnia and daytime drowsiness observed in SAD patients. It follows that a decrease in circulating melatonin may lead to remission of these symptoms. However, concentrations of melatonin were similar following treatment in subjects who responded to phototherapy and those who did not, indicating that merely decreasing melatonin concentration in the morning is not sufficient in itself to induce clinical remission.

The finding of the present study would seem to indicate that green light is able to modulate secretion of melatonin by reducing morning concentrations, at least in the second stage of the crossover. Others have reported (Brainard et al., 1985; Horne et al., 1991) that green light can acutely suppress melatonin secretion. Together, these findings suggest that the light-induced suppression of melatonin and the photic regulation of the circadian rhythm may be initiated by the same class of photoreceptor in the retina, namely, that which has a spectral sensitivity to the green waveband of light (Nathans et al., 1986). To date, no other studies have been performed on the action spectrum of the photic regulation of the circadian rhythm of melatonin.

In summary, morning concentrations of melatonin and depression scores are decreased following 1 week of phototherapy compared with pretreatment. The decrease in morning melatonin concentrations following phototherapy is consistent with a phase advance in the timing of the melatonin rhythm. However, decreases in melatonin concentrations were observed in subjects who achieved clinical remission and in subjects who remained depressed. It appears likely that advancing the timing of the decline of nocturnal melatonin secretion is not sufficient to induce clinical remission in SAD patients. Green light has an efficacy comparable to that of FS light in reducing depression scores and modulating melatonin secretion. The action spectrum for the antidepresant effect of light may lie within the green waveband. However, treatment response for both FS and green light can be strongly influenced by subjective experience during treatment.

Chapter 3. Effect of Eye versus Head Exposure to Light on Melatonin Concentrations and Depression Scores in SAD Patients

Introduction

The antidepressant effect of light is believed to be dependent upon eye exposure (Rosenthal et al., 1984). Retinal absorption of light is the first step in the photic regulation of circadian rhythms which are believed to be involved in the antidepressant effect of light (Lewy et al., 1980; Czeisler et al., 1989). Skin exposure to light in the absence of retinal exposure is not as effective as eye exposure in reducing depressive symptoms in SAD patients (Wehr et al., 1987). However, it is not known whether skin exposure may supplement the antidepressant effect of eye exposure. For example, depressed patients, including SAD patients, frequently exhibit decreased immune function (Calabrese et al., 1987; Kasper et al., 1991). UVA radiation is known to affect immune function through dermal absorption (Morison, 1985). SAD patients treated with phototherapy exhibit an increase in immune function (Kasper et al., 1991).

Expectations for treatment often predict outcome (Evans, 1985; Wehr et al., 1987). Additionally, physiological and psychological experience during treatment may influence treatment response as shown in Chapter 2. Whether expectations for treatment measured prior to undergoing phototherapy are directly related to subjective experience during treatment response is unknown.

Therefore, an experiment was conducted to determine the effect of eye versus full head exposure to light on depression scores and melatonin concentrations in SAD patients. A second objective of the experiment was to determine whether expectations for treatment predict subjective experience during treatment and treatment response.

Materials and Methods

Subjects. Subject recruitment and admission into the study were as described in Chapter 2. Based upon consultation with an oncologist, melanoma was added to the exclusion criteria. Patients were assessed for color blindness by the Ishihara Test, but were not excluded if they tested positive. At the initial assessment, subjects had the treatment conditions explained and treatment apparatus shown to them. Subjects were asked to evaluate their expectations for each treatment condition by means of a scale (-4 to +4) on which -4 indicated an expectation of very much worsening, 0 indicated an expectation of no improvement, and +4 indicated an expectation of very much improvement. The experiment was performed with the approval of UCRIHS (IRB#90-498).

Experimental Design. The experimental design was a 2 x 2 crossover design as described in Chapter 1. In brief, pretreatment measures of melatonin were obtained 1 day before the start of treatment and pretreatment measures of depression 2 days before. Treatment measures of depression were obtained on day 6 of the treatment week and treatment measures of melatonin on the following day.

Phototherapy. Phototherapy was administered in each subject's home for 6 days between 0600 and 0800 h. The light source for phototherapy consisted of four full spectrum (FS; Vita-Lite F40; Duro-Test) fluorescent tubes. Subjects sat 60 cm away from the light source which resulted in an illuminance of 2500 lux at eye level. The two treatments were head phototherapy and eye phototherapy. Head phototherapy consisted of light exposure to the eyes and the skin of the face, head, neck, and hands. In eye phototherapy, only the eyes were exposed to light. Subjects wore cotton gloves, long-sleeve shirts, and a black double-knit face mask which

completely covered the head and neck with the exception of eyes, nose, and mouth. Illuminance on the skin under the face mask was 25 lux.

Depression Ratings. Depression ratings (HRSD, SAD, SIGH-SAD) were obtained according to the protocol described in Chapters 1 and 2. In brief, depression ratings were obtained on four occassions: pretreatment and treatment in stage 1 of the crossover and pretreatment and treatment in stage 2 of the crossover.

Saliva Handling and Assay. Subjects followed the protocol and schedule for collection of morning (0600-0900 h) saliva samples as described in Chapter 2. Samples were obtained at pretreatment and treatment in stage 1 of the crossover and pretreatment and treatment in stage 2. Samples were stored at -20° C until the time of assay for melatonin as described in Chapter 1.

Statistical Analysis. As described in Chapter 1, a split plot crossover design was used to model the effect of phototherapy on HRSD, SAD, and SIGH-SAD scores with treatment (eye v. head) and stage (1 v. 2) as main plot (between subjects) effects and period (pretreatment v. treatment) as the repeated factor in the sub-plot. The effect of phototherapy on melatonin concentration was modeled similarly with sampling time (0600-0900) added as the sub-sub plot. Comparisons of means within treatments (or stages) was tested with the Bonferroni t-test. Clinical remission criteria was a 50% decrease in HRSD score to a value less than eight.

Results

Potential subjects (n=105) were interviewed to determine study eligibility. Of these, 39 underwent medical assessment at the Psychiatry Clinic and 36 (92%) met the diagnostic criteria for SAD. Thirteen subjects entered the study and 12 (7 women, 5 men) completed the crossover (one

female subject developed severe insomnia with eye phototherapy). The mean (±SD) age of subjects was 40.2±7.3 (range: 24-49). The mean age of onset of SAD in subjects was 27.2±9.2 (range: 15-43). One male subject was red-green color blind. One subject had previously participated in a study of phototherapy. Subjects reported no adverse effects during phototherapy with either treatment, other than one subject who reported ocular pain and pressure during eye phototherapy.

Analysis of variance for the effect of phototherapy on HRSD, SAD, and SIGH-SAD scores melatonin concentrations is in Appendix D. There was no difference in the effects of eye versus head phototherapy on HRSD scores ($p=.5$), SAD scores ($p=.3$), or SIGH-SAD scores ($p=.4$). There was no interaction between treatment and period. Thus, treatment results were pooled for eye and head exposure. Depression scores did not differ between stages 1 and 2 of the crossover. Phototherapy reduced HRSD, SAD, and SIGH-SAD scores ($p<.0001$; Figure 11).

Subjects' expectations for treatment did not predict response. Six subjects expected no improvement from either treatment, two subjects expected both treatments to yield improvement, and four subjects expected eye+skin phototherapy to be superior to eye phototherapy. Only two out of the twelve subjects correctly predicted their response to phototherapy based upon the treatment evaluation of the nurse. Expectations of subjects did not enhance treatment effect. Subjects (10 observations) who had positive expectations for treatment averaged 21.4 on the HRSD scale before treatment and 9.1 following treatment. Subjects (14 observations) who had no expectations for treatment (0 on the expectation scale) averaged 22.0 before phototherapy and 10.1 following phototherapy on the HRSD scale.

Figure 11. HRSD, SAD, and SIGH-SAD scores at pretreatment and treatment. Treatment consisted of 6 days of daily phototherapy (0600-0800 h) with either eye or head exposure to light. Pretreatment scores were obtained 2 days before the start of treatment; treatment scores were obtained on day 6 of treatment. Treatment results were pooled for eye and head phototherapy. Phototherapy reduced ($p<.0001$) HRSD, SAD, and SIGH-SAD scores compared with pretreatment.

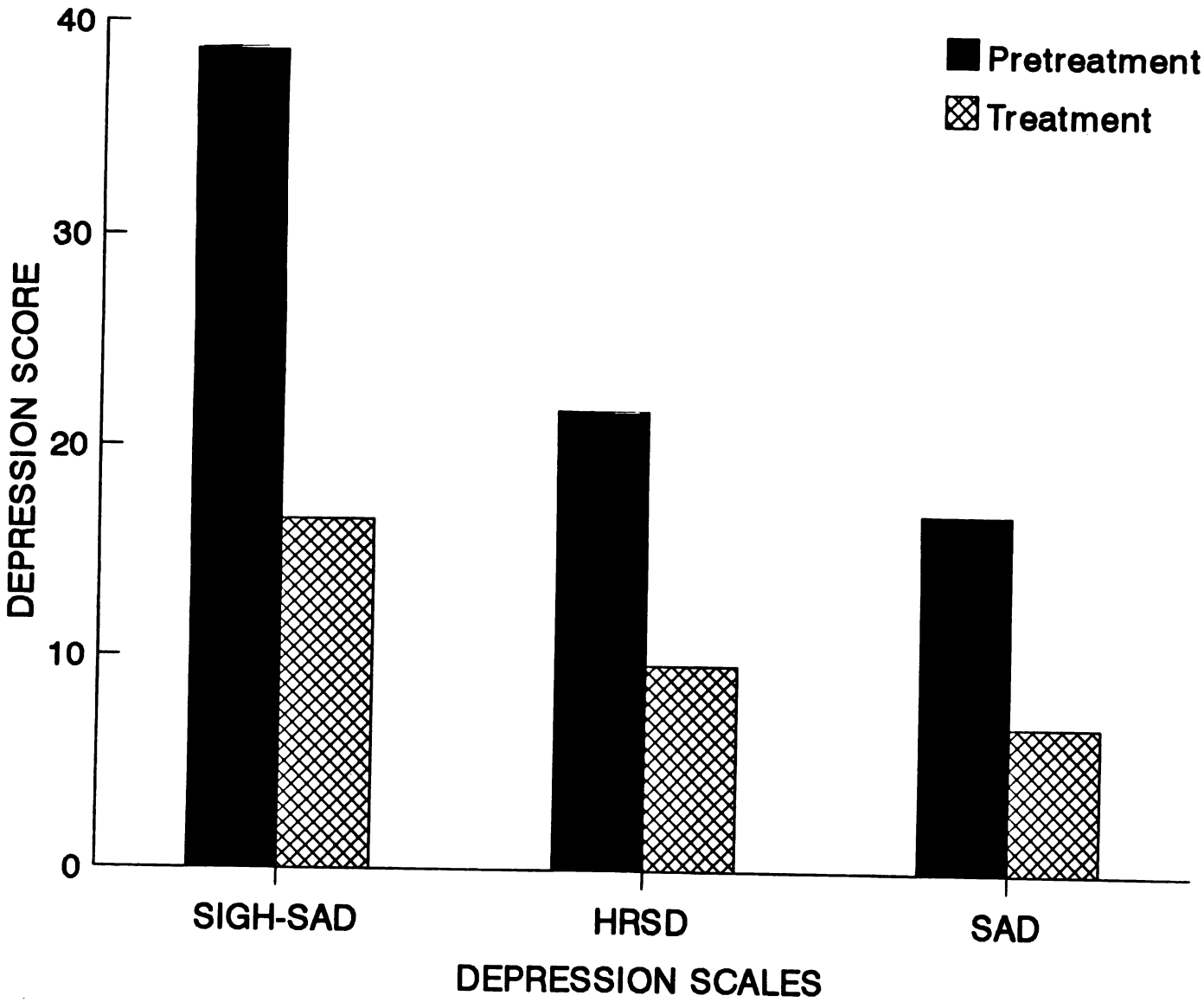
40
30
20
10
0
DEPRESSION SCORE
Pretreatment
Treatment
SIGH-SAD
HRSD
SAD
DEPRESSION SCALES

Figure 11

Subjects reported similar experiences during both stages of the crossover and with both light treatments. No subjects reported intense dislike for or discomfort with either light condition.The frequency of clinical remission was similar (X^2=.4, p>.9) between head phototherapy (6 observations) and eye phototherapy (4 observations). Individually, three subjects responded to both light treatments, three responded only to head phototherapy, one responded to eye phototherapy, and five did not respond to either light treatment. All subjects relapsed during the withdrawal week and immediately crossed over to stage 2.

