

## Highlights of the Abstract Program of the Fifteenth Annual Society for Light Treatment and Biological Rhythms Virtual Meeting 2003

Robert D. Levitan and Anthony J. Levitt

Department of Psychiatry, University of Toronto, Toronto, Canada

### ABSTRACT

Our 2003 proceedings are now written in stone, thanks to the impetus of the SARS outbreak just before we were scheduled to meet in Toronto. The submitted abstracts made clear that there were several new findings of fundamental importance to the field of circadian regulation, melatonin and seasonal affective disorder; these have now been described in the set of peer-reviewed reports that follow this overview. Here we present a critical summary of this work, organized into general topic areas of interest to the Society. As a guide to readers, we refer to items in the collection by topic section and order within section (e.g., #3.6), with the abstract number placed before each abstract title. Citations of earlier literature are found in the References.

### SECTION 1: EPIDEMIOLOGY AND PHENOMENOLOGY

One emerging area of work in seasonal affective disorder (SAD) relates to negative life events and social support. Although the definition of SAD according to the last major edition of the *Diagnostic and Statistical Manual for Mental Disorders* (American Psychiatric Association, 1994) removes predictable psychosocial seasonal stressors as a precipitating factor, psychosocial risk factors may still be a long-term vulnerability factor, as was previously demonstrated in a UK primary care setting (Michalak et al., 2003). A new study (Michalak et al., #1.1) extends this finding to psychiatric outpatients in Canada, reminding us that psychosocial interventions may be a neglected area of

1139

DOI: 10.1081/CBI-120026505  
Copyright © 2003 by Marcel Dekker, Inc.

0742-0528 (Print); 1525-6073 (Online)  
www.dekker.com

MARCEL DEKKER, INC.  
270 Madison Avenue, New York, New York 10016



consideration in SAD. Future work in this area will need to address cause-effect relationships and state-dependent effects when studying these associations.

In a prior study it was reported that suicidal patients with major depressive disorder (MDD) had increased somatic anxiety, psychic anxiety, and hostility relative to SAD patients (Pendse et al., 1999). In their current study, Pendse et al. (#1.2) found higher self-reported levels of hostility, worrying, and other symptoms in a SAD group relative to a suicidal depressed group. This suggests that *subjective* morbidity in SAD patients may be disproportionately high relative to other measures of illness. Dew and Tan's research group (#1.3, #1.4) illustrate this point using a different approach, by demonstrating a marked cognitive sensitivity of SAD patients to winter-related stimuli, with marked subjective impairment particularly from atypical neurovegetative symptoms.

Young and Reardon (#1.5) found further evidence that the temporal trajectory of subjective energy and motivation changes around the spring equinox. They note that at the equinox, the change in the photoperiodic signal is close to zero for a brief period, followed by a change in trajectory establishing a new signal that triggers a parallel change in energy and motivation. This finding is robust, having previously been shown in clinical populations as well.

Historically, one of the criticisms of research on the atypical spectrum of depression has been the lack of a comprehensive assessment tool that can fully assess and differentiate the most important atypical symptoms. Terman et al. (#1.6) have developed a novel instrument called the *Diagnostic Interview for Atypical Depression* (DIAD) to more accurately and specifically address this issue. In addition to demonstrating the reliability of the DIAD, these investigators found that increased eating was much more frequent in seasonal vs. nonseasonal depression, while rejection sensitivity showed the opposite pattern. These data further validate the notion that chronic atypical depression (as defined by the Columbia group) and SAD are distinct syndromes, with the former more closely related to personality disturbance while vegetative changes characterize the latter.

