

Pathophysiology of seasonal affective disorder: a review

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The study of the pathophysiology of seasonal affective disorder (SAD, also known as winter depression) has historically been intimately linked to investigations into the mechanisms of action of light therapy. This paper reviews the studies on the pathophysiology of SAD with emphasis on circadian, neurotransmitter, and genetic hypotheses. There is substantial evidence for circadian phase shift and serotonergic hypotheses, but conflicting results may indicate that SAD is a biologically heterogeneous condition. Recent progress in defining the molecular mechanisms of the human circadian clock and retinal phototransduction of light will provide important new directions for future studies of the etiology and pathophysiology of SAD.

L'étude de la pathophysiologie du trouble affectif saisonnier (TAS) (aussi appelé dépression hivernale) a toujours été reliée intimement aux études sur les modes d'action de la photothérapie. Dans ce document, les auteurs passent en revue des études réalisées sur la pathophysiologie du TAS et mettent l'accent sur des hypothèses reliées au rythme circadien, aux neurotransmetteurs et à la génétique. D'importantes données probantes appuient les hypothèses relatives au déphasage du rythme circadien et à la dépression sérotoninergique, mais les résultats contradictoires peuvent indiquer que le TAS est un problème hétérogène sur le plan biologique. Les progrès réalisés récemment dans la définition des mécanismes moléculaires de l'horloge biologique humaine et de la phototransduction rétinienne de la lumière établiront d'importantes orientations nouvelles pour des études à venir sur l'étiologie et la pathophysiologie du TAS.

Seasonal affective disorder (SAD), or recurrent winter depression,¹ is considered a clinical subtype of major depression. The criteria for "winter seasonal pattern" in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, which are similar to other definitions of SAD, specify a recurrent pattern of major depressive episodes during winter and remission of symptoms during summer, in the absence of seasonal psychosocial

stressors. Using these criteria, the prevalence of SAD has been estimated at less than 1% in the US² and at 1% to 3% in Canada.³ Much of the interest in SAD has been sparked by its response to exposure to bright, artificial light, known as light therapy or phototherapy. Clinical consensus guidelines have recommended light therapy as a first-line treatment for SAD,⁴ based on the evidence of numerous studies showing efficacy, including large

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randomized controlled trials^{5,6} and meta-analyses.^{7,8}

SAD and light therapy were identified from basic studies of circadian and seasonal rhythms in animals. Kripke et al^{9,10} had proposed circadian-rhythm hypotheses for nonseasonal depression and first published reports showing that bright light exposure could improve mood in patients with depression. Many seasonal rhythms are mediated through changes in melatonin, a neurohormone secreted by the pineal gland during the subjective night. Melatonin secretion is controlled by the endogenous circadian clock, but it can also be suppressed by exposure to light. In 1980, Lewy et al¹¹ demonstrated that melatonin suppression required brighter light in humans than in animals. This finding led to the use of bright light in the treatment of a patient with winter depression¹² and to the first systematic studies involving patients with SAD.¹³ Thus, the theories of the pathophysiology of SAD are intimately tied to the mechanisms of light therapy. This paper reviews the major biological hypotheses for SAD and light therapy, focusing on circadian rhythms, neurotransmitter function, and genetics, and defines important future directions for research.

Circadian rhythms in SAD

Photoperiod and melatonin

One of first hypotheses about SAD was that the shorter winter photoperiod (light–dark cycle) led to depressive symptoms.¹ This seemed consistent with early studies showing that the prevalence of SAD increases with more northerly latitude, where the photoperiod is shorter in winter.^{14,15} Therefore, bright light exposure at the beginning and end of the winter day should simulate a summer photoperiod and restore summer behaviours. The first light therapy studies in SAD used 3 hours of light exposure given at 6:00 am to 9:00 am and 4:00 pm to 7 pm.¹ This photoperiod extension method led to significant improvement. However, subsequent treatment studies showed that photoperiod extension alone was not effective for SAD,¹⁶ and that single daily pulses of light were as effective as the morning plus evening pulses of photoperiod extension (summarized by Terman et al¹). Subsequent prevalence studies of SAD showed little or no effect of latitude,^{2,3} indicating that the correlation between photoperiod and SAD is smaller than previously believed.¹⁷

Attention also focused on a melatonin hypothesis for

SAD because, in many animals, the photoperiod signal is mediated by the duration of nocturnal melatonin secretion, and light suppresses melatonin secretion. However, the 24-hour melatonin rhythm in winter was no different between SAD patients and controls, and did not change with light treatment.^{18,19} Melatonin suppression alone is also not enough to produce a therapeutic response.²⁰ Atenolol, a long-acting β -blocker that suppresses melatonin secretion, was not effective for SAD.²¹ However, a study using a short-acting β -blocker, propranolol, to truncate the melatonin secretion curve in the early morning (an effect similar to that of morning bright light exposure) found beneficial effects for SAD.²²

Melatonin has also been investigated as a treatment for SAD. In one study, a 5-mg dose of melatonin, given in the morning or the evening, was not effective against SAD.²³ In contrast, studies of melatonin given in smaller, more physiological doses at a specific time to produce a circadian phase-shift in patients found evidence of effectiveness (see next section).²⁴

Recent studies, however, have revived the photoperiod hypothesis. The nocturnal duration of melatonin secretion reflects changes in the photoperiod in humans.²⁵ In normal subjects in naturalistic living conditions, no changes in melatonin profiles were found between summer and winter, suggesting that artificial indoor light may suppress the melatonin response to seasonal changes in photoperiod.²⁶ In a study comparing patients with SAD with normal controls, only those with SAD had a significant seasonal variation in their dim-light nocturnal melatonin profile. This finding suggests that the patients with SAD, but not the control subjects, respond to seasonal photoperiodic signals (T.A. Wehr: personal communication, February 2000). A longer nocturnal melatonin duration in SAD is consistent with the findings from the propranolol treatment study,²² because the truncation of the early-morning melatonin secretion would “normalize” the melatonin profile. Photoperiod may also be more important in the onset of the vegetative symptoms found in SAD.^{27,28} These findings suggest that the photoperiod hypothesis is worth pursuing.

Circadian phase shift

Light is the most potent zeitgeber (synchronizer) of the circadian pacemaker, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and bright light exposure can reliably shift the phase of the circadian

rhythm in humans. The timing of light exposure relative to the circadian cycle dictates the direction and magnitude of circadian rhythm phase shifts. Building on circadian and phase-advance hypotheses for nonseasonal depression,^{9,29,30} Lewy et al^{31,32} proposed a phase-delay hypothesis for SAD. Their theory is that SAD results from internal circadian rhythms that are phase-delayed relative to the external clock or to other rhythms such as the sleep-wake cycle, and that light therapy exerts its therapeutic effect by correcting the abnormal phase delay. In a phase-delay hypothesis, morning light therapy is predicted to be superior to evening light because morning light exposure results in a corrective phase-advance, while evening light exposure should further delay the circadian phase. Light exposure in the middle of the day generally has no effect on circadian rhythms, and hence should have no therapeutic effect.