Pretreatment melatonin concentrations in saliva averaged 30.7±20.2 and 26.8±15.1 pg/ml in eye- and head-exposed subjects, respectively (p>.25). Melatonin concentrations following treatment averaged 22.2±11.1 and 22.8±11.8 pg/ml in saliva in eye- and head-exposed subjects, respectively (p>.25). Concentrations of melatonin in saliva tended (p=.06) to decrease between pretreatment and treatment (Figure 12). Stage of the crossover did not affect (p=.8) melatonin concentration. Melatonin concentrations were lower (p<.0005) at pretreatment in subjects (10 observations) who subsequently failed to achieve clinical remission than in subjects (14 observations) who subsequently achieved clinical remission. However, following the week of phototherapy, concentrations of melatonin were similar in both groups due to a decrease (p<.0005) in subjects who achieved clinical remission (Figure 13).

Discussion

In agreement with previous studies (Rosenthal et al., 1984; Wehr et al., 1987), depression scores were reduced in SAD patients following 1 week of eye exposure to light. Exposure of facial skin to light did not augment the antidepressant response observed with eye exposure alone. This finding is

Figure 12. Salivary melatonin concentrations (0600-0900 h) at pretreatment and treatment. Treatment consisted of 6 days of phototherapy (0600-0800 h) with either eye or head exposure to light. Pretreatment profiles were obtained 1 day before the start of treatment; treatment profiles were obtained on the morning following the last treatment day. Treatment results (eye v. head phototherapy) were pooled. Sample collection was performed under indoor (<300 lux) illumination levels. Phototherapy reduced (p=.06) the mean concentration of melatonin in saliva compared with pretreatment.

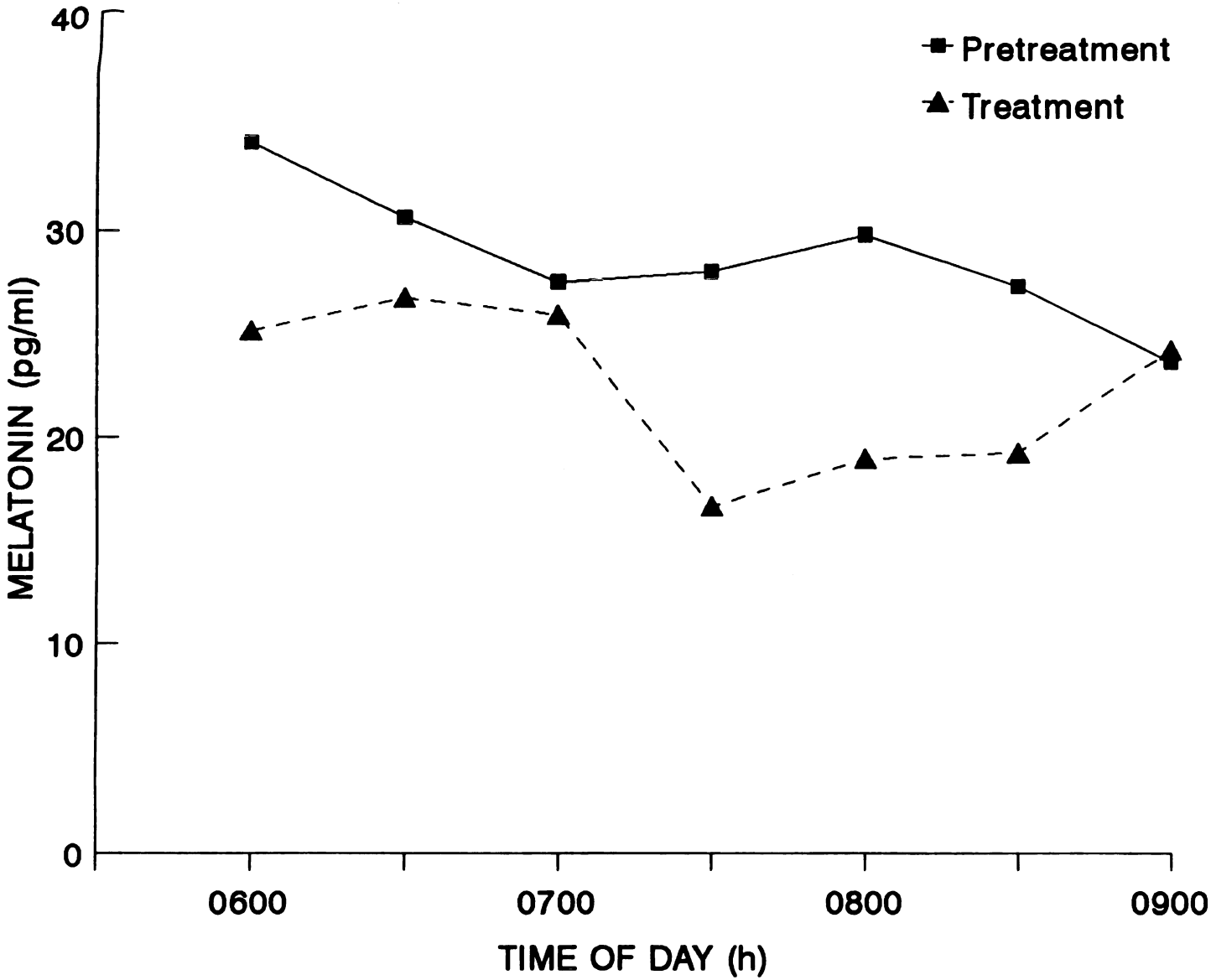
40
30
20
10
0
MELATONIN (pg/ml)
Pretreatment
Treatment
0600
0700
0800
0900
TIME OF DAY (h)

Figure 12

Figure 13. Salivary melatonin concentrations (0600-0900 h) at treatment in subjects who achieved clinical remission (10 observations) and subjects who did not achieve clinical remission (depressed; 14 observations). Treatment consisted of 6 days of phototherapy (0600-0800 h) with either eye or head exposure to light. Treatment profiles were obtained on the day following the last treatment day. Treatment results were pooled for eye and head exposure. Sample collection was performed under indoor (<300 lux) illumination levels. Mean concentrations of melatonin were similar ($p>.05$) in subjects who responded positively to phototherapy compared with subjects who did not achieve clinical remission.

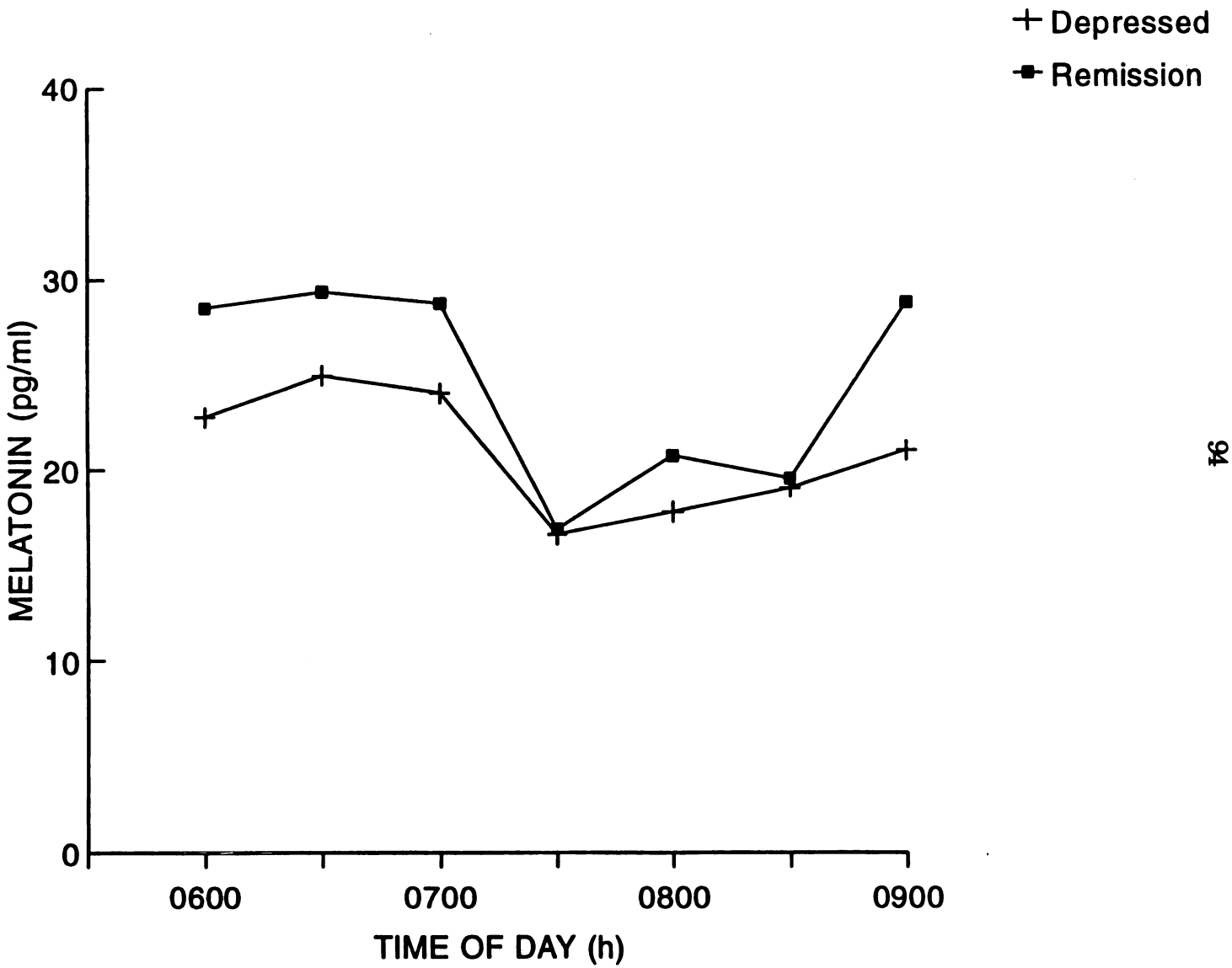
Depressed
Remission
40
30
20
10
0
MELATONIN (pg/ml)
0600
0700
0800
0900
TIME OF DAY (h)

Figure 13

consistent with the report of Wehr et al. (1987) that eye phototherapy (eyes open to light, no skin exposure) is more effective than skin phototherapy (eyes covered by goggles, maximal skin exposure) in reducing depression scores in SAD patients. Since partial skin exposure in this experiment did not increase treatment response, it appears likely that the antidepressant effect is dependent upon eye exposure only. The antidepressant effect of eye exposure to light is evident even during sleep (Avery et al., 1990) with closed eyelids (Moseley et al., 1988).