## SECTION 2: CIRCADIAN RHYTHMS AND SLEEP

New insights into the human circadian system in both health and disease are reported. Animal studies have shown that the quantity of retinal photopigment changes with different lighting conditions, such that a constant number of photons is absorbed each day, a process called photostasis (Penn and Williams, 1986). Similar "memory" effects on melatonin suppression have been found in humans (Hébert et al., 2002). Rufiange et al. (#2.1) now report that the circadian system of indoor workers is more sensitive to light than that of outdoor workers, further suggesting that photostasis occurs in humans. A negative correlation between the dim light melatonin onset (DLMO) and light exposure during waking hours was also found. A related finding by Wirz-Justice et al. (#2.2) is that increased outdoor light exposure also predicts an earlier sleep phase, but only on workdays in the winter. In summer and on weekends, the opposite pattern was found. Taken together, these studies suggest that workplace lighting conditions affect sleep/activity phase whether work is done indoors or outdoors, although other external factors may modify or eliminate these relationships.

One group that does not have to worry much about daytime light is Antarctic-based night-shift workers. Here the problem is adaptation to extreme conditions of darkness, and



Ng et al. (#2.3) show that while there are large individual differences, the vast majority of healthy individuals adapt to this demand within several days. Having an evening diurnal preference helps in this regard. This same study demonstrates that robust phase shifts are associated with low-fasting triacylglycerol (TAG) levels, although the cause-effect relationship between these variables will need to be sorted out with follow-up studies. This finding might have relevance for cardiovascular risk, in that high rates of cardiovascular disease in female shift workers has been reported (Kawachi et al., 1995), perhaps reflecting a circadian strain on TAG physiology.

While many light-based circadian studies compare the relative effects of high or low intensities of light, Prichard et al. (#2.4) are exploring the importance of relative vs. absolute illuminance. They show that the same low level of light can have either an alerting or hypnotic effect in rats, depending on whether it is paired with brighter or dimmer background light. This may be an important consideration in the design and interpretation of light-based circadian studies. The fact that this effect appears to be hard-wired and not subject to altered rearing conditions further adds to the importance of this finding. One aspect of sleep that is not hard-wired is the distribution of REM sleep. In a separate study, Prichard et al. (#2.5) show that the neonatal lighting environment (constant darkness vs. constant light, or DD vs. LL) significantly alters the sleep distribution in rats exposed to a light-dark (LD) cycle. DD-rearing exaggerates the tendency to trigger REM sleep and lights-on suppression of REM, while LL attenuates this effect. Might these findings generalize to humans? If so, this could be an interesting model for the intergenerational transmission of major depression. Perhaps because of their own altered sleep/activity rhythms, sensitivity to light, or both, depressed parents may be more likely to expose their growing children to unusual or maladaptive LD cycles. It could be that some of these offspring thus develop a REM-based change in sleep architecture, establishing an increased risk for later depression. It has previously been shown that the sleep-EEG abnormalities that characterize MDD are present in never-mentally-ill individuals at high risk for the illness (Fulton et al., 2000).

In our busy lives, the time of day we choose to exercise is usually dictated by convenience and work schedules. Bird and Tarpenning (#2.6) provide a new rationale for evening workouts for men based on the levels or secretion pattern of the hormones cortisol (C) and testosterone (T). Evening exercise produced lower cortisol levels and a higher T/C ratio than did morning exercise; the lower ratio may result in less catabolism and greater recovery of skeletal muscle growth.

Monk et al. (#2.7) report on an interaction between the impact of Modafinil, a psychostimulant medication that enhances arousal and mood, on the circadian temperature rhythm and restriction in sleep. This study demonstrates that certain compounds may affect specific parameters of circadian rhythms, but only in the circumstance of recent manipulations of sleep.

Several of the reports point to potential novel uses of circadian-based interventions in medical populations in whom pharmacotherapy is limited. For example, Parry et al. (#2.8) found that in postpartum depression, several neuroendocrine rhythms show amplitude and phase disturbances. These women may form an ideal population for use of light and/or sleep interventions, given the obvious risk of medications during the period of breast-feeding.

Breast cancer patients commonly experience disabling fatigue. While several factors are contributory, Liu et al. (#2.9) found that increased fatigue is linked to decreased light



exposure during the first week of chemotherapy. They propose that a positive feedback loop related to desynchronized circadian rhythms and decreased light exposure may be responsible, which suggests that light therapy may be useful for these patients.