Initial studies used the dim-light melatonin onset (DLMO, the time that melatonin begins to be secreted by the pineal gland during controlled, dim-light conditions) as a marker of circadian phase because it is relatively free of masking effects. Patients with SAD were found to have phase-delayed DLMO compared with control subjects; furthermore, morning light exposure resulted in phase advances, while evening light exposure resulted in phase delays, and only the morning exposure led to clinical improvement.³³ A subsequent study found only a trend to phase-delayed DLMO in the patients with SAD at baseline, but greater phase advances with morning light exposure in the patients with SAD than in the controls.³⁴ Again, morning light exposure was superior to evening light (which did not result in significant phase-delays relative to baseline in the patients with SAD) in the therapeutic response. A larger study of morning versus evening bright-light exposure (51 patients with SAD and 49 controls) confirmed that morning light therapy was superior to evening light.³⁵ However, the DLMO was significantly delayed relative to controls in only 2 of 3 time points (pre-baseline and withdrawal), but not at baseline.

Another study found that patients with SAD had significantly delayed melatonin rhythms, and the melatonin cycle phase advanced with both morning light alone and morning light in combination with evening light.³⁶ Morning bright light also significantly phase-advanced cortisol, temperature, and melatonin rhythms in patients with SAD, although the sleep-wake cycle also advanced.³⁷ The circadian activity-rest cycle was also

found to be significantly delayed in patients with SAD.³⁸

The study of circadian rhythms is complicated by masking effects of environmental factors, including sleep, light exposure, activity, feeding, etc. One method to control for these factors is the “constant routine” technique, in which subjects are studied for 36 hours in a controlled setting to unmask endogenous circadian rhythms. In a constant routine study of 6 patients with SAD compared with 6 control subjects, the patients with SAD had phase delays of the DLMO, core temperature rhythm and cortisol rhythm.^{39,40} Light therapy advanced the circadian rhythms in the patients with SAD, but improvement in depression scores was not correlated with the magnitude of the phase advance.

The phase-shift hypothesis predicts that other stimuli that affect phase, e.g., medications or sleep changes, would also be effective for SAD. Preliminary studies indicate that low-dose melatonin, when appropriately timed to achieve a circadian phase advance, has therapeutic effects in SAD,²⁴ and that clinical response is correlated to the degree of phase advance.⁴¹

Other studies, however, have not supported circadian phase abnormalities in SAD. The circadian rhythm of core body temperature was no more phase-delayed in patients with SAD than in normal controls.⁴² Although morning light exposure advanced the phase of temperature rhythm more in the patients than in controls, the relation between phase changes and improvement in depression was opposite to that predicted by the phase-delay hypothesis. No phase differences between patients with SAD and controls were found in the 24-hour core body temperature profile before and after light therapy in winter.⁴³ Both groups had significant phase-delays of temperature in the summer compared with the winter, effects opposite to the phase-advances found after light therapy in the winter.⁴⁴ The 24-hour circadian profiles of various hormones in plasma, including cortisol, prolactin and thyrotropin, did not differ between patients with SAD and control subjects before and after light therapy.⁴⁵

In the phase-delay hypothesis, evening or mid-day light exposure should not have significant antidepressant effects in SAD. Although morning light is usually statistically superior to evening light in controlled comparisons^{6,35} and in most^{7,46} but not all⁴⁷ meta-analyses, there are large individual studies showing that evening light is more effective than placebo⁶ and as effective as morning light.^{5,48} In a morning-evening comparison study, the phase position of 6-sulphatoxymelatonin, the

urinary metabolite of melatonin, was also determined, and most patients with SAD showed evidence of phase-delay.⁴⁸ However, the phase position did not predict preferential response to morning or evening timing of light therapy. Similarly, a phase advance of nocturnal salivary melatonin secretion was not associated with response to light therapy.⁴⁹

In a constant routine study of female patients with SAD and controls, no phase changes were found in most parameters of core body temperature, but mid-day light exposure did result in some phase advances of the temperature rhythm.⁵⁰ However, no differences were found in melatonin onset or duration (by salivary melatonin assay), either between groups or before and after light treatment.

The conflicting results from these circadian studies are likely due to several factors. Most studies have small sample sizes, so that the study populations may not be comparable. For example, some studies specifically selected hypersomnic patients, who may be more likely to show phase-delayed circadian rhythms; although the majority of patients with SAD display hypersomnia, they still may not be representative of all patients with SAD. Ambulatory measurements of core body temperature may not be indicative of endogenous circadian rhythms because of the masking effect of environmental factors such as sleep and activity, whereas the constant routine studies control for those factors. Similarly, 24-hour sampling of melatonin rhythms can be masked by external light exposure. Most light therapy studies are done in ambulatory patients over a week or two; hence, nonphotic zeitgebers (e.g., activity, social cues) may confound the circadian effects of bright light exposure.

Another confounding factor is that group mean data may not represent individual circadian responses. For example, light exposure at a constant clock time (as given in most light treatment studies) may vary according to individual circadian time through a range of 5 hours.⁵¹ This means that the magnitude of light-induced phase shift varies considerably for an individual patient. In a study of morning versus evening light in SAD, Terman et al⁵¹ found that there was no relation between clinical response and whether patients had a phase advance or a phase delay (as measured by DLMO). However, the magnitude of individual phase advances was significantly correlated with the degree of clinical improvement.⁵² Hence, studies that do not include measurements of individual circadian phase may be prone to negative findings.

It should also be noted that any positive relation between clinical response and phase-advance does not necessarily mean that they are causally related. Other factors that affect morning light exposure (sitting closer to the light, better compliance with light exposure, greater retinal sensitivity to light) may lead to greater improvement and greater phase advance, even if phase advance had nothing to do with the treatment response. A more rigorous test of the phase-delay hypothesis would be to reverse or prevent the therapeutic effect of morning light therapy, which presumably works through a corrective phase advance, by providing melatonin at a circadian time that produces a counteractive phase delay.

In summary, studies involving the most reliable measures of endogenous circadian phase (using DLMO or constant routine) have shown evidence for circadian phase delays in SAD. There is also some evidence that clinical response to light therapy and melatonin is related to the degree of corrective phase advances, although these findings do not necessarily imply causality. However, there remains a subset of patients with SAD who do not have demonstrable phase-delayed circadian rhythms or who do not require a phase shift for response to light therapy or both. Hence, circadian mechanisms may not be the only explanation for SAD.