In previous studies of SAD, subject's expectations for treatment have been measured before subjects began phototherapy, but actual experience during treatment has not been assessed. In the present study, both expectations for treatment and subjective experience during phototherapy were recorded during each treatment week. Expectations for treatment did not predict treatment outcome. Subjects for the most part expected little therapeutic benefit from phototherapy. Only two subjects correctly predicted their response to treatment. This finding is in contrast to the report of Wehr et al. (1987) at the National Institute for Mental Health in which subjects expected positive results from treatment and treatment results satisfied those expectations. The difference between the present study and the Wehr study may be due to expectations for treatment being higher at a prestigious research institution (Eastman, 1990). Another possibility is that apparent differences between treatments within each study influenced expectations for treatment. In the Wehr study, treatments varied considerably (subjects wore goggles and swim suits in the skin condition versus total skin coverage in the eye condition) and subjects expected eye phototherapy to be superior. In the present study, treatments were relatively similar in that both allowed eye exposure to white light. Since

both treatment conditions were similar with regard to eye exposure, subjects may have assumed the treatments would be equally efficacious.

In contrast to the findings with green and FS light in Chapter 2, subjective experience during phototherapy in this experiment was neutral in both stages of the crossover and with both light conditions. Subjects reported neither a dislike for nor discomfort with either treatment. There was no stage effect observed in either depression scores or melatonin concentrations. HRSD scores following phototherapy averaged just above the cut-off for complete clinical remission. This observation confirms the results of Chapter 1 in which subjects reported a neutral experience during phototherapy and mean depression scores were near the cut-off point for complete clinical remission. This finding is also consistent with the results from the sub-group of subjects in Chapter 2 who reported a neutral experience with phototherapy.

Melatonin concentrations were similar following eye exposure and full head exposure to light. Full head exposure to light allowed for dermal absorption of light (Anderson and Parrish, 1981) and possibly cranial transmission of light (Lucey and Hewitt, 1976; Wan et al., 1981; Svaasand and Ellingsen, 1983). However, any supplemental absorption of light in the full head exposure condition did not affect melatonin secretion. This is not unexpected since the retinal-hypothalamic-pineal pathway is the only known anatomical route for photic regulation of melatonin secretion.

Melatonin concentrations (0600-0900 h) were decreased following 1 week of phototherapy compared with pretreatment. This finding confirms the results reported in Chapter 2 for the cumulative effect of 6 days of morning phototherapy on salivary melatonin concentrations. The decrease in melatonin concentrations between pretreatment and the

morning following day 6 of treatment may reflect a phase advance in the morning decline (offset) of nocturnal melatonin secretion (Terman and Schlager, 1990).

Melatonin concentrations were similar following treatment in subjects who achieved clinical remission and in those who did not. This finding confirms the results of the previous study. However, in contrast to the results of Chapters 1 and 2, melatonin concentrations at pretreatment varied between subjects who subsequently achieved clinical remission and those who did not. Melatonin concentrations were already low before treatment in subjects who failed to respond positively to phototherapy and no further decrease was noted following treatment. This result is not readily explanable since the two groups were similar in age, sex, and depressive symptomatology.

In summary, skin exposure to light during phototherapy does not increase the magnitude of the antidepressant effect of light. Expectations of subjects for treatment effects did not predict treatment outcome. On the whole, depression scores and melatonin concentrations decreased following 1 week of morning phototherapy compared with pretreatment. In the subgroup of patients who did not achieve clinical remission, the concentration of melatonin at pretreatment was low and remained stable following phototherapy in contrast to the light-induced decrease in melatonin observed in subjects who did achieve clinical remission.

Chapter 4. Effect of White Light of Different Spectral Composition on Melatonin Concentrations and Depression Scores in SAD Patients

Introduction

Depression scores in SAD patients are decreased by daily (0600-0800 h) exposure to full spectrum white light (Rosenthal et al., 1984;Winton et al., 1989). Concentrations of melatonin in plasma are increased in the evening (1800-2300 h) and exhibit an earlier nocturnal rise relative to pretreatment following 1 week of morning phototherapy (Lewy et al., 1987; Sack et al., 1990). It was shown in Chapters 2 and 3 that concentrations of melatonin in saliva in the morning are decreased following 1 week of morning phototherapy. It is unknown whether these light-induced changes in evening and morning melatonin concentrations are synchronized to each other. Furthermore, it is unknown whether synchronized shifts in the melatonin rhythms are functionally related to the antidepressant effect. If the antidepressant effect and circadian phase shifting effect of light are responses to the same waveband of light, it would suggest they may be related. There is no information available on the action spectra for advancing the timing of the melatonin rhythm, although green light is more effective than red or blue light in suppressing melatonin secretion (Brainard et al., 1985). Red and blue light are not as effective as full spectrum light in reducing depression scores in SAD patients (Brainard et al., 1990).

Difficulties arise in using narrow spectrum light to determine the action spectrum for the antidepressant effect of light. Narrow spectrum light is strongly colored light; thus, subjects are not blind to treatment differences. Humans often have a psychological response to specific colors. Since patients' expectations for treatment response often predict outcome (Wehr et al., 1987), narrow spectrum light that elicits favorable expectations may strongly influence treatment response. Conversely, light that is

strongly disliked by subjects may lead to poor compliance with phototherapy protocol (e.g., decreased eye exposure) and, consequently, may negatively influence treatment response (Stewart et al., 1991). Narrow spectrum light can also produce undesirable effects such as headache, vertigo, and nausea (Sisson and Kendall, 1973) which may further influence treatment response.

However, it is possible to blend complementary pairs of narrow spectrum light to produce white light. For example, blending blue and yellow light produces white light without the green and red wavebands. Thus, subjects can be exposed to narrow bands of light, but without perceiving color differences between treatments. This methodology can be used to investigate the action spectrum of the antidepressant effect of light without having expectations for treatment responsible for a large component of treatment response. An experiment was performed to measure the cumulative effect of daily exposure to blended white light on depression scores and melatonin secretion in SAD patients.

Materials and Methods

Subjects. Subjects were recruited through an advertisement in the Lansing State Journal newspaper and through referrals from local clinicians. The admission criteria for the study remained the same as described in Chapters 1-3. Potential subjects underwent medical assessment at the Psychiatry Clinic as described in Chapter 3. The experiment was performed with the approval of UCRIHS (IRB#90-498).

Experimental Design. The design of the study was a 3 x 2 (3 treatments within 2 stages) crossover study. Treatment assignment was by a 2 X 2 Latin square in which subjects represented the two rows of the

square and stages represented the two columns. Three squares were performed in order that each treatment occurred twice in each stage and each subject received two treatments (Table 1).

Pretreatment and treatment measures of depression and melatonin were obtained in stages 1 and 2 of the crossover as described in Chapter 2. In brief, pretreatment depression scores were obtained 2 days before the start of treatment; pretreatment melatonin profiles were obtained the day before the start of treatment. Treatment depression scores were obtained on the last of phototherapy (day 6 in the treatment week) and treatment melatonin profiles were obtained on the following day on which no phototherapy was administered (day 7).

Phototherapy. Phototherapy was administered from 0600 to 0800 h at the Psychiatry Clinic for 6 days. The three treatments were full spectrum (FS) light, blended white light composed of blue and yellow wavebands (BY), and blended white light composed of red and green wavebands (RG). The FS treatment, described in Chapter 3, produced an illumination of 2500 lux. The goal of the two blended white light sources was to create a convincing match to white full spectrum (2500 lux) light with subjects blind to wavelength, and thus color, composition. BY blended white light was produced with narrow spectrum blue fluorescent lamps (Sylvania F40T12B) and narrow spectrum yellow fluorescent lamps (Sylvania F40T12GO). The half-peak bandwidth (bandwidth with at least 50% of peak emission) of narrow spectrum blue light was between 430 and 470 nm. The half-peak bandwidth of narrow spectrum yellow light was between 550 and 650 nm. RG blended white light was produced with narrow spectrum red fluorescent lamps (Sylvania F40T12R) and narrow spectrum green fluorescent lamps (Sylvania F40T12G). The half-peak bandwidth for red

Table 1. 2 X 2 Latin squares for a two-stage crossover design for three treatments. Treatments consisted of full spectrum light (FS), blue-yellow blended white light (BY), and red-green blended white light (RG). Six subjects (subj) completed two stages of phototherapy. Each treatment was administered four times within the experiment.

	Stage of Crossover							
	1	2		1	2		1	2
Subj			Subj			Subj		
1:	FS	BY	3:	FS	RG	5:	BY	RG
2:	BY	FS	4:	RG	FS	6:	RG	BY

light was between 620 and 680 nm and for green light, between 510 and 555 nm. Cumulative spectral power distributions for BY and RG blended light are given in Figures 14 and 15, respectively. For the BY treatment, three blue lamps and three yellow lamps were used which yielded an illuminance of 2500 lux. For the RG treatment, ten red and four green lamps were used which yielded an illuminance of 2800 lux.

A light box was built to produce the blended white light treatments. The light box was 48" tall and trapezoid in shape (15" wide in the front, 24" wide in the back, and 30" wide on the sides. A 24" x 48" white matte board (reflectance >.9) served as the back wall of the light box. The diagonal sides of the trapezoid were made from a series of fluorescent light fixtures. The metal frames of the light fixtures formed the outside walls of the box and the bare fluorescent lamps formed the inner walls. The front wall of the box consisted of a 15" x 48" clear acrylic diffuser. The light box rested on the floor and was covered on the top with a piece of white matte board. Light from each side of the box fell on the white matte board. The two complementary colors of light blended at the surface of the matte board to create white light. The white light was reflected off the matte board and transmitted through the clear diffuser. The subject sat outside the light box at a distance of 30 cm in front of the diffuser.

Depression Ratings. Depression ratings were obtained by a psychiatric nurse who was blind to treatment assignments. Depression ratings (HRSD, SAD, and SIGH-SAD) were obtained on four occasions: pretreatment and treatment in stage 1 of the crossover and pretreatment and treatment in stage 2 of the crossover. The criterion for clinical remission was a 50% decrease in HRSD score to a value less than eight.

Figure 14. Spectral power distribution for BY blended white light composed of narrow spectrum blue and narrow spectrum yellow light. Radiant power is measured in wavebands that correspond to colors of light: Ultraviolet (<380 nm), violet (380-430 nm), blue (430-490 nm), green (490-560 nm), yellow (560-590 nm), orange (590-630 nm), red (630-800 nm).