Ancoli-Israel et al. (#2.10) extend their work on circadian rhythms in Alzheimer's disease by showing a positive relationship between severity of illness and disruption of circadian rhythmicity, but only in a subgroup that initially shows greater disturbance. An important negative finding was the lack of a clear relationship between mental state and rhythm patterns in the group as a whole. Harper et al. (#2.11) report on a novel morning light therapy protocol based on a measure of individuals' circadian time, rather than external clock time, in Alzheimer's patients. The expected phase advance in core body temperature was accompanied by an unexpected increase in nocturnal locomotor activity. Consistent with the activating effect, apathy scores were reduced. The authors suggest that longer treatment periods that allow for further adaptation to a new circadian lighting schedule may prove to be beneficial. Might evening light prove to have a paradoxical effect on decreasing nocturnal motor activity in this population?

### SECTION 3: MELATONIN

Several of the reports extend recent observations that shorter (blue) wavelengths of light have a greater suppressive effect on melatonin than longer wavelengths (Brainard et al., 2001; Thapan et al., 2001). Lack and Wright (#3.1) show that three short wavelengths of light also have a greater ability both to phase delay and advance the human melatonin rhythm than do longer wavelengths, an important consideration when developing clinical applications for circadian disorders. Also important for clinical applications, Glickman et al. (#3.2) demonstrate the ability of light-emitting diodes (LEDs) at 470 nm to strongly suppress melatonin, while equivalent 700 nm light does not have this effect. Riesenbergs et al. (#3.3) tested the effect of green LED light administered through the eyelids between 2400h and 0300h in normal volunteers. A significant melatonin suppression effect was observed relative to a dim light control, which sets the stage for future applications in clinical populations. Sasseville et al. (#3.4) report on the possible utility of orange lens glasses for night shift workers returning home from work in the morning. These glasses specifically block the short wavelengths of light known to suppress melatonin, while leaving other wavelengths unfiltered. When these glasses were worn, melatonin levels dropped by only 5.6% under bright light conditions. If replicated in naturalistic settings, this method could help promote morning sleep in night shift workers who might otherwise experience marked suppression of melatonin and associated insomnia.

Remé et al. (#3.5) have been studying the toxic effects of short wavelengths of light, and report animal data suggesting that non-coherent blue light, but not green light, damages the retina. As blue light treatments for circadian disorders in humans are being considered, it becomes clear that the therapeutic index of such treatments needs to be established.

Several treatment studies using exogenous melatonin also are included. Autism and mental retardation are known to be associated with circadian rhythm dysfunction, and impulsive aggression often follows a circadian pattern in such cases. Chevrette et al. (#3.6) present a case report of a 17-year-old with autism and bimodal aggressive outbreaks who



responded remarkably well to melatonin given at night for 18 months. Daytime sleep bouts were markedly decreased and violent episodes diminished by 79.1%. Melatonin appears to be a highly promising option for this particularly difficult-to-treat population.

Legally blind individuals frequently have free-running rhythms due to lack of entrainment to a strong zeitgeber, and light therapy is not a feasible solution. Several landmark studies have shown that melatonin can entrain blind free-runners. However, it has been suggested that administration of melatonin may be ineffective if it is given on the delay zone of the melatonin phase response curve (PRC). Emens et al. (#3.7) examined such a regimen in seven blind individuals and found that all subjects did, in fact, entrain to a nightly dose of melatonin initiated on the delay zone. Melatonin is thus a sufficiently strong zeitgeber to entrain free-running rhythms even if given on the delay zone of the melatonin PRC.