Neurotransmitter function in SAD

In reviewing the contributions of individual neurotransmitter systems to SAD, several methodological issues must be considered. The major monoamine transmitters implicated in mood disorders (i.e., serotonin, dopamine and norepinephrine) are functionally linked at many levels, making it unlikely that an isolated abnormality in a single transmitter system is responsible for a given disorder. Related to this, while abnormal results on a variety of challenge tests have been found in SAD and other psychiatric disorders, it is not known whether the observed abnormalities are mediated at the transmitter system under investigation, or proximally or distally to it. It must also be considered that, in humans, certain neurotransmitters are more easily investigated than are others; for example, the risk of inducing psychosis or addiction greatly limits our ability to directly examine the dopamine system in patients. Hence, there is much more data available for the serotonin system than for the dopamine system in the literature on depression.

Notwithstanding these limitations, there is considerable evidence from converging areas of research pointing to a major role of monoamine neurotransmitter systems in the pathophysiology of SAD.

Serotonin

While there has been an explosion of research on serotonergic functioning in all mood disorders over the past decade, there is a unique rationale for hypothesizing that serotonergic dysfunction plays a major role in SAD in particular. In animals and normal humans, various measures of serotonin (5-hydroxytryptamine, 5-HT) activity fluctuate markedly across the seasons. The serotonin content in the hypothalamus in human post mortem samples has a marked seasonal variation, with the lowest levels found during the winter months of December and January.⁵³ Given the role of hypothalamic serotonin in satiety and feeding regulation, this could explain the tendency of patients with SAD to crave carbohydrates and gain weight during winter depressive episodes. 5-HIAA is the major metabolite of serotonin, and cerebrospinal fluid (CSF) 5-HIAA levels are derived from several factors, including serotonin synthesis and turnover, the firing rate of serotonin neurons, and the acid transport system responsible for 5-HIAA excretion. The finding of low CSF 5-HIAA levels in springtime is relatively robust,^{54,55} and may (or may not) reflect the cumulative effect of low brain serotonergic activity over the winter. Seasonal fluctuations in other monoamine metabolites have been described as well, but the magnitude of these changes is greatest for the serotonin system.⁵⁴

L-tryptophan is the amino acid precursor of serotonin, and various measures of tryptophan metabolism and availability have been compared across seasons. In a longitudinal study that measured free and total tryptophan levels in normal controls, the highest levels were found in April and May, whereas levels dipped significantly in the late summer/early fall.⁵⁶ Another study also found higher plasma levels of free tryptophan in the spring, with lower levels in both the early summer and winter periods.⁵⁷ These findings were not simply attributable to dietary fluctuations; however, their overall significance remains unclear in that several other factors, such as protein intake, influence the degree to which plasma tryptophan crosses the blood-brain barrier. Furthermore, the fact that tryptophan levels are highest when 5-HIAA levels are lowest is difficult to rationalize using a singular model of serotonin activity.

Patients with SAD report increased activation following high-carbohydrate meals, whereas normal controls feel more sedated;⁵⁸ this may be consistent with altered tryptophan and serotonin metabolism in patients with SAD, since dietary carbohydrates are believed to enhance serotonin synthesis and transmission via increased tryptophan uptake into the brain.^{59,60}

In more recent studies, a tryptophan depletion protocol has been used to examine a possible vulnerability factor for SAD related to the serotonergic system. Plasma tryptophan levels can be reduced to 20% of normal within 5 hours by administering an oral tryptophan-free mixture of large, neutral amino-acids.⁶¹ Positron-emission tomographic studies have shown that serotonin synthesis is reduced markedly in response to this depletion protocol.⁶² Two separate studies have shown that patients with SAD in remission after light therapy experience a clear relapse of depressive symptoms with tryptophan depletion.^{63,64} In the latter study, "atypical" symptoms such as carbohydrate craving were especially sensitive to the depletion protocol, suggesting an important role for serotonergic mediation of this symptom cluster in particular. These results also point to a serotonergic mechanism for light therapy in SAD. The effects of tryptophan depletion during summer remission, however, are less consistent: one report showed relapse,⁶⁵ while another did not.⁶⁶ Taken as a whole, tryptophan-depletion studies offer significant evidence that serotonin plays a role in SAD. However, the fact that patients with nonseasonal depression also show sensitivity to tryptophan depletion⁶⁷ calls into question the specificity of these results to SAD.

Another line of research has studied tryptophan as a potential treatment for SAD. Two studies compared light therapy with tryptophan in a repeated-measures cross-over design, finding similar efficacy for the 2 treatments.^{68,69} There was some evidence that relapse after withdrawal from treatment was slower following tryptophan discontinuation.⁶⁹ In one sample of patients with SAD that was either partially or completely nonresponsive to light therapy, adding tryptophan (3 g per day) produced a robust response in nine of 14 patients (64%).⁷⁰ Given the role of tryptophan in brain serotonin activity, these results support the hypothesis that serotonin plays a role in the pathophysiological features of SAD.

Other medications that enhance serotonin function by different mechanisms also have beneficial effects in SAD. D-fenfluramine, a serotonin-releasing medication, was found to be effective in small double-blind con-

trolled studies.⁷¹ Larger studies indicate that the serotonin reuptake inhibitors fluoxetine⁷² and sertraline⁷³ are effective in SAD.

Neuroendocrine studies of SAD have shown relatively robust findings to date. Serotonergic neurons play an intrinsic role in release of prolactin, growth hormone, corticotropin (ACTH) and cortisol and are likely to play a role in mediating subjective responses to serotonergic agonists. Studies found abnormal responses to the non-selective 5-HT agonists 5-hydroxytryptophan⁷⁴ and D,L-fenfluramine,⁷⁵ although an earlier study with D,L-fenfluramine was negative.⁷⁶ Double-blind, placebo-controlled studies indicate that, compared with normal controls, patients with SAD had blunted hormonal responses, and experienced increased subjective activation/euphoria responses, following administration of the postsynaptic 5-HT_{2C} agonist m-chlorophenylpiperazine (m-CPP),^{77,78} thereby confirming results from previous non-placebo-controlled studies.⁷⁹⁻⁸¹ There was a normalization of the subjective responses following successful light therapy, suggesting that activation/euphoria in response to a post-synaptic serotonergic agent may be a state marker for winter depression, mediated by an alteration in the sensitivity of post-synaptic serotonin receptors.⁷⁷ These various findings may be relatively specific for SAD, in that patients with major depression do not show altered responses to m-CPP challenge.⁸² m-CPP also has some affinity for other receptors, including 5-HT_{1A} and 5-HT₇; however, no behavioural or neuroendocrine effects were found in a challenge study with ipsapirone, a selective 5-HT_{1A} receptor agonist.⁸³ Blunted growth hormone responses to the 5-HT_{1D} agonist sumatriptan were also reported in SAD, with normalization after light therapy.⁸⁴

In summary, there are consistent, replicated studies of abnormal neuroendocrine and behavioural responses to serotonergic agents that indicate dysfunction at, or downstream to, 5-HT receptors in SAD. Most of the evidence implicates 5-HT_{2C} or 5-HT₇ receptors, although other receptors such as 5-HT_{1D} may be involved.