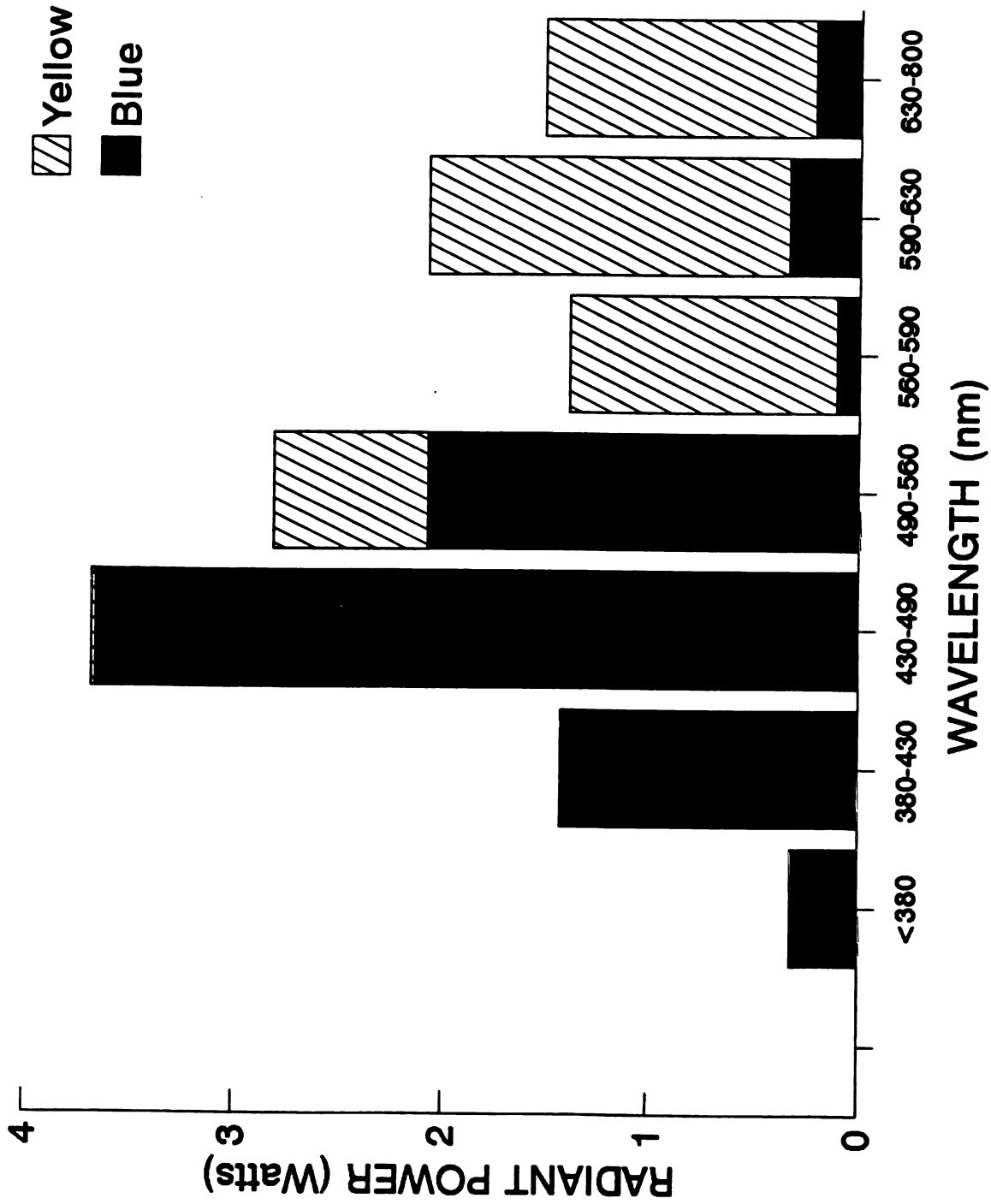
Yellow
Blue
RADIANT POWER (Watts)
0
1
2
3
4
<380
380-430
430-490
490-560
560-590
590-630
630-800
WAVELENGTH (nm)

Figure 14

Figure 15. Spectral power distribution for RG blended white light composed of narrow spectrum red and narrow spectrum green light. Radiant power is measured in wavebands that correspond to colors of light (see legend for Figure 14).

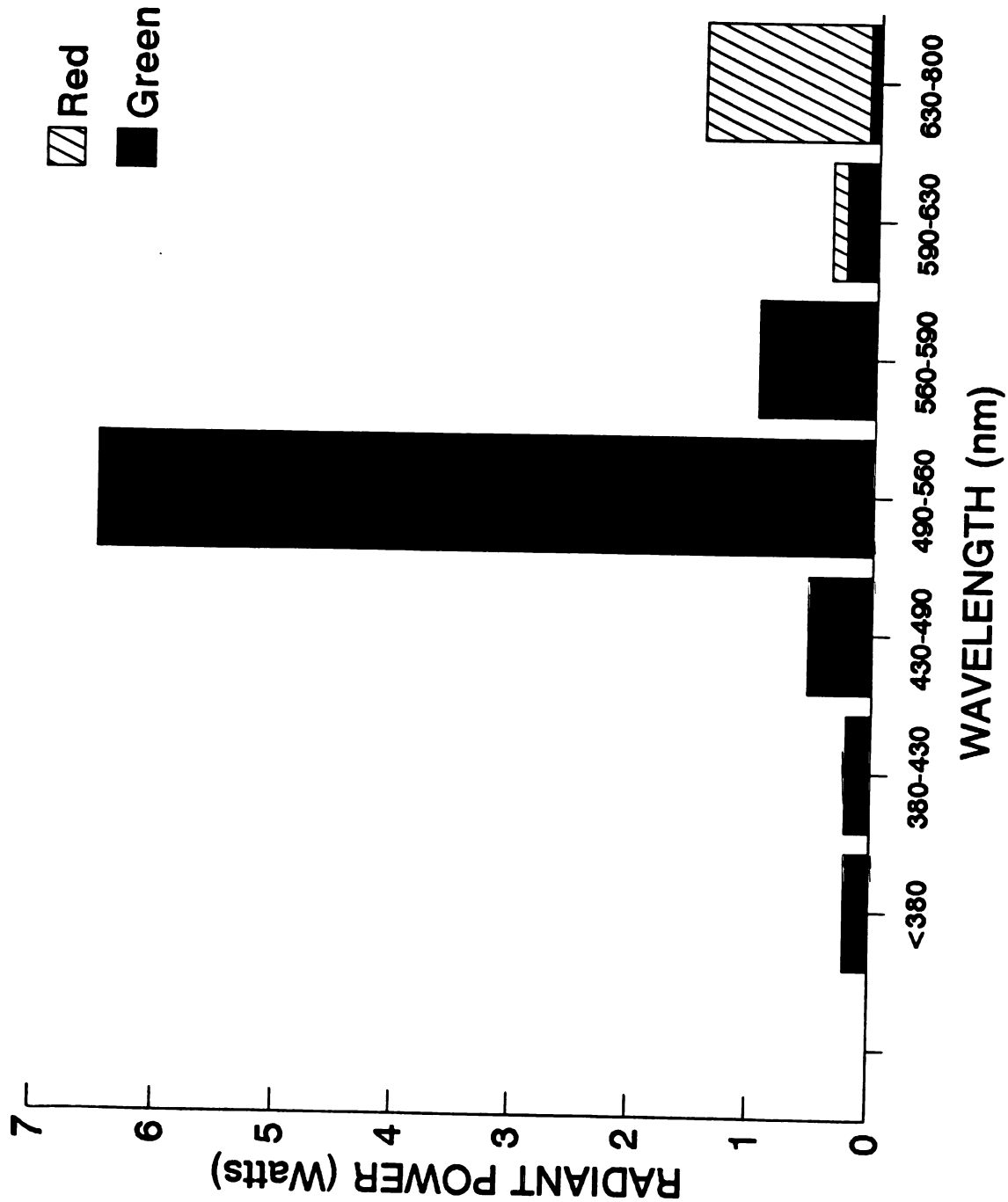
Red
Green
RADIANT POWER (Watts)
0
1
2
3
4
5
6
7
<380
380-430
430-490
490-560
560-590
590-630
630-800
WAVELENGTH (nm)

Figure 15

Saliva Handling and Assay. Serial saliva samples were collected on four occasions: pretreatment and treatment in stage 1 of the crossover and pretreatment and treatment in stage 2 of the crossover. On each occasion, samples were collected every 30 minutes for a 3-h interval in the morning (0600-0900) and a 3-h interval in the evening (2000-2300). The protocol for sample collection and storage was as described in Chapters 2 and 3. Samples were assayed for melatonin as previously described in Chapter 1.

Statistical Analysis. As described in previous chapters, a split plot crossover design was used to model the effect of phototherapy on HRSD, SAD and SIGH-SAD scores and a double split plot crossover for melatonin. In brief, hormone concentrations were averaged within sample periods to get a representative mean. A pretreatment to treatment change score was calculated for depression scores and mean melatonin concentrations within each treatment and tested with the Student's t-test (Gill, 1978). Separate analyses of variance were performed on morning (0600-0900 h) and evening (2000-2300 h) melatonin concentrations.

Results

Potential candidates (n=35) were interviewed to determine eligibility and interest in the study. Of these, 22 underwent medical assessment at the Psychiatry Clinic and 21 (95%) met the criteria for SAD. Six subjects (all female) entered and completed the study (four subjects per treatment). The mean age of subjects was 41±6 (range:22-58). The mean age of onset of SAD was 29.7±14.3 (range: 10-49).

Subjects could not determine the spectral (color) composition of BY light. Some subjects initially perceived RG light as having a greenish tint. However, after a few minutes of exposure, these subjects reported that the light appeared white. Subjects who underwent RG phototherapy reported

that white objects appeared pink immediately following the completion of phototherapy (duration < 1 h). One subject experienced headache, vertigo, and nausea with BY and RG light. Two subjects experienced an increase in depressive symptoms during phototherapy (one with RG light and one with FS light). One subject experienced prolonged (2 days) alteration in color vision after BY light in which red objects appeared intensely bright.

Analysis of variance of HRSD, SAD, and SIGH-SAD scores and melatonin concentrations is in Appendix E. There was no difference ($p>.6$) in HRSD scores between light treatments. Thus, treatment results were pooled for FS, BY, and RG light. There was a trend ($p<.1$) for HRSD scores to decrease between pretreatment and treatment (22.3 ± 3.6 v. 11.8 ± 8.5, respectively; Figure 16). Stage of the crossover did not affect HRSD scores ($p>.8$). There was no difference ($p>.8$) in SAD scores between light treatments. Pooled for treatments, there was a trend ($p<.09$) for SAD scores to decrease between pretreatment and treatment (14.4 ± 4.2 v. 6.6 ± 6.2, respectively). Stage of the crossover did not affect SAD score. There was no difference ($p>.7$) in SIGH-SAD scores between light treatments. Pooled for treatment, there was a trend ($p<.09$) for SIGH-SAD scores to decrease between pretreatment and treatment (36.8 ± 6 v. 18.4 ± 13.8, respectively). Stage of the crossover did not affect ($p>.9$) SIGH-SAD score.

In terms of clinical significance, one out of four subjects achieved clinical remission (50% decrease in HRSD score to a value less than eight) with FS light, one out of four with RG light, and two out of four with BY light. The frequency of clinical remission was similar ($X^2=.51$; $p>.9$) between treatments. All subjects who achieved clinical remission in stage 1 relapsed during the withdrawal week. Three subjects reported a neutral

Figure 16. HRSD, SAD, and SIGH-SAD scores at pretreatment (Pre) and on day 6 of treatment (Trt) with full spectrum (FS), blended blue-yellow white light (BY), and blended red-green white light (RG). Pooled for treatment, phototherapy tended to decrease HRSD ($p<.1$), SAD ($p<.09$), and SIGH-SAD ($p<.09$) scores relative to pretreatment.