Considering that abnormal melatonin secretion and sleep are typical in major depressive disorder, exogenous melatonin has been studied as an adjunctive treatment with promising results for sleep measures in particular. Serfaty et al. (#3.8) report a new randomized double-blind trial that compared 6 mg slow-release melatonin to placebo in 33 depressed patients, most of whom were on a stable dose of an antidepressant. Both groups showed significant improvement in sleep measures and mood, with the melatonin group showing a small relative benefit. Given the positive findings but very small statistical power in several such studies to date, there is a sound rationale for conducting large, multi-center trials of melatonin for MDD. Identification of subgroups with optimum benefit from this approach would also be made possible with larger studies.

#### SECTION 4: BIOLOGY OF SEASONAL AFFECTIVE DISORDER

Three studies report significant insights into the role of the visual system in SAD. White and Terman (#4.1) extend the Columbia group's prior findings related to iris pigmentation and SAD, based on new data from a large web-based database of the Horne-Östberg scale. Dark-eyed subjects reported greater eveningness and delayed sleep phase relative to light-eyed subjects, particularly at  $<35^\circ$  latitude in North America in wintertime, when daylength is relatively longer than at northerly latitudes. The authors hypothesize that evening light may stimulate residual photopigment in dark but not light eyes, effectively extending winter daylength. Future photoreceptor studies would be of great interest in testing this hypothesis directly, as genetic differences (e.g., in circadian clock genes) among different ethnic populations might also play a role in these results.

Prior work with electroretinography has shown that retinal mechanisms are likely to play a role in both SAD and subsyndromal SAD. Hébert et al. (#4.2) report new data showing that in the depressed state, 41% of SAD patients have a retinal sensitivity, as measured by electroretinogram, at least one standard deviation below that of control subjects. This clear demonstration of retinal hyposensitivity in SAD sets the stage for further studies to dissect out the relative importance of different transmitter systems on photic activation of cones vs. rods. Wesner and Gallant (#4.3) studied spatial contrast in SAD, nonseasonal depression and control subjects, and report that in winter, both SAD and non-SAD depressed patients show greater sensitivity to high-frequency gratings. An unexpected and paradoxical finding was that only the nonseasonal depressed group showed a decrease in this measure in the summer, while SAD and control groups were unchanged. The basis for this contrasting effect remains unclear.



Two genetic studies shed light on the origins of increased eating behavior in SAD. Willeit et al. (#4.4) found an over-representation of the rare *Ser/Ser* genotype of the 5-HT<sub>2C</sub> receptor gene in SAD probands relative to matched control subjects. This receptor is most prevalent in the medial hypothalamus, an area known to play a role in feeding regulation and satiety. Furthermore, human studies with the 5-HT<sub>2C</sub> agonist mCPP have found abnormal responses in both bulimia nervosa and in SAD (Levitan et al., 1997; 1998; Schwartz et al., 1997). Like serotonin, dopamine also plays roles in mood regulation and eating behavior, and Levitan et al. (#4.5) now report an association between the hypofunctioning 7-repeat allele of the dopamine-4 receptor gene and both increased body mass and binge eating in female SAD probands. This may reflect a gene-environment interaction, in that low brain dopamine activity might predispose individuals to the rewarding properties of highly palatable/high caloric foods, which have become more readily available in developed countries over recent decades. Consistent with a reward model, prior work has shown that SAD patients consume such foods to modify negative mood states (Kräuchi et al., 1997).

Also relevant to eating behavior in SAD, Wirz-Justice et al. (#4.6) studied dietary and seasonal effects of two cytokines, leptin and tumor necrosis factor (TNF). No seasonal effects related to leptin were found, however a novel and significant winter decrease in TNF-alpha was discovered. This may have relevance to hibernation models of SAD, considering that hibernating squirrels show a similar pattern. Further work with healthy controls and other populations with abnormal eating behavior will be of great interest.