Norepinephrine

To determine whether serotonin dysfunction alone can explain the pathophysiology of SAD, Neumeister et al⁸⁵ administered both tryptophan depletion and catecholamine depletion protocols, in random order, to patients with SAD in remission after light therapy. Sham depletions were also included in the protocol. Both

active depletions caused a temporary relapse of depressive symptoms, demonstrating that catecholamines, in addition to serotonin, likely play a role in SAD.

Clinically, patients with SAD frequently present with core symptoms of hypersomnia and increased eating, in contrast to patients with classic melancholic depression, who exhibit insomnia and weight loss when depressed. One possible interpretation of this difference is that patients with SAD are in a state of central hypo-arousal, while those with melancholic depression are in a state of central hyper-arousal. Several research findings are consistent with this hypothesis. Untreated patients with SAD tended to have lower baseline norepinephrine concentrations than normal controls, and than after light treatment.⁷⁷ In this same study, patients with SAD had blunted norepinephrine responses to the serotonin and α -noradrenergic agonist m-CPP, both with and without light therapy treatment. Other studies have found an increase in both plasma norepinephrine levels⁸⁶ and in turnover of norepinephrine⁸⁷ following light therapy. An inverse relation between resting cerebrospinal fluid levels of norepinephrine metabolites and depression scores in patients with SAD has also been reported.⁸⁸

These various lines of evidence may be consistent with decreased basal sympathetic tone or decreased activation of norepinephrine-associated arousal systems in patients with SAD. More work is needed to confirm and extend these preliminary findings, and to determine which components of the norepinephrine system may play a role in the clinical features of SAD.

Dopamine

Few studies have directly examined dopamine functioning in patients with SAD; however, several lines of indirect evidence point to dopaminergic involvement in this disorder. Low resting prolactin levels have been interpreted as reflecting low functional activity of dopamine, with compensatory up-regulation of D₂ receptors, in patients with SAD.^{89,90} This decrease was evident across seasons and was unaffected by subtype of depression (bipolar II versus unipolar), suggesting that it may be a trait marker for the disorder.⁹⁰ This same group has found decreased eye blink rates, which may reflect low dopamine activity, in subjects with SAD,⁹¹ although other groups have not replicated this finding.⁹² Additional evidence for dopamine dysfunction in SAD comes from studies that have examined thermoregula-

tory heat loss. Compared with controls, patients with SAD exhibit blunted thermoregulatory heat loss in the winter, a finding that normalized after light therapy, and in the euthymic summer state.^{93,94} Both light treatment and summer may facilitate central dopamine functioning and normalize thermoregulatory heat loss in patients with SAD.

Dopamine is the major retinal transmitter involved in the light response. Oren⁹⁵ has speculated that light therapy might work in SAD by stimulating the production of retinal dopamine. There is some evidence from retinal electrophysiological studies for subtle reductions in retinal light sensitivity, which can be reversed with light therapy, in patients with SAD compared with controls.⁹⁶⁻⁹⁹ In contrast, another study using a dark adaptation threshold procedure has shown supersensitivity to light in winter in patients with SAD compared with control subjects.¹⁰⁰ Still other studies using different electrophysiological methods have not found changes in retinal or ophthalmic function.^{101,102} Hence, there is not yet consistent evidence of retinal dopamine or other retinal dysfunction in SAD.

Furthermore, a treatment test of the dopamine hypothesis, via a double-blind, placebo-controlled trial of L-dopa combined with carbidopa, found no significant response overall in SAD.¹⁰³ Of note, however, was that premenopausal women showed the greatest responses to L-dopa in this study, consistent with findings in past studies that premenopausal women were also more likely to show abnormalities in dopamine function.

It has recently been reported that adults with residual attention-deficit disorder, particularly women with impulsive characteristics, have very high seasonality scores.¹⁰⁴ One of the classic models of attention-deficit disorder proposes that, in particular, the impulsive subtype of this disorder is mediated by a state of central under-arousal; this would explain the robust therapeutic effects of psychostimulants (primarily dopaminergic drugs) in attention-deficit disorder.¹⁰⁵ It has also been speculated that the core symptoms of SAD may reflect a state of low central arousal.¹⁰⁶ It is thus interesting to speculate whether patients with "seasonal" attention-deficit disorder might be in a state of chronic under-arousal mediated by low dopamine activity, compounded by light-deprivation and a further decrease in dopamine activity in the fall/winter months. Interestingly, recent neuroimaging studies have found global decreases in cerebral metabolism in both atten-

tion-deficit disorder¹⁰⁷ and in SAD¹⁰⁸ that are consistent with such a model.

Genetics in SAD

There is emerging evidence that one or more genetic factors establish vulnerability to, or protection from, seasonality and SAD. One line of study has sought to determine whether genetic selection within the Icelandic population over centuries might have played a role in their adaptation to the long arctic winter.^{109,110} These authors studied rates of seasonal depression in native Icelanders and in a group of adults in Manitoba, Canada, who were wholly descended from Icelandic emigrants. Both native Icelanders and emigrated Icelandic descendants were found to have much lower rates of SAD than populations along the east coast of the US, despite living at more northerly latitudes. This is consistent with a genetic model of seasonality and suggests possible genetic protective factors in the Icelandic population.

The largest study of possible genetic factors in SAD used univariate and multivariate genetic analysis of 4639 adult twin pairs from a volunteer-based registry in Australia.¹¹¹ Genetic effects accounted for 29% of the variance in seasonality (as assessed using a self-report questionnaire) in this nonclinical sample. Overall, genetic predisposition to seasonality was associated with so-called "atypical" vegetative symptoms of depression, such as increased food intake, weight gain and increased sleep, compatible with treatment studies showing these symptoms to be the best predictors of a good response to light therapy.^{112,113}

Sex factors have been studied in the relative importance of genetic versus environmental influences in seasonal mood change. Using a seasonality questionnaire in 339 twin pairs, one study found that genetics accounted for 69% of the variance in seasonality scores in men and 45% in women.¹¹⁴ Changes in sleep patterns, social activity, mood, appetite and energy were accounted for primarily by additive genetic effects in both sexes, although genotype analyses suggested that the genetic factors mediating seasonality in men may be different from those in women.

From a genetic point of view, mood disorders such as SAD are best thought of as complex phenotypes or "spectrum" disorders. Traditional family-linkage studies, which follow the segregation of marker alleles in multiplex pedigrees with several affected members, are

of limited value when studying complex traits. Genetic association studies test whether polymorphic DNA markers in candidate genes contribute to the disease phenotype, and are more suited to genetic studies of complex disorders such as SAD.