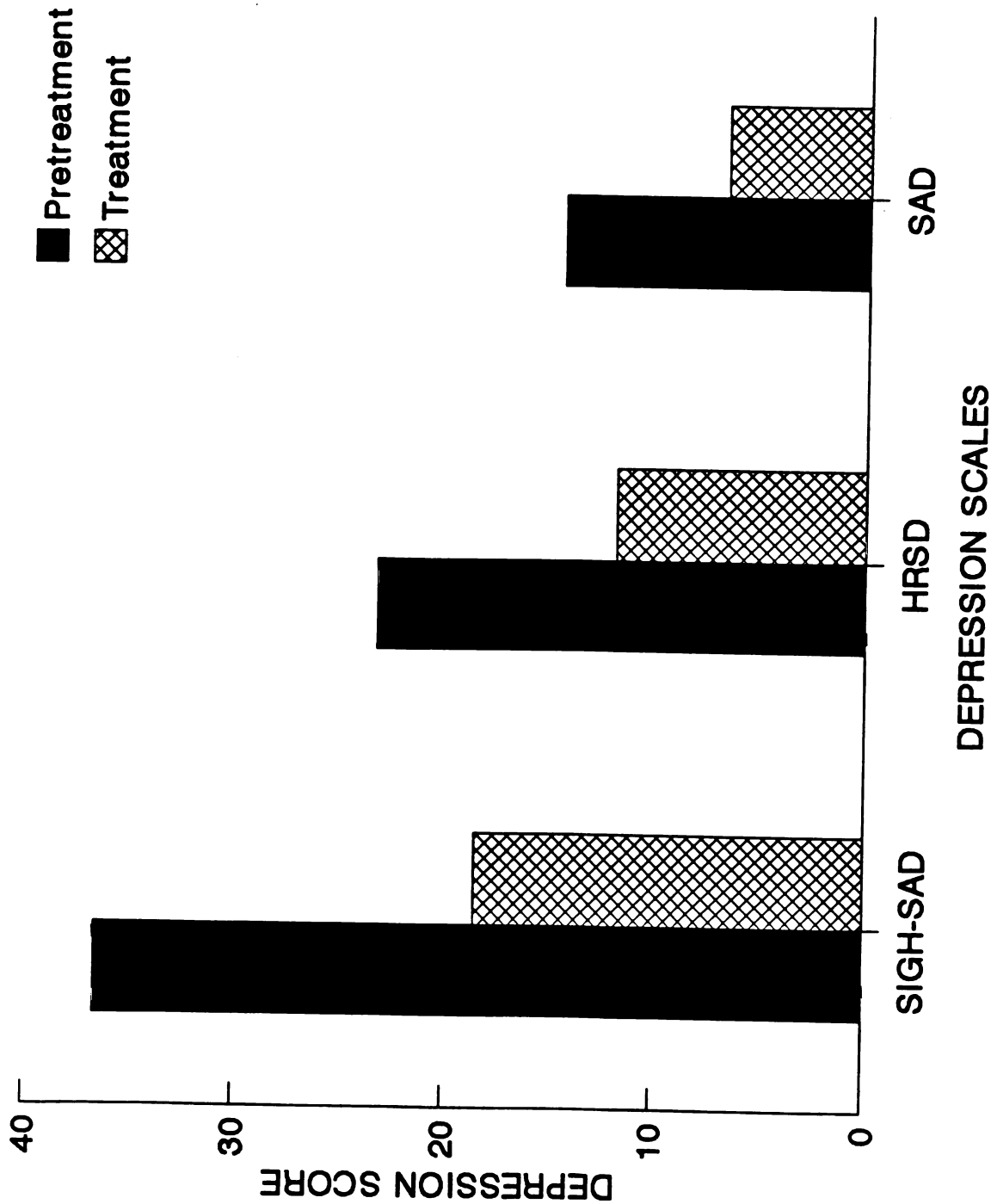
Pretreatment
Treatment
DEPRESSION SCORE
40
30
20
10
0
SIGH-SAD
HRSD
SAD
DEPRESSION SCALES

Figure 16

experience during both phototherapy trials. One subject reported intense dislike and discomfort during both trials of phototherapy (BY and RG). One subject reported intense dislike for FS light and a positive experience with RG light. Another subject reported intense dislike for RG light and a positive experience with BY light. Subjective experience during phototherapy predicted treatment response in terms of HRSD score. Subjects (2 observations) who reported a positive experience during phototherapy averaged the lowest HRSD scores following phototherapy (3.5±2.1). Subjects (4 observations) who reported a negative experience averaged the highest post-treatment HRSD scores (21.5±7). Subjects (6 observations) who reported a neutral experience scored intermediate on the HRSD scale (8.2±3).

Melatonin concentrations declined steadily ($p=.0001$) from 0600 to 0900 h (32.8±20.3. v. 14.5±16.7 pg/ml). Melatonin concentrations were similar ($p>.8$) between all three treatments. Pooled for treatment, melatonin concentrations were not different ($p>.3$) between pretreatment and treatment (23.4±9.9 v. 16.9±8.7 pg/ml, respectively; Figure 17). Stage of the crossover did not affect ($p>.7$) melatonin concentration at pretreatment or treatment. However, within the RG light condition, melatonin concentrations decreased between pretreatment and treatment (29.2±14.9 v. 16.5±9 pg/ml; $p<.025$; Table 2).

Evening (2000-2300 h) melatonin concentrations were similar ($p>.3$) between treatments. Melatonin concentrations (pooled for treatments) were similar ($p>.8$) between pretreatment and treatment (20.6±12.3 v. 19.9±12.2 pg/ml, respectively; Figure 18). Stage of the crossover did not influence ($p>.9$) melatonin concentration at pretreatment or treatment. However,

Figure 17. Morning (0600-0900 h) melatonin concentrations in saliva at pretreatment and treatment. Treatment consisted of 6 days of daily phototherapy (0600-0800 h) with either FS, BY, or RG light. Treatment samples were collected on the morning following day 6 of phototherapy. Samples were collected every 30 minutes under indoor (<300 lux) lighting. Mean concentrations of melatonin were similar ($p>.3$) at pretreatment and following 6 days of treatment. Results were pooled for FS, BY, and RG light.

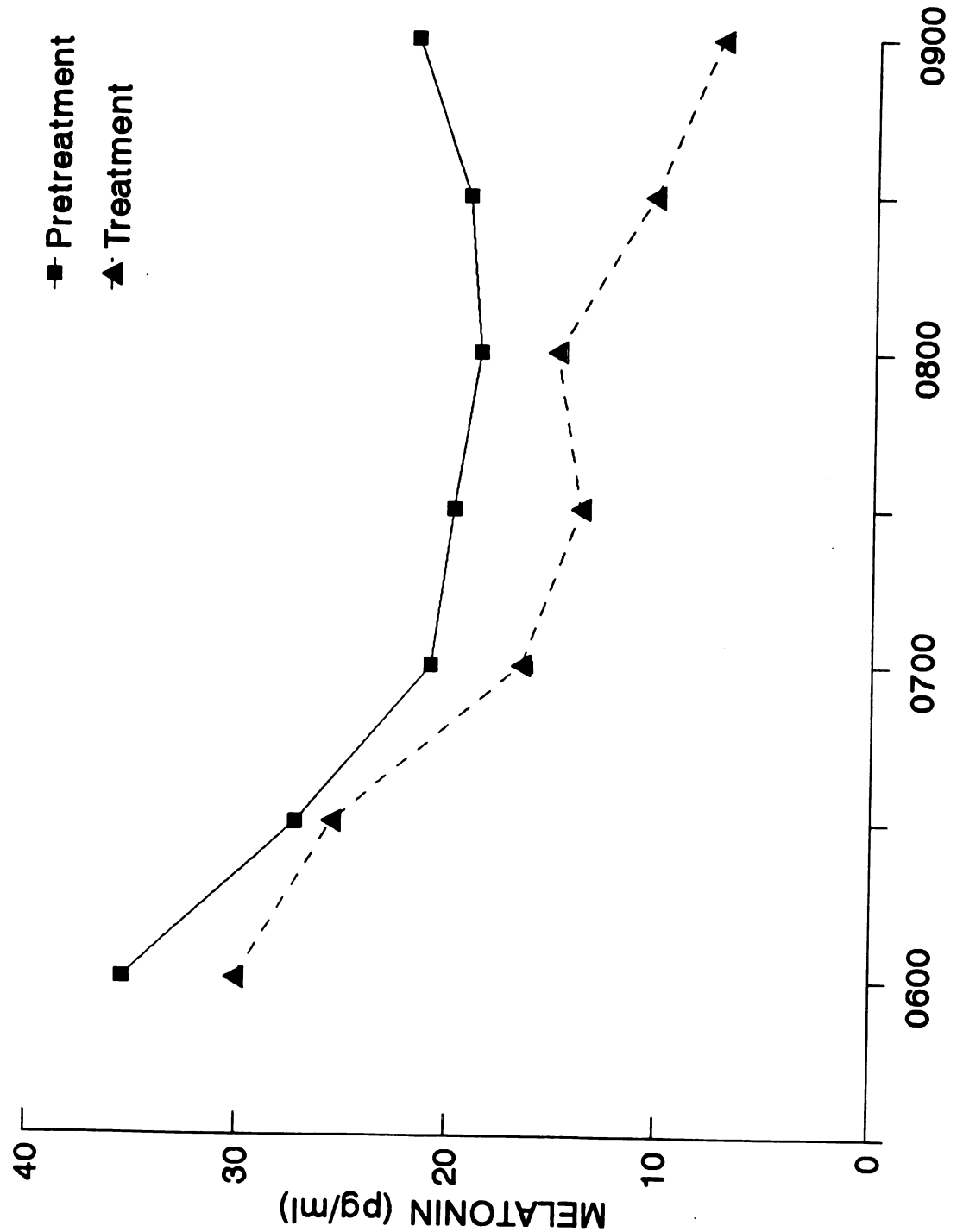
Pretreatment
Treatment
MELATONIN (pg/ml)
40
30
20
10
0
0600
0700
0800
0900
TIME OF DAY (h)

Figure 17

Table 2. Mean (+SD) salivary melatonin concentrations in the morning (0600-0900 h) and evening (2000-2300 h) at pretreatment and the morning following day 6 of treatment (treatment) between full spectrum light (FS), blended blue-yellow white light (BY), and blended red-green white light (RG).

		Treatment		
		FS	BY	RG
Morning Melatonin (pg/ml)	Pretrt	21.8±5.2	19.1±9.4	29.2±14.9[a]
	Trt	17.5±12.8	16.8±10.4	16.5±9[a]
Evening Melatonin (pg/ml)	Pretrt	16.6±5.2	13.5±9	31.8±13.6[b]
	Trt	18.5±8.3	16.9±15.3	24.5±14.8[b]

[a]Change in pretreatment to treatment; $p<.025$

[b]Change in pretreatment to treatment; $p<.025$

Figure 18. Evening (2000-2300 h) melatonin concentrations in saliva at pretreatment and treatment. Treatment consisted of 6 days of daily phototherapy (0600-0800 h) with either FS, BY, or RG light. Treatment samples were collected the evening following the last day of phototherapy. Samples were collected every 30 minutes under indoor (<300 lux) lighting. Treatment results were pooled for FS, BY, and RG light. Mean concentrations of melatonin were similar ($p>.8$) at pretreatment and treatment.