Danilenko and colleagues (#4.7) provide an interesting attempt to link two previously observed phenomena: first, that timed carbohydrate (CHO) rich meals can phase shift individuals, and second, that phase shifting in subjects with SAD is associated with response to treatment. Unfortunately, the study found no differences in clinical outcomes in SAD patients between morning and afternoon CHO rich meals. There may have been an overwhelming impact on variance in outcome measures of other factors such as body fat, number of hours of sunshine in the previous 4 days, and day of the menstrual cycle. The study demonstrates the difficulties inherent in studying treatment outcomes in SAD subjects who may be very responsive to environmental and menstrual influences.

It is interesting to consider that the atypical neurovegetative symptoms of SAD may reflect a state of low arousal. Indeed, prior work has shown that central CRH neurons may be underactive in SAD (Joseph-Vanderpool et al., 1991). In a study of stress hormones in SAD, Pendse et al. (#4.8) may have found further evidence for this model: baseline plasma CRH levels were lower in SAD patients relative to control subjects, although suicidal MDD patients showed a similar result. Differences in delta-sleep-inducing peptide (DSIP) in SAD vs. suicidal MDD patients sheds further light on arousal models of SAD by offering a possible explanation for the prevalent wintertime hypersomnia, although the lower levels of DSIP in SAD subjects might reflect a secondary effect or compensatory mechanism.

## SECTION 5: TREATMENT STUDIES AND CLINICAL TRIALS

### Nonseasonal Applications of Light

Over the past decade, data have been accumulating that support the use of light therapy for conditions other than winter depression. Several reports have suggested light



therapy may have efficacy in the treatment of nonseasonal major depression. Now, Goel et al. (#5.1) report on a study that treated chronic, nonseasonal depression with light therapy (active) vs. high-density negative air ions (active) vs. low-density ions (placebo) over 5 weeks. Both active treatments were significantly superior to placebo. Remission occurred in half the subjects in the active treatment groups but in none of the subjects treated with placebo. These data provide exciting new possibilities in several respects. First, they confirm the potential value of light therapy as a treatment for nonseasonal depression. Second, they add to growing evidence that high-density negative air ions may indeed have specific therapeutic action in depression. Finally, both these treatment modalities appear to have been effective in subjects with chronic depression, a condition that is notoriously unresponsive to treatment. Considering that remission rates of 50% were achieved in the active groups suggests these treatments may turn out to be excellent alternatives to antidepressant medications, or good choices for antidepressant augmentation.

Epperson et al. (#5.2) also support the use of light therapy in nonseasonal depression. In this study, 10 pregnant women with major depression were randomized to 5 weeks of 7000 lux vs. 500 lux light therapy. The study currently has a small sample size (six subjects completed 10 weeks of treatment), which limits any substantive conclusions. Nonetheless, there is the suggestion of some effect of light therapy in a population that may not be eligible to take traditional antidepressant treatments for their major depressive episodes.

### Parameters of Treatment for Winter Depression

Although substantial attention has been paid to dosing variables that may affect treatment response in seasonal depression, several questions remain regarding optimum parameters of light exposure, the timing of treatment relative to circadian phase and the capacity of treatments to phase shift. Danilenko and Hayes (#5.3) hypothesized that the therapeutic effects of light differ depending on whether it is polarized or non-polarized. However, they found no difference between polarized and non-polarized light in SAD, which echoes biological findings that light polarization has no effect on melatonin suppression.

Light therapy studies of shorter duration have similar response rates to those with a longer duration, which suggests that informing subjects and treatment teams of the length of a trial may alter expectations and therefore the rate of response. Indeed, initial tests by Levitt and Levitan (#5.4) confirm such an outcome. They randomized 34 subjects with seasonal depression to either a 2- or 5-week trial of bright vs. dim light. Although response rates by the end of treatment were similar in the 2- and 5-week groups, at week 2 the 2-week group achieved a 50% response rate, while the 5-week group only achieved a 22% response rate. Such results, if extended, may affect decision-making about treatment duration in future trials, whether for light or antidepressant medications, and seasonal or nonseasonal depression.