Genetic association studies of SAD have begun to emerge. An association between the short allele of the serotonin transporter promoter gene and the trait of seasonality was reported in a sample of 97 patients with SAD and 71 controls.¹¹⁵ In a similar study, an association was found between SAD (but not seasonality *per se*) and the 5-HT_{2a} promoter polymorphism -1438G/A.¹¹⁶ An association between the 218C allele of tryptophan hydroxylase and SAD in a small sample of female patients with increased eating behaviour was also found.¹¹⁷ In contrast, Ozaki et al reported a lack of association between SAD and naturally occurring amino acid polymorphisms of the serotonin 5-HT_{2A} gene¹¹⁸ and other 5-HT receptor candidate genes.¹¹⁹

Overall, while this early work has been encouraging, each of these studies must be considered preliminary and needs to be replicated in much larger samples before firmer conclusions can be drawn. Nuclear family controls, as opposed to population-based controls, will also be needed to avoid false-positive findings attributable to population stratification effects.

Future directions

Important progress has been made in defining the pathophysiological mechanisms in SAD and the mode of action of light therapy. However, the conflicting results of studies indicate that there is likely substantial heterogeneity in the etiology and pathophysiology of SAD. This may be due in part to diagnostic issues. There is increasing evidence that seasonality, as a dimensional factor, is a more valid construct than the DSM-IV diagnosis of SAD/seasonal pattern.¹²⁰ A dual-vulnerability hypothesis, in which SAD results from separate seasonality and depression factors (each of which may have different pathophysiological mechanisms), has been proposed to explain the heterogeneity found in SAD studies.^{27,121}

The major hypotheses proposed for SAD include phase-shifted circadian rhythms, serotonergic dysfunction, and genetic vulnerability. It should be recognized, however, that these hypotheses may not be mutually exclusive. Recent findings have highlighted important relations between serotonin and circadian rhythms.

Direct and indirect serotonergic projections from the midbrain raphe nuclei are involved in the nonphotic signalling to the SCN,¹²² and 5-HT agonists can modulate photic responses of SCN cells.¹²³ Systemic administration of 5-HT agonists may also shift circadian rhythms,¹²⁴ but these effects may occur at the level of the raphe nuclei and may be mediated by other neurotransmitters (such as γ -aminobutyric acid) in the SCN.¹²⁵ Serotonergic pathways are also likely involved in SCN projections to effector systems, including the hypothalamus, where regulation of neuroendocrine and sleep-wake functions occur. Further studies to link serotonergic dysfunction with dysregulated circadian rhythms in SAD will likely be informative.

What will also shape future studies of the circadian basis for SAD are results from recent intense and remarkable research activity into the molecular mechanisms of circadian regulation, including the identification of the first mammalian clock genes *clock*, *per* and *tim*.¹²⁶⁻¹²⁸ There are already preliminary indications that alterations in these genes affect human circadian rhythms. For example, a polymorphism of the human *clock* gene is associated with diurnal preference as measured by a morning-eveningness questionnaire.¹²⁹ Similar genetic association studies will be important in SAD. Other recent findings suggest that there is a dedicated retinal pathway for circadian signalling that is separate from the visual pathways, and that the ocular photoreceptors of this circadian pathway do not involve rod or cone cells.¹³⁰ Cryptochromes, which are photoactive protein pigments in the mammalian retina, are potential candidates for the circadian photoreceptive component.^{131,132} Although it now appears that cryptochromes have a more complex role in regulation of circadian rhythm,^{133,134} and they are likely not the only photopigments involved in processing the light signal,¹³⁵ cryptochromes will likely be another fruitful area for SAD and circadian research.

In an elegant closing of the circle, basic studies of mammalian circadian rhythms gave rise to the study of SAD and light therapy; a decade and a half later, basic molecular science will offer sophisticated new circadian hypotheses to be tested. However, attention should also focus on the noncircadian effects of bright light. Further study of noncircadian effects is particularly important, since light therapy is being investigated for other psychiatric disorders that may not involve circadian mechanisms, including nonseasonal depression,¹³⁶ premenstrual depressive disorder¹³⁷ and bulimia nervosa.^{138,139}