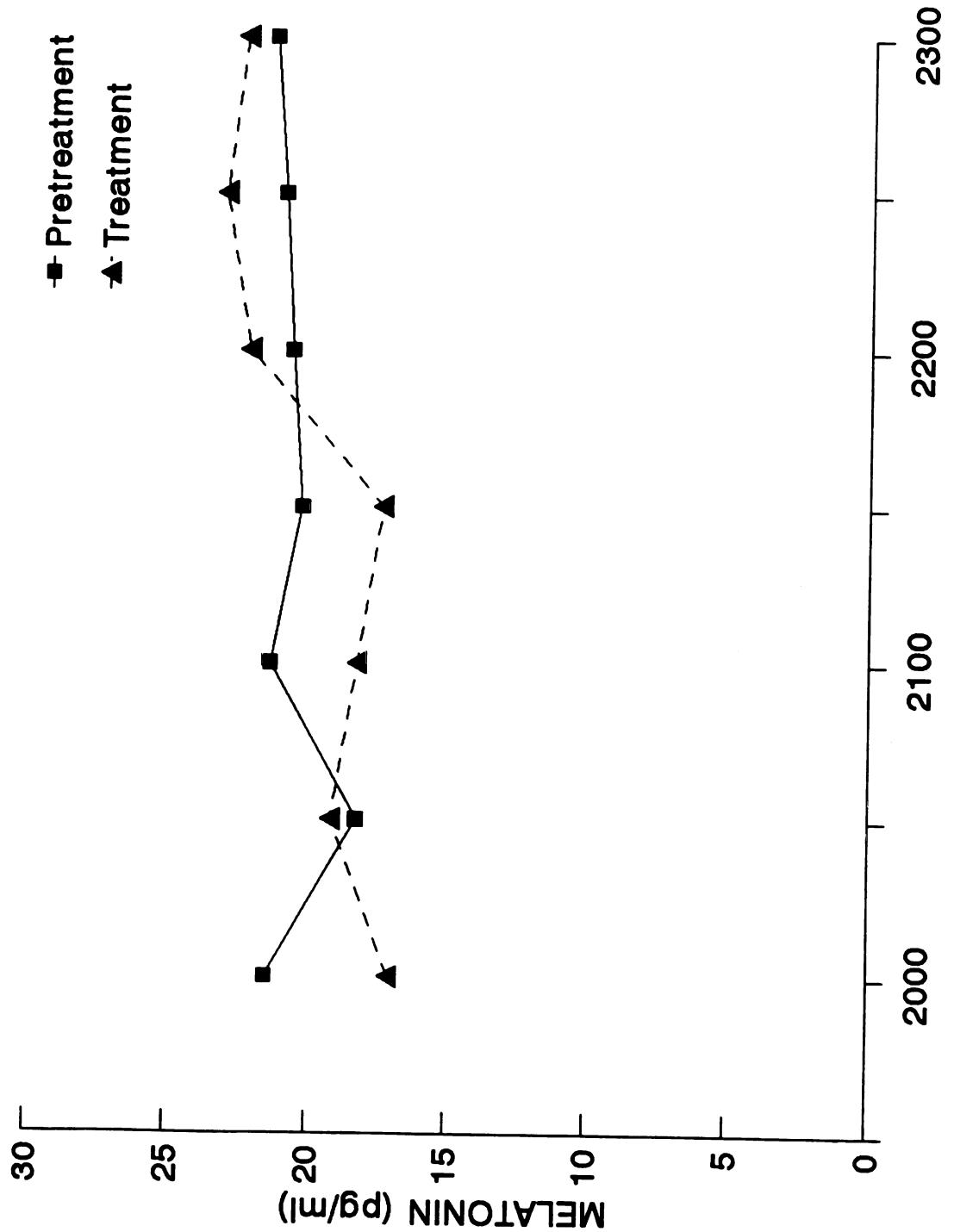
Pretreatment
Treatment
MELATONIN (pg/ml)
30
25
20
15
10
5
0
2000
2100
2200
2300
TIME OF DAY (h)

Figure 18

within the RG light condition, melatonin concentrations decreased ($p<.025$) between pretreatment and treatment. There was no effect of food consumption on melatonin concentrations.

Morning melatonin concentrations were similar between subjects who achieved clinical remission (four observations) and subjects who did not (8 observations) at pretreatment ($p>.25$) and at treatment ($p>.2$; Figure 19). Evening melatonin concentrations were similar between subjects who achieved clinical remission and subjects who did not at pretreatment ($p>.25$) and at treatment ($p>.25$; Figure 20).

Discussion

The results of this experiment indicate that complementary pairs of narrow spectrum light can be blended convincingly to appear as white light. This finding raises the possibility of a placebo control for phototherapy. Upon elucidation of the action spectrum for the antidepressant effect of light, blended white light that lacks the action spectrum can be used as a placebo control. Blended white light can be produced to match the illuminance (2500 lux) of bright light phototherapy, adding to its credibility. However, while subjects cannot perceive the spectral composition of blended white light, alterations in color vision occur which can influence the experience of phototherapy.

The trend for scores on all three depression scales to decrease between pretreatment and day 6 of treatment is consistent with the results of the previous three chapters. Treatment results were similar with all three light conditions.

Figure 19. Morning (0600-0900 h) melatonin concentrations in saliva following 6 days of daily phototherapy (0600-0800 h) in subjects who achieved clinical remission (4 observations) and subjects who did not achieve clinical remission (depressed; 8 observations). Treatment results were pooled for FS, BY, and RG light. Mean concentrations of melatonin were similar ($p>.2$) at pretreatment and treatment.

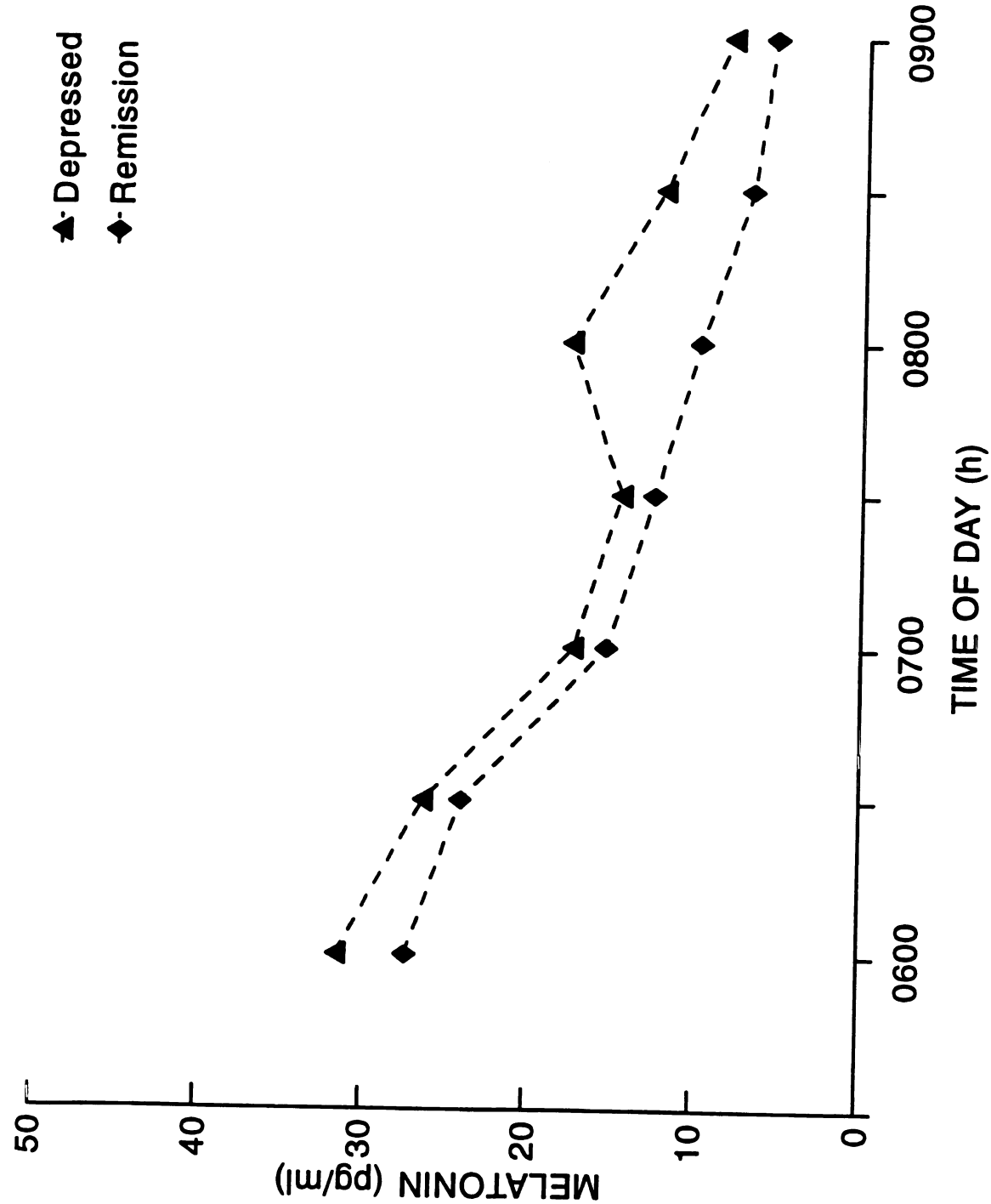
Depressed
Remission
MELATONIN (pg/ml)
50
40
30
20
10
0
0600
0700
0800
0900
TIME OF DAY (h)

Figure 19

Figure 20. Evening (2000-2300 h) melatonin concentrations in saliva following 6 days of daily phototherapy (0600-0800 h) in subjects who achieved clinical remission (4 observations) and subjects who did not achieve clinical remission (remission; 8 observations). Treatment results were pooled for FS, BY, and RG light. Mean conceentrations of melatonin were similar ($p>.25$) at pretreatment and treatment.

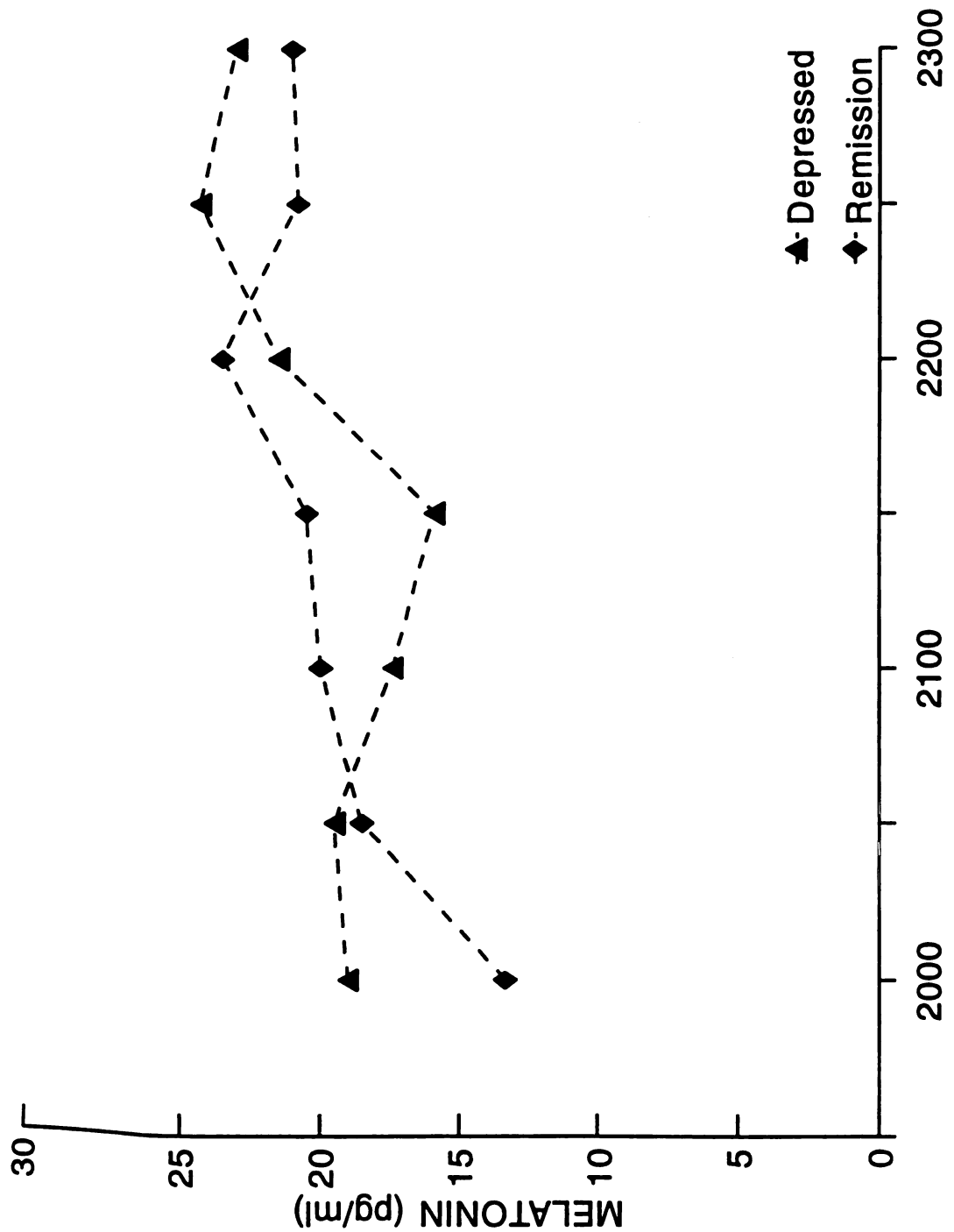
MELATONIN (pg/ml)
30
25
20
15
10
5
0
2000
2100
2200
2300
TIME OF DAY (h)
Depressed
Remission

Figure 20

The small number of subjects in the study was a result of the frequency and severity of adverse effects experienced by subjects. Short-term alterations (<1 h) in color vision were reported by all four subjects who underwent RG phototherapy. This was not unexpected since green light in RG phototherapy was of sufficient intensity to bleach the photopigment in the retinal cone cells that selectively absorb green light. Upon later exposure to full spectrum light, these cone cells could not be further stimulated by the green waveband and, consequently, the complementary color within white light (red) is perceived. One subject experienced a prolonged (2 days) alteration in color vision following BY light in which red objects appeared extremely bright. This was most likely caused by a supersensitivity in red-sensitive cone cells resulting from a lack of stimulation during BY phototherapy. Side effects such as these need to be addressed before further studies with blended white light are performed.