A large study by Lewy et al. (#5.5) concentrated on the effect of timing of melatonin administration on therapeutic response and circadian phase shifting in patients with SAD. They randomized 100 patients to either placebo or melatonin given either in the morning or afternoon/evening. There was no significant therapeutic effect on depression in either the active or placebo groups, even though the timed melatonin treatments produced the appropriate phase shifts. However, there was a relationship between severity of depression



and the degree of phase delay of melatonin onset at baseline and after 3 weeks of treatment. Although these data provide a new line of evidence in support of Lewy's phase shift hypothesis of winter depression, the relevance to clinical intervention is limited by the lack of therapeutic benefit in this study. Nonetheless, this study adds to the growing consensus that it is important to "match" phase shifting strategies to the individual's phase type. It seems clear that neither self-reports of sleep time, nor clock time of the melatonin onset are sufficient to determine the appropriate timing of an intervention. This brings into question the clinical utility of more global measures of phase typing in determining the parameters of treatment for seasonal depression. There is a pressing need to establish (a) that phase typing can be used in a practical way to choose the optimum treatment or treatment timing strategy for seasonal depression; and (b) the most reproducible, practical, cost effective, and clinically meaningful way to perform phase typing. The search for these indicators continues to yield important and fascinating information about the biology of seasonal and nonseasonal depression.

### New Treatments for Seasonal Affective Disorder

Light therapy continues to be the common first-line choice for seasonal depression. However, response rates are in the 60% range, and a small but important proportion of these responders will fail to maintain their response. Antidepressant drugs are also effective, but have a more burdensome side effect profile than light therapy and are often less acceptable to patients with seasonal depression. There is a need for new alternatives to light therapy. Lundt (#5.6) reports on an open trial of the psychostimulant Modafinil in 13 patients with seasonal depression. Modafinil may be of particular interest in SAD, as it rapidly enhances both arousal and mood, very similar to what is observed with bright light therapy and in contrast to the delayed effects of standard antidepressants. Modafinil was effective, especially in resolving fatigue and improving wakefulness. This compound may prove to be of interest in the treatment of SAD or as an adjunct to light therapy; however, 38% of subjects experienced headaches, which, among other side effects, may prove to be a limiting factor. Larger scale studies may help to give a better indication of the risk-benefit ratio of this treatment in seasonal depression.

There is a dearth of literature on psychotherapy for seasonal depression. In their current report, Rohan et al. (#5.7) update their impressive investigation of cognitive behavioral therapy (CBT) for seasonal depression. They enrolled 33 subjects who were randomized to 4 treatments: CBT, light therapy (LT), CBT + LT, vs. a placebo (minimal contact, delayed light) over 6 weeks. LT was delivered twice a week—which is an unusually sparse regimen—for 1.5 hours in a group format. Overall CBT + LT and CBT were statistically superior to placebo. Although LT was quantitatively superior, the difference did not reach statistical significance. These findings are of particular interest for several reasons. First, CBT may prove to be an excellent alternative to light therapy, either as a first-line treatment or in cases of light therapy failure. Second, the combination of LT and CBT may be better than either alone. Certainly, the recent depression literature supports the combination of antidepressant medication and CBT as more effective than that of either as a monotherapy (Hirschfield et al., 2002).



## CONCLUSION

The breadth of scientific investigation and collection of new and important data presented in this collection is truly impressive, and sets the stage for the next phase of this Virtual Meeting, the Society's listserv discussion between presenters and colleagues. In an ironic way, our 2003 interactions are deepened compared with the usual two-day meeting: there is no time restriction on the question/answer session, there is no way you can miss a paper because you have been called out of the room and there is no handicap because you could not travel the distance. The publication in journal format, accompanied by the structured opportunity for open discussion, will serve substantially to advance the field and improve communication between researchers. However, it does more than that—it demonstrates a unique and effective response to a devastating epidemic that nearly paralyzed a city but could not dampen the scientific spirit.