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References

- Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y, et al. Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry* 1984;41:72-80.
- Blazer DG, Kessler RC, Swartz MS. Epidemiology of recurrent major and minor depression with a seasonal pattern. The National Comorbidity Survey. *Br J Psychiatry* 1998;172:164-7.
- Levitt AJ, Boyle MH. Latitude and the variation in seasonal depression and seasonality of depressive symptoms. [abstract] *9th Annual Meeting of the Society for Light Treatment and Biological Rhythms* 1997. p. 14.
- Lam RW, Levitt AJ. *Canadian consensus guidelines for the treatment of seasonal affective disorder*. Vancouver: Clinical & Academic Publishing; 1999.
- Eastman CI, Young MA, Fogg LF, Liu L, Meaden PM. Bright light treatment of winter depression: a placebo-controlled trial. *Arch Gen Psychiatry* 1998;55:883-9.
- Terman M, Terman JS, Ross DC. A controlled trial of timed bright light and negative air ionization for treatment of winter depression. *Arch Gen Psychiatry* 1998;55:875-82.
- Terman M, Terman JS, Quitkin FM, McGrath PJ, Stewart JW, Rafferty B. Light therapy for seasonal affective disorder. A review of efficacy. *Neuropsychopharmacology* 1989;2:1-22.
- Lee TM, Chan CC. Dose-response relationship of phototherapy for seasonal affective disorder: a meta-analysis. *Acta Psychiatr Scand* 1999;99:315-23.
- Kripke DF, Mullaney DJ, Atkinson ML, Wolf S. Circadian rhythm disorders in manic-depressives. *Biol Psychiatry* 1978; 13:335-51.
- Kripke DF. Photoperiodic mechanisms for depression and its treatment. In: Perris C, Struwe G, Janson B, editors. *Biological Psychiatry*. Amsterdam: Elsevier Press; 1981. p. 1248-52.
- Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in humans. *Science* 1980;210:1267-9.
- Lewy AJ, Kern HA, Rosenthal NE, Wehr TA. Bright artificial light treatment of a manic-depressive patient with a seasonal mood cycle. *Am J Psychiatry* 1982;139:1496-8.
- Rosenthal NE, Sack DA, Carpenter CJ, Parry BL, Mendelson WB, Wehr TA. Antidepressant effects of light in seasonal affective disorder. *Am J Psychiatry* 1985;142:163-70.
- Potkin SG, Zetin M, Stamenkovic V, Kripke D, Bunney WE, Jr. Seasonal affective disorder: prevalence varies with latitude and climate. *Clin Neuropharmacol* 1986;9:181-3.
- Rosen LN, Targum SD, Terman M, Bryant MJ, Hoffman H, Kasper SF, et al. Prevalence of seasonal affective disorder at four latitudes. *Psychiatry Res* 1990; 31:131-44.
- Winton F, Corn T, Huson LW, Franey C, Arendt J, Checkley SA. Effects of light treatment upon mood and melatonin in patients with seasonal affective disorder. *Psychol Med* 1989;19:585-90.
- Mersch PP, Middendorp HM, Bouhuys AL, Beersma DG, van den Hoofdakker RH. Seasonal affective disorder and latitude: a review of the literature. *J Affect Disord* 1999;53:35-48.
- Checkley SA, Murphy DG, Abbas M, Marks M, Winton F, Palazidou E, et al. Melatonin rhythms in seasonal affective disorder. *Br J Psychiatry* 1993;163:332-7.
- Partonen T, Vakkuri O, Lamberg-Allardt C, Lonqvist J. Effects of bright light on sleepiness, melatonin, and 25-hydroxyvitamin D(3) in winter seasonal affective disorder. *Biol Psychiatry* 1996;39:865-72.
- Wehr TA, Jacobsen FM, Sack DA, Arendt J, Tamarkin L, Rosenthal NE. Phototherapy of seasonal affective disorder. Time of day and suppression of melatonin are not critical for antidepressant effects. *Arch Gen Psychiatry* 1986;43:870-5.
- Rosenthal NE, Jacobsen FM, Sack DA, Arendt J, James SP, Parry BL, et al. Atenolol in seasonal affective disorder: a test of the melatonin hypothesis. *Am J Psychiatry* 1988;145:52-6.
- Schlager DS. Early-morning administration of short-acting beta blockers for treatment of winter depression. *Am J Psychiatry* 1994;151:1383-5.
- Wirz-Justice A, Graw P, Krauchi K, Gisin B, Arendt J, Aldhous M, et al. Morning or night-time melatonin is ineffective in seasonal affective disorder. *J Psychiatr Res* 1990;24:129-37.
- Lewy AJ, Bauer VK, Cutler NL, Sack RL. Melatonin treatment of winter depression: a preliminary study. *Psychiatry Res* 1998;77:57-61.
- Wehr TA. The durations of human melatonin secretion and sleep respond to changes in daylength (photoperiod). *J Clin Endocrinol Metab* 1991;73:1276-80.
- Wehr TA, Giesen HA, Moul DE, Turner EH, Schwartz PJ. Suppression of men's responses to seasonal changes in day length by modern artificial lighting. *Am J Physiol* 1995;269:R173-8.
- Young MA, Watel LG, Lahmeyer HW, Eastman CI. The temporal onset of individual symptoms in winter depression: differentiating underlying mechanisms [published erratum appears in *J Affect Disord* 1992;24:207]. *J Affect Disord* 1991;22:191-7.
- Young MA, Meaden PM, Fogg LF, Cherin EA, Eastman CI. Which environmental variables are related to the onset of seasonal affective disorder? *J Abnorm Psychol* 1997;106:554-62.
- Kripke DF. Phase-advance theories for affective illness. In: Wehr TA, Goodwin FK, editors. *Circadian Rhythms in Psychiatry*. Pacific Grove (CA): Boxwood Press; 1983. p. 41-69.
- Wehr TA, Wirz-Justice A, Goodwin FK, Duncan W, Gillin JC. Phase advance of the circadian sleep-wake cycle as an antidepressant. *Science* 1979;206:710-3.
- Lewy AJ, Sack RL, Singer CM. Treating phase-typed chronobiological sleep and mood disorders using appropriately timed bright artificial light. *Psychopharmacol Bull* 1985;21:368-72.
- Lewy AJ, Sack RL, Singer CM, White DM, Hoban TM. Winter depression and the phase-shift hypothesis for bright light's therapeutic effects: history, theory, and experimental evidence. *J Biol Rhythms* 1988;3:121-34.
- Lewy AJ, Sack RL, Miller LS, Hoban TM. Antidepressant and circadian phase-shifting effects of light. *Science* 1987;235:352-4.
- Sack RL, Lewy AJ, White DM, Singer CM, Fireman MJ, Vandiver R. Morning vs evening light treatment for winter depression. Evidence that the therapeutic effects of light are mediated by circadian phase shifts [published erratum appears in *Arch Gen Psychiatry* 1992;49:650]. *Arch Gen Psychiatry*