Subjects who reported a dislike for and discomfort with phototherapy actually worsened in depressive symptomatology. This observation confirms the finding in Chapter 2 in which a negative experience during phototherapy predicted a poor response to light. Differences in spectral sensitivity between individuals may account for the discomfort experienced with blended white light (Curcio, et al., 1989).

The finding that morning (0600-0900 h) melatonin concentrations did not decrease between pretreatment and treatment is at odds with results reported in Chapters 2 and 3. However, in the two previous experiments, changes in melatonin concentrations between pretreatment and treatment did not vary with different types of light or light exposure. In the present experiment, the absence of a decrease in melatonin concentration between pretreatment and treatment is the result of combining treatments that have

different effects. Within the RG treatment, morning melatonin concentrations decreased 43% between pretreatment and treatment, an observation consistent with the effect of green light in stage 1 in Chapter 2. This finding suggests that the action spectrum for decreasing morning melatonin concentrations and perhaps phase advancing the circadian rhythm of melatonin is within the green waveband of light.

Evening melatonin concentrations did not change between pretreatment and treatment. This finding is at odds with the 30% increase in melatonin concentration following 1 week of phototherapy observed in Chapter 1. This discrepancy is most likely due to differences in the length of the melatonin profile (3 h in the present experiment and 6 h in Chapter 1). The evening profile of melatonin in the present experiment excluded sampling times 2330 and 2400 h which exhibited the highest melatonin concentrations in Chapter 1. There was no effect of food consumption on melatonin concentrations as observed in Chapter 1. This was most likely due to a longer time interval (2 h) between the evening meal and the beginning of saliva sampling in the current experiment.

Within the RG light condition, evening melatonin concentrations actually decreased. This finding is inconsistent with a phase advance in the onset of nocturnal melatonin secretion. This finding suggests that alterations in evening onset and morning decline of nocturnal melatonin secretion may be mediated by different wavelengths of light.

Between individuals, morning and evening melatonin profiles showed large variation in response to light. On three occasions melatonin concentrations increased in both the morning and evening profiles following phototherapy. On three other occasions melatonin concentrations decreased in both the morning and evening profiles following phototherapy.

On the remaining six occasions, melatonin concentrations showed inconsistent changes. These results indicate that the evening onset and morning offset of nocturnal melatonin secretion are not necessarily coupled in terms of photic responsiveness.

The observation that melatonin concentrations were similar between subjects who responded to phototherapy and those who did not is consistent with the findings reported in Chapters 1-3. Melatonin concentrations did not differentiate between those who achieved clinical remission from those who did not at pretreatment. This finding indicates that pretreatment melatonin concentrations in saliva at the time of evening onset or morning offset of nocturnal melatonin secretion are not predictors of response to phototherapy. Moreover, melatonin concentrations at the time of evening onset or morning offset of nocturnal melatonin secretion following 1 week of phototherapy were not correlated with clinical improvement.

In summary, blended white light composed of complementary pairs of narrow spectrum light can be used as a convincing match for phototherapy. All three types of white light (FS, blended BY, and blended RG) tended to decrease depression scores following 6 days of phototherapy. Blended white light composed of narrow spectrum green and narrow spectrum red light decreased melatonin concentrations at the time of evening onset and morning offset of nocturnal melatonin secretion. However, clinical remission was not correlated with changes in evening or morning melatonin concentrations, indicating that the time of onset and offset of nocturnal melatonin secretion may not be associated with clinical improvement.

Summary and Conclusions

Phototherapy is a fast-acting, effective treatment for SAD. In the 49 subjects who underwent two week-long trials of phototherapy in this series of experiments, complete clinical remission was achieved 40% of the time. However, relapse occurred within 1 week of withdrawal from treatment. Minor side effects, such as headache and eye irritation, occurred in 7% of trials; severe side effects occurred in 4% of trials, but only with narrow spectrum phototherapy.

Expectations of subjects for treatment effects measured prior to phototherapy do not predict treatment outcome. However, subjective experience during phototherapy can influence results. For example, subjects who reported a negative experience during phototherapy in terms of physiological and psychological discomfort showed little, if any, improvement in depressive symptoms following 1 week of treatment. However, this effect was limited primarily to the second stage of crossover trials. Conversely, subjects who reported a positive experience during phototherapy received a greater antidepressant effect than subjects who reported a neutral experience. This effect was also limited by stage of the crossover occurring primarily in stage one.

Phototherapy with either FS or CW (2500 lux) light is effective in reducing depressive symptoms in SAD patients. The antidepressant effect appears to be dependent solely upon retinal exposure to light. Skin exposure to light does not supplement the antidepressant effect. Phototherapy with narrow spectrum green light is equally effective as FS light in reducing depressive symptoms as long as subjects have a neutral

experience during the trial. Intense discomfort during phototherapy with the green waveband inhibits the antidepressant effect.

Blended white light composed of complementary pairs of narrow spectrum light can be used as a convincing match for full spectrum phototherapy. Blended white light has an advantage over monochromatic light in blinding subjects to color composition and thus avoiding subjective color preferences. However, while the human brain adapts well to exposure to blended light, subjects may experience both short- (< 1 h) and long-term (>2 d) alterations in color vision. These alterations in spectral sensitivity may be associated with a negative experience during phototherapy.

Serial saliva samples can be used to measure melatonin and to monitor light-induced changes in its circadian rhythm. Saliva sampling offers a safe, non-invasive alternative to blood sampling for collecting data on human circadian rhythmicity.

One week of phototherapy in the early morning (0600-0800 h) decreases the concentration of melatonin in morning samples (0600-0900 h). Moreover, phototherapy in the early morning increases the concentration of melatonin in evening (1800-2400 h) saliva samples. The light-induced changes in morning and evening melatonin concentrations may reflect a phase advance of the melatonin rhythm. Morning and evening melatonin concentrations revert back to the initial pretreatment concentrations following a 1-week withdrawal from phototherapy. The effects of light on melatonin secretion are dependent upon the retinal-hypothalamic-pineal pathway and are not modulated by supplemental skin exposure. Green light, whether administered monochromatically or in conjunction with red light to produce blended white light, appears to have equal potency as FS

light in reducing morning melatonin concentrations. However, a subject's psychological and physiological experience of phototherapy may influence melatonin secretion. For example, a negative experience during phototherapy is associated with a larger decrease in morning melatonin concentrations compared with a neutral experience.

Clinical remission and decreased concentrations of melatonin in the morning occur following 1 week of phototherapy. Moreover, clinical remission and increased concentrations of melatonin in the evening occur following 1 week of phototherapy. However, these light-induced changes in melatonin secretion are not directly related to the antidepressant response. For example, melatonin concentrations are similar following phototherapy in subjects who achieve clinical remission and those who are still depressed. Similarly, evening melatonin concentrations following phototherapy are similar in subjects who achieve clinical remission and subjects who do not. It appears that an advance in the timing of nocturnal melatonin secretion is not sufficient to induce clinical remission in SAD patients. However, light-induced alterations in other aspects of the melatonin circadian rhythm, such as peak concentration, amplitude, and total 24-h secretion, cannot be ruled out in playing a role in clinical remission.

It is concluded that early morning exposure to bright light decreases depressive symptoms in SAD patients. Furthermore, daily exposure to bright light in the morning increases evening melatonin concentrations and decreases morning melatonin concentrations in SAD patients. However, decreases in depressive symptoms do not appear to be mediated through light-induced changes in melatonin secretion. Retinal exposure to light alone accounts for the antidepressant effect and the changes in

melatonin secretion. Subjects' expectations for treatment do not influence treatment results, but subjective experience during phototherapy, both positive and negative, affects clinical outcomes. The mechanism through which phototherapy decreases depression scores appears not to be dependent upon modulation of evening onset or morning offset of nocturnal melatonin secretion. Light within the green waveband appears to be at least partially responsible for the decreasing depression scores and modulating the melatonin rhythm. However, the antidepressant effect of light may ultimately depend upon the physiological effects of light and the psychological experience of undergoing treatment.

APPENDICES

APPENDIX A

Depression Rating Scales

Hamilton Rating Scale for Depression

1. Depressed Mood
   - 0 Absent
   - 1 These feeling states indicated only on questioning
   - 2 These feeling states spontaneously reported verbally
   - 3 Communicates feeling states non-verbally -- i.e., through facial expression, posture, voice, and tendency to weep
   - 4 Patient reports virtually only these feeling states in his spontaneous verbal and non-verbal communication

2. Feelings of Guilt
   - 0 Absent
   - 1 Self-reproach, feels she or he had let people down
   - 3 Present illness is a punishment. Delusions of guilt
   - 4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. Suicide
   - 0 Absent
   - 1 Feels life is not worth living
   - 2 Wishes she or he were dead or any thoughts of possible death to self
   - 3 Suicide ideas or gesture
   - 4 Attempts at suicide

4. Insomnia (Early)
   - 0 No difficulty falling asleep
   - 1 Complains of occasional difficulty falling asleep -- i.e., more than 1/2 hour
   - 2 Obvious and severe; more than 1/2 hour usually

5. Insomnia (Middle)
   - 0 No difficulty
   - 1 Complains of being restless and disturbed during the night
   - 2 Waking during the night -- any getting out of bed rates 2 (except for purposes of voiding)

6. Insomnia (Late)
   - 0 No difficulty
   - 1 Waking in early hours of the morning but goes back to sleep
   - 2 Unable to fall asleep again if she or he gets out of bed

7. Work Activities
   - 0 No difficulty
   - 1 Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies
   - 2 Loss of interest in activities, hobbies, or work -- either directly reported by patient, or indicated in listlessness, indecision and vacillation (feels she or he has to push self to work or activities)
   - 3 Decrease in actual time spent in activities or decrease in productivity
   - 4 Stopped working because of present illness

8. Retardation
   - 0 Normal speech and thought
   - 1 Slight retardation at interview
   - 2 Obvious retardation at interview
   - 3 Interview difficult
   - 4 Complete stupor

9. Agitation
   - 0 None
   - 1 Fidgetiness
   - 2 Playing with hands, hair, etc.
   - 3 Moving about, can't sit still
   - 4 Hand wringing, nail biting, hair pulling, biting of lips

10. Anxiety (Psychic)
    - 0 No difficulty
    - 1 Subjective tension and irritability
    - 2 Worry about minor matters
    - 3 Apprehensive attitude apparent in face or speech
    - 4 Fears expressed without questioning