## REFERENCES

- American Psychiatric Association (1994). *Diagnostic and Statistical Manual for Mental Disorders*, 4th ed. Washington, D.C: American Psychiatric Association.
- Brainard, G. C., Hanifin, J. P., Greeson, J. M., Byrne, B., Glickman, G., Gerner, E., Rollag, M. D. (2001). Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J. Neurosci.* 21:6405–6412.
- Fulton, M. K., Armitage, R., Rush, A. J. (2000). Sleep electroencephalographic coherence abnormalities in individuals at high risk for depression: a pilot study. *Biol. Psychiatr.* 47:618–625.
- Hébert, M., Martin, S. K., Lee, C., Eastman, C. I. (2002). The effects of prior light history on the suppression of melatonin by light in humans. *J. Pineal Res.* 33:198–203.
- Hirschfeld, R. M., Dunner, D. L., Keitner, G., Klein, D. N., Koran, L. M., Kornstein, S. G., Markowitz, J. C., Miller, I., Nemeroff, C. B., Ninan, P. T., Rush, A. J., Schatzberg, A. F., Thase, M. E., Trivedi, M. H., Borian, F. E., Crits-Christoph, P., Keller, M. B. (2002). Does psychosocial functioning improve independent of depressive symptoms? A comparison of nefazodone, psychotherapy, and their combination. *Biol. Psychiatr.* 51(2):123–133.
- Joseph-Vanderpool, J. R., Rosenthal, N. E., Chrousos, G. P., Wehr, T. A., Skwerer, R., Kasper, S., Gold, P. W. (1991). Abnormal pituitary-adrenal responses to corticotropin-releasing hormone in patients with seasonal affective disorder: clinical and pathophysiological implications. *J. Clin. Endocrinol. Metab.* 72:1382–1387.
- Kawachi, I., Colditz, G. A., Stampfer, M. J., Willett, W. C., Manson, J. E., Speizer, F. E., Hennekens, C. H. (1995). Prospective study of shift work and risk of coronary heart disease in women. *Circulation* 92:3178–3182.
- Kräuchi, K., Reich, S., Wirz-Justice, A. (1997). Eating style in seasonal affective disorder: who will gain weight in winter? *Compr. Psychiatr.* 38:80–87.
- Levitan, R. D., Kaplan, A. S., Joffe, R. T., Levitt, A. J., Brown, G. M. (1997). Hormonal and subjective responses to intravenous meta-chlorophenylpiperazine in bulimia nervosa. *Arch. Gen. Psychiatr.* 54:521–527.
- Levitan, R. D., Kaplan, A. S., Brown, G. M., Vaccarino, F. J., Kennedy, S. H., Levitt, A. J., Joffe, R. T. (1998). Hormonal and subjective responses to intravenous m-chlorophenylpiperazine in women with seasonal affective disorder. *Arch. Gen. Psychiatr.* 55:244–249.



- Michalak, E. E., Wilkinson, C., Hood, K., Dowrick, C., Wilkinson, G. (2003). Seasonality, negative life events and social support in a community sample. *Br. J. Psychiatr.* 182:434–438.
- Pendse, B., Westrin, A., Engstrom, G. (1999). Temperament traits in seasonal affective disorder, suicide attempters with non-seasonal major depression and healthy controls. *J. Affect. Disord.* 54:55–65.
- Penn, J. S., Williams, T. P. (1986). Photostasis: regulation of daily photon-catch by rat retinas in response to various cyclic illuminances. *Exp. Eye Res.* 43:915–928.
- Schwartz, P. J., Murphy, D. L., Wehr, T. A., Garcia-Borreguero, D., Oren, D. A., Moul, D. E., Ozaki, N., Snelbaker, A. J., Rosenthal, N. E. (1997). Effects of meta-chlorophenylpiperazine infusions in patients with seasonal affective disorder and healthy control subjects. Diurnal responses and nocturnal regulatory mechanisms. *Arch. Gen. Psychiatry* 54:375–385.
- Thapan, K., Arendt, J., Skene, D. J. (2001). An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. *J. Physiol.* 535:261–267.