- 1990;47:343-51.
35. Lewy AJ, Bauer VK, Cutler NL, Sack RL, Ahmed S, Thomas KH, et al. Morning vs evening light treatment of patients with winter depression. *Arch Gen Psychiatry* 1998;55:890-6.
 36. Terman M, Terman JS, Quitkin FM, Cooper TB, Lo ES, Gorman JM, et al. Response of the melatonin cycle to phototherapy for Seasonal Affective Disorder. Short note. *J Neural Transm* 1988;72:147-65.
 37. Endo T. Morning bright light effects on circadian rhythms and sleep structure of SAD. *Jikeikai Med J* 1993;40:295-307.
 38. Glod CA, Teicher MH, Polcari A, McGreener CE, Ito Y. Circadian rest-activity disturbances in children with seasonal affective disorder. *J Am Acad Child Adolesc Psychiatry* 1997;36:188-95.
 39. Dahl K, Avery DH, Lewy AJ, Savage MV, Brengelmann GL, Larsen LH, et al. Dim light melatonin onset and circadian temperature during a constant routine in hypersomnic winter depression. *Acta Psychiatr Scand* 1993;88:60-6.
 40. Avery DH, Dahl K, Savage MV, Brengelmann GL, Larsen LH, Kenny MA, et al. Circadian temperature and cortisol rhythms during a constant routine are phase-delayed in hypersomnic winter depression [published erratum appears in *Biol Psychiatry* 1997;42:636]. *Biol Psychiatry* 1997;41:1109-23.
 41. Lewy AJ, Bauer VK, Bish HA, Evces CE, Hasler BP, Emens JS, et al. Antidepressant response correlates with the phase advance in winter depressives. [abstract] *Soc Light Treatment Biol Rhythms Abst* 2000;12:22.
 42. Eastman CI, Gallo LC, Lahmeyer HW, Fogg LF. The circadian rhythm of temperature during light treatment for winter depression. *Biol Psychiatry* 1993;34:210-20.
 43. Rosenthal NE, Levendosky AA, Skwerer RG, Joseph-Vanderpool JR, Kelly KA, Hardin T, et al. Effects of light treatment on core body temperature in seasonal affective disorder. *Biol Psychiatry* 1990;27:39-50.
 44. Levendosky AA, Josep-Vanderpool JR, Hardin T, Sorek E, Rosenthal NE. Core body temperature in patients with seasonal affective disorder and normal controls in summer and winter. *Biol Psychiatry* 1991;29:524-34.
 45. Oren DA, Levendosky AA, Kasper S, Duncan CC, Rosenthal NE. Circadian profiles of cortisol, prolactin, and thyrotropin in seasonal affective disorder. *Biol Psychiatry* 1996;39:157-70.
 46. Thompson C, Rodin I, Birtwhistle J. Light therapy for seasonal and nonseasonal affective disorder: a Cochrane meta-analysis. [abstract] *Society for Light Treatment and Biological Rhythms Abstr* 1999. p. 11.
 47. Lee TM, Blashko CA, Janzen HL, Paterson JG, Chan CC. Pathophysiological mechanism of seasonal affective disorder. *J Affect Disord* 1997;46:25-38.
 48. Wirz-Justice A, Graw P, Krauchi K, Gisin B, Jochum A, Arendt J, et al. Light therapy in seasonal affective disorder is independent of time of day or circadian phase. *Arch Gen Psychiatry* 1993;50:929-37.
 49. Rice J, Mayor J, Tucker HA, Bielski RJ. Effect of light therapy on salivary melatonin in seasonal affective disorder. *Psychiatry Res* 1995;56:221-8.
 50. Wirz-Justice A, Krauchi K, Brunner DP, Graw P, Haug HJ, Leonhardt G, et al. Circadian rhythms and sleep regulation in seasonal affective disorder. *Acta Neuropsychiatrica* 1995;41-3.
 51. Terman M. On the specific action and clinical domain of light treatment. In: Lam RW, editor. *Seasonal affective disorder and beyond: light treatment for SAD and non-SAD conditions*. Washington: American Psychiatric Press; 1998. p. 91-116.
 52. Terman M, Terman JS. Morning vs. evening light: Effects on the melatonin rhythm and antidepressant response in winter depression. [abstract] *Soc Light Treatment Biol Rhythms Abst* 2000;12:1.
 53. Carlsson A, Svennerhom L, Winblad B. Seasonal and circadian monoamine variations in human brain examined post mortem. *Acta Psychiatrica Scandinavica (Suppl)* 1980;280:75-83.
 54. Asberg M, Bertilsson L, Rydin E. Monoamine metabolites in cerebrospinal fluid in relation to depressive illness, suicidal behaviour and personality. In: Angrist B, Burrows GD, Lader M, editors. *Recent advances in neuropsychopharmacology: Selected papers from the 12th Congress of the Collegium Internationale Neuro-Psychopharmacologicum*. Oxford (England): Pergamon Press; 1981. p. 257-71.
 55. Brewerton TD, Berrettini WH, Nurnberger JI Jr, Linnoila M. Analysis of seasonal fluctuations of CSF monoamine metabolites and neuropeptides in normal controls: findings with 5-HIAA and HVA. *Psychiatry Res* 1988;23:257-265.
 56. Wirz-Justice A, Richter R. Seasonality in biochemical determinations: a source of variance and a clue to the temporal incidence of affective illness. *Psychiatry Res* 1979;1:53-60.
 57. Swade C, Coppen A. Seasonal variations in biochemical factors related to depressive illness. *J Affect Disord* 1980;2:249-55.
 58. Rosenthal NE, Genhart MJ, Caballero B, Jacobsen FM, Skwerer RG, Coursey RD, et al. Psychobiological effects of carbohydrate- and protein-rich meals in patients with seasonal affective disorder and normal controls. *Biol Psychiatry* 1989;25:1029-40.
 59. Fernstrom JD, Wurtman RJ. Brain serotonin content: increase following ingestion of carbohydrate diet. *Science* 1971;174:1023-5.
 60. Wurtman RJ. Nutrients that modify brain function. *Sci Am* 1982;246:50-9.
 61. Young SN, Smith SE, Pihl R, Ervin FR. Tryptophan depletion causes a rapid lowering of mood in normal males. *Psychopharmacology* 1985;87:173-7.
 62. Benkelfat C, Seletti B, Palmour RM, Hillel J, Ellenbogen M, Young SN. Tryptophan depletion in stable lithium-treated patients with bipolar disorder in remission. *Arch Gen Psychiatry* 1995;52:154-6.
 63. Lam RW, Zis AP, Grewal A, Delgado PL, Charney DS, Krystal JH. Effects of rapid tryptophan depletion in patients with seasonal affective disorder in remission after light therapy. *Arch Gen Psychiatry* 1996;53:41-4.
 64. Neumeister A, Praschak-Rieder N, Besselmann B, Rao ML, Gluck J, Kasper S. Effects of tryptophan depletion on drug-free patients with seasonal affective disorder during a stable response to bright light therapy. *Arch Gen Psychiatry* 1997;54:133-8.
 65. Neumeister A, Praschak-Rieder N, Hesselmann B, Vitouch O, Rauh M, Barocka A, et al. Effects of tryptophan depletion in fully remitted patients with seasonal affective disorder during summer. *Psychol Med* 1998;28:257-64.
 66. Lam RW, Bowering TA, Tam EM, Grewal A, Yatham LN, Shiah IS, et al. Effects of rapid tryptophan depletion in patients with seasonal affective disorder in natural summer remission. *Psychol Med* 2000;30:79-87.
 67. Bremner JD, Innis RB, Salomon RM, Staib LH, Ng CK, Miller HL, et al. Positron emission tomography measurement of cerebral metabolic correlates of tryptophan depletion-induced depressive relapse. *Arch Gen Psychiatry* 1997;54:364-74.
 68. McGrath RE, Buckwald B, Resnick EV. The effect of L-tryptophan on seasonal affective disorder. *J Clin Psychiatry* 1990;51:162-3.
 69. Ghadirian AM, Murphy BE, Gendron MJ. Efficacy of light versus tryptophan therapy in seasonal affective disorder. *J Affect Disord* 1998;50:23-7.
 70. Lam RW, Levitan RD, Tam EM, Yatham LN, Lamoureux S, Zis