11. Anxiety (Somatic)
    Physiological concomitants of anxiety, such as:
    Gastrointestinal - dry mouth, wind, indigestion, diarrhea, cramps
    Cardiovascular - palpitations, headaches
    Respiratory - hyperventilation, sighing
    Sweating
    - 0 Absent
    - 1 Mild
    - 2 Moderate
    - 3 Severe
    - 4 Incapacitating

12. Somatic Symptoms (Gastrointestinal)
    0 None
    1 Loss of appetite but eating without encouragement. Heavy feeling in abdomen
    2 Difficulty eating without urging. Requests or requires laxatives or medication for bowels or medication for G.I. symptoms

13. Somatic Symptoms (General)
    0 None
    1 Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
    2 Any clear-cut symptom rates 2

14. Genital Symptoms
    symptoms such as loss of libido, menstrual disturbance
    0 Absent
    1 Mild
    2 Severe

15. Hypochondriasis
    0 Not present
    1 Self-absorption (bodily)
    2 Preoccupation with health
    3 Frequent complaints, requests for help, etc.
    4 Hypochondriacal delusions

16. Loss of Weight
    0 No weight loss
    1 Probable wieght loss associated with present illness
    2 Definite (according to patient) weight loss

17. Insight
    0 Acknowledges being depressed and ill
    1 Acknowledges illness but attibutes cause to bad food, climate, overwork, virus, need for rest, etc.
    2 Denies being ill at all

APPENDIX A

Depression Rating Scales

Seasonal Affective Disorder Rating Scale

1. Fatigability (or low energy level, or feelings of being heavy, laden, weighed down)
   - 0 Does not feel more fatigued than usual
   - 1 Feels more fatigued than usual but this has not impaired function significantly
   - 2 More fatigued than usual; at least 1 hour a day; three days a week
   - 3 Fatigued much of the time, most days
   - 4 Fatigued almost all the time

2. Social withdrawal
   - 0 Interacts with other people as usual
   - 1 Less interested in socializing with others but continues to do so
   - 2 Interacting less with other people in social (optional) situations
   - 3 Interacting less with other people in work or family situations
   - 4 Marked withdrawal from others in family or work situations

3. Appetite increase
   - 0 No increase in appetite
   - 1 Wants to eat a little more than usual
   - 2 Wants to eat somewhat more than usual
   - 3 Wants to eat much more than usual

4. Increased eating
   - 0 Is not eating more than usual
   - 1 Is eating a little more than usual
   - 2 Is eating somewhat more than usual
   - 3 Is eating much more than usual

5. Carbohydrate craving
   - 0 No change in food preference
   - 1 Eating more carbohydrates (starches or sugars) than before
   - 2 Eating much more carbohydrates than before
   - 3 Irrestible craving for sweets or starches

6. Weight gain
   0 No weight gain
   1 Probable weight gain associated with present illness
   2 Definite weight gain

7. Hypersomnia
   0 No increase in sleep length
   1 At least 1 hour increase in sleep length
   2 2+ hour increase in sleep length
   3 3+ hour increase in sleep length
   4 4+hour increase in sleep length

APPENDIX B

Analysis of variance of the effect of full spectrum v. cool white phototherapy

HRSD Scores

Source of Variance	df	F value	P
Subject	9	3.09	.06
Treatment	1	.44	.5
Stage	1	1.41	.3
Error	8		
Period	1	93.12	.0001
Period*Subject	9	2.06	.2
Period*Treatment	1	.01	.9
Period*Stage	1	.88	.4
Error(Period)	8		

APPENDIX B

Analysis of variance of the effect of full spectrum v. cool white phototherapy

SAD Scores

Source of Variance	df	F value	P
Subject	9	1.01	.5
Treatment	1	.08	.8
Stage	1	.02	.9
Error	8		
Period	9	168.37	.0001
Period*Subject	1	1.75	.2
Period*Treatment	1	3.31	.1
Period*Stage	1	5.31	.05
Error(Period)	8		

APPENDIX B

Analysis of variance of the effect of full spectrum v. cool white phototherapy

Melatonin Concentrations

Source of Variance	df	F value	P
Subject	9	4.28	.03
Treatment	1	.95	.4
Stage	1	1.36	.3
Error	8		
Period	1	8.53	.02
Period*Subject	9	1.16	.4
Period*Treatment	1	.43	.5
Period*Stage	1	.00	.9
Error(Period)	8		
Sample	12	32.74	.0001
Sample*Subject	108	5.3	.0001
Sample*Treatment	12	.62	.8
Sample*Stage	12	.53	.9
Error(Sample)	96		
Period*Sample	12	2.06	.03
Period*Sample*Subject	108	2.34	.0001
Period*Sample*Treatment	12	.54	.9
Period*Sample*Stage	12	.56	.9
Error(Period*Sample)	96		

APPENDIX C

Analysis of variance of the effect of full spectrum v. narrow spectrum green light

HRSD Scores

Source of Variance	df	F value	P
Subject	17	.96	.5
Treatment	1	2.14	.2
Stage	1	23.9	.0002
Error	16		
Period	1	74.75	.0001
Period*Subject	17	1.2	.4
Period*Treatment	1	2.81	.1
Period*Stage	1	20.69	.0003
Error(Period)	16		

APPENDIX C

Analysis of variance of the effect of full spectrum v. narrow spectrum green light

SAD Scores

Source of Variance	df	F value	P
Subject	17	4.06	.004
Treatment	1	2.61	.13
Stage	1	12.45	.003
Error	16		
Period	1	37.8	.0001
Period*Subject	17	.7	.8
Period*Treatment	1	1.86	.2
Period*Stage	1	11.71	.004
Error(Period)	16		

APPENDIX C

Analysis of variance of the effect of full spectrum v. narrow spectrum green light

SIGH-SAD Scores

Source of Variance	df	F value	P
Subject	17	1.94	.1
Treatment	1	3.94	.06
Stage	1	29.78	.0001
Error	16		
Period	1	70.42	.0001
Period*Subject	17	.82	.7
Period*Treatment	1	2.95	.1
Period*Stage	1	20.37	.004
Error(Period)	16		

APPENDIX C

Analysis of variance of the effect of full spectrum v. narrow spectrum green light

Melatonin Concentrations

Source of Variance	df	F value	P
Subject	17	8.38	.0001
Treatment	1	.02	.9
Stage	1	.00	1
Error	16		
Period	1	16.25	.001
Period*Subject	17	2.25	.06
Period*Treatment	1	1.09	.31
Period*Stage	1	4.84	.04
Error(Period)	16		
Sample	6	7.8	.0001
Sample*Subject	102	1.14	.26
Sample*Treatment	6	1.74	.12
Sample*Stage	6	2.16	.05
Error(Sample)	96		
Period*Sample	6	1.43	.2
Period*Sample*Subject	102	1.19	.2
Period*Sample*Treatment	6	1.74	.12
Period*Sample*Stage	6	1.5	.19
Error(Period*Sample)	96		

APPENDIX D

Analysis of variance of the effect of eye v. head phototherapy

HRSD Scores

Source of Variance	df	F value	P
Subject	11	1.42	.3
Treatment	1	.42	.5
Stage	1	.01	.9
Error	10		
Period	1	55.08	.0001
Period*Subject	11	1.46	.3
Period*Treatment	1	2.05	.2
Period*Stage	1	.44	.5
Error(Period)	10		

APPENDIX D

Analysis of variance of the effect of eye v. head phototherapy

SAD Scores

Source of Variance	df	F value	P
Subject	11	1.55	.2
Treatment	1	1.23	.3
Stage	1	.05	.8
Error	10		
Period	1	50.56	.0001
Period*Subject	11	1.21	.4
Period*Treatment	1	1.4	.3
Period*Stage	1	1.7	.2
Error(Period)	10		

APPENDIX D

Analysis of variance of the effect of eye v. head phototherapy

SIGH-SAD Scores

Source of Variance	df	F value	P
Subject	11	1.27	.4
Treatment	1	.84	.4
Stage	1	.02	.9
Error	10		
Period	1	64.56	.0001
Period*Subject	11	1.47	.3
Period*Treatment	1	2.12	.2
Period*Stage	1	1.13	.3
Error(Period)	10		

APPENDIX D

Analysis of variance of the effect of eye v. head phototherapy Melatonin Concentrations

Source of Variance	df	F value	P
Subject	11	4.81	.01
Treatment	1	.37	.6
Stage	1	.05	.8
Error	10		
Period	1	4.64	.06
Period*Subject	11	2.82	.06
Period*Treatment	1	.6	.5
Period*Stage	1	3.66	.08
Error(Period)	10		
Sample	6	2.63	.02
Sample*Subject	66	1.6	.03
Sample*Treatment	6	1.18	.3
Sample*Stage	6	1.41	.2
Error(Sample)	60		
Period*Sample	6	1.51	.2
Period*Sample*Subject	66	1.7	.02
Period*Sample*Treatment	6	.5	.8
Period*Sample*Stage	6	.97	.5
Error(Period*Sample)	60		

APPENDIX E

Analysis of variance of the effect of blended white light

HRSD Scores

Source of Variance	df	F value	P
Subject	5	.48	.8
Treatment	2	.21	.8
Stage	1	.13	.7
Error	3		
Period	1	5.97	.09
Period*Subject	5	.35	.9
Period*Treatment	2	.45	.7
Period*Stage	1	.04	.9
Error(Period)	3		

APPENDIX E

Analysis of variance of the effect of blended white light

SAD Scores

Source of Variance	df	F value	P
Subject	5	4.11	.1
Treatment	2	1.38	.4
Stage	1	19.97	.02
Error	3		
Period	1	6.11	.09
Period*Subject	5	.1	1.0
Period*Treatment	2	.19	.8
Period*Stage	1	0	1.0
Error(Period)	3		

APPENDIX E

Analysis of variance of the effect of blended white light

SIGH-SAD Scores

Source of Variance	df	F value	P
Subject	5	.95	.6
Treatment	2	.12	.9
Stage	1	2.06	.2
Error	3		
Period	1	6.35	.09
Period*Subject	5	.21	.9
Period*Treatment	2	.34	.7
Period*Stage	1	.01	.9
Error(Period)	3		

APPENDIX E

Analysis of variance of the effect of blended white light

Melatonin Concentrations (0600-0900 h)

Source of Variance	df	F value	P
Subject	5	4.95	.1
Treatment	2	2.41	.2
Stage	1	8.12	.07
Error	3		
Period	1	1.26	.3
Period*Subject	5	.2	.9
Period*Treatment	2	.2	.8
Period*Stage	1	.11	.8
Error(Period)	3		
Sample	6	12.9	.0001
Sample*Subject	30	1.56	.2
Sample*Treatment	12	1.08	.4
Sample*Stage	6	.97	.5
Error(Sample)	18		
Period*Sample	6	1.39	.3
Period*Sample*Subject	30	1.4	.2
Period*Sample*Treatment	12	1.49	.2
Period*Sample*Stage	6	3.21	.03
Error(Period*Sample)	18		

APPENDIX E

Analysis of variance of the effect of blended white light

Melatonin Concentrations (2000-2300 h)

Source of Variance	df	F value	P
Subject	5	1.73	.3
Treatment	2	1.75	.3
Stage	1	1.78	.3
Error	3		
Period	1	.05	.8
Period*Subject	5	.58	.7
Period*Treatment	2	1.32	.4
Period*Stage	1	0	1.0
Error(Period)	3		
Sample	6	1.72	.2
Sample*Subject	30	2.69	.02
Sample*Treatment	12	1.79	.1
Sample*Stage	6	.69	.7
Error(Sample)	18		
Period*Sample	6	.61	.7
Period*Sample*Subject	30	.39	1.0
Period*Sample*Treatment	12	.31	1.0
Period*Sample*Stage	6	1.11	.4
Error(Period*Sample)	18		

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