- AP. L-tryptophan augmentation of light therapy in patients with seasonal affective disorder. *Can J Psychiatry* 1997;42:303-6.
71. O'Rourke DA, Wurtman JJ, Brzezinski A, Nader TA, Chew B. Serotonin implicated in etiology of seasonal affective disorder. *Psychopharmacol Bull* 1987;23:358-9.
 72. Lam RW, Gorman CP, Michalon M, Steiner M, Levitt AJ, Corral MR, et al. Multicenter, placebo-controlled study of fluoxetine in seasonal affective disorder. *Am J Psychiatry* 1995;152:1765-70.
 73. Moscovitch A, Blashko C, Wiseman R, Goldberg M, Martindale J. A double-blind, placebo-controlled study of sertraline in patients with seasonal affective disorder. *New Research Abstracts, American Psychiatric Association Annual Meeting*. 1995.
 74. Jacobsen FM, Sack DA, Wehr TA, Rogers S, Rosenthal NE. Neuroendocrine response to 5-hydroxytryptophan in seasonal affective disorder. *Arch Gen Psychiatry* 1987;44:1086-91.
 75. Coiro V, Volpi R, Marchesi C, De Ferri A, Davoli C, Caffarra P, et al. Abnormal serotonergic control of prolactin and cortisol secretion in patients with seasonal affective disorder. *Psychoneuroendocrinology* 1993;18:551-6.
 76. Yatham LN, Michalon M. Hormonal responses to dl-fenfluramine challenge are not blunted in seasonal affective disorder. *Psychoneuroendocrinology* 1995;20:433-8.
 77. Schwartz PJ, Murphy DL, Wehr TA, Garcia-Borreguero D, Oren DA, Moul, et al. Effects of meta-chlorophenylpiperazine infusions in patients with seasonal affective disorder and healthy control subjects. Diurnal responses and nocturnal regulatory mechanisms. *Arch Gen Psychiatry* 1997;54:375-85.
 78. Levitan RD, Kaplan AS, Brown GM, Vaccarino FJ, Kennedy SH, Levitt AJ, et al. Hormonal and subjective responses to intravenous m-chlorophenylpiperazine in women with seasonal affective disorder. *Arch Gen Psychiatry* 1998;55:244-9.
 79. Garcia-Borreguero D, Jacobsen FM, Murphy DL, Joseph-Vanderpool JR, Chiara A, Rosenthal NE. Hormonal responses to the administration of m-chlorophenylpiperazine in patients with seasonal affective disorder and controls. *Biol Psychiatry* 1995;37:740-9.
 80. Jacobsen FM, Mueller EA, Rosenthal NE, Rogers S, Hill JL, Murphy DL. Behavioral responses to intravenous meta-chlorophenylpiperazine in patients with seasonal affective disorder and control subjects before and after phototherapy. *Psychiatry Res* 1994;52:181-97.
 81. Joseph-Vanderpool JR, Jacobsen FM, Murphy DL, Hill JL, Rosenthal NE. Seasonal variation in behavioral responses to m-CPP in patients with seasonal affective disorder and controls. *Biol Psychiatry* 1993;33:496-504.
 82. Anand A, Charney DS, Delgado PL, McDougale CJ, Heninger GR, Price LH. Neuroendocrine and behavioral responses to intravenous m-chlorophenylpiperazine (mCPP) in depressed patients and healthy comparison subjects. *Am J Psychiatry* 1994;151:1626-30.
 83. Schwartz PJ, Turner EH, Garcia-Borreguero D, Sedway J, Veticad RG, Wehr TA, et al. Serotonin hypothesis of winter depression: behavioral and neuroendocrine effects of the 5-HT_{1A} receptor partial agonist ipsapirone in patients with seasonal affective disorder and healthy control subjects. *Psychiatry Res* 1999;86:9-28.
 84. Yatham LN, Lam RW, Zis AP. Growth hormone response to sumatriptan (5-HT_{1D} agonist) challenge in seasonal affective disorder: effects of light therapy. *Biol Psychiatry* 1997;42:24-9.
 85. Neumeister A, Turner EH, Matthews JR, Postolache TT, Barnett RL, Rauh M, et al. Effects of tryptophan depletion vs catecholamine depletion in patients with seasonal affective disorder in remission with light therapy. *Arch Gen Psychiatry* 1998;55:524-30.
 86. Skwerer RG, Jacobsen FM, Duncan CC, Kelly KA, Sack DA, Tamarkin L, et al. Neurobiology of seasonal affective disorder and phototherapy. *J Biol Rhythms* 1988;3:135-54.
 87. Anderson JL, Vasile RG, Mooney JJ, Bloomingdale KL, Samson JA, Schildkraut JJ. Changes in norepinephrine output following light therapy for fall/winter seasonal depression. *Biol Psychiatry* 1992;32:700-4.
 88. Rudorfer MV, Skwerer RG, Rosenthal NE. Biogenic amines in seasonal affective disorder: effects of light therapy. *Psychiatry Res* 1993;46:19-28.
 89. Depue RA, Arbisi P, Spont MR, Krauss S, Leon A, Ainsworth B. Seasonal and mood independence of low basal prolactin secretion in premenopausal women with seasonal affective disorder. *Am J Psychiatry* 1989;146:989-95.
 90. Depue RA, Arbisi P, Krauss S, Iacono WG, Leon A, Muir R, et al. Seasonal independence of low prolactin concentration and high spontaneous eye blink rates in unipolar and bipolar II seasonal affective disorder. *Arch Gen Psychiatry* 1990;47:356-64.
 91. Depue RA, Iacono WG, Muir R, Arbisi P. Effect of phototherapy on spontaneous eye blink rate in subjects with seasonal affective disorder. *Am J Psychiatry* 1988;145:1457-9.
 92. Barbato G, Moul DE, Schwartz P, Rosenthal NE, Oren DA. Spontaneous eye blink rate in winter seasonal affective disorder. *Psychiatry Res* 1993;47:79-85.
 93. Arbisi PA, Depue RA, Spont MR, Leon A, Ainsworth B. Thermoregulatory response to thermal challenge in seasonal affective disorder: a preliminary report. *Psychiatry Res* 1989;28:323-34.
 94. Arbisi PA, Depue RA, Krauss S, Spont MR, Leon A, Ainsworth B, et al. Heat-loss response to a thermal challenge in seasonal affective disorder. *Psychiatry Res* 1994;52:199-214.
 95. Oren DA. Retinal melatonin and dopamine in seasonal affective disorder. *J Neural Transm Gen Sect* 1991;83:85-95.
 96. Lam RW, Beattie CW, Buchanan A, Remick RA, Zis AP. Low electrooculographic ratios in patients with seasonal affective disorder. *Am J Psychiatry* 1991;148:1526-9.
 97. Lam RW, Beattie CW, Buchanan A, Mador JA. Electroretinography in seasonal affective disorder. *Psychiatry Res* 1992;43:55-63.
 98. Ozaki N, Rosenthal NE, Moul DE, Schwartz PJ, Oren DA. Effects of phototherapy on electrooculographic ratio in winter seasonal affective disorder. *Psychiatry Res* 1993;49:99-107.
 99. Ozaki N, Rosenthal NE, Myers F, Schwartz PJ, Oren DA. Effects of season on electro-oculographic ratio in winter seasonal affective disorder. *Psychiatry Res* 1995;59:151-5.
 100. Terman JS, Terman M. Photopic and scotopic light detection in patients with seasonal affective disorder and control subjects. *Biol Psychiatry* 1999;46:1642-8.
 101. Oren DA, Moul DE, Schwartz PJ, Alexander JR, Yamada EM, Rosenthal NE. An investigation of ophthalmic function in winter seasonal affective disorder. *Depression* 1993;1:29-37.
 102. Murphy DG, Murphy DM, Abbas M, Palazidou E, Binnie C, Arendt J, et al. Seasonal affective disorder: response to light as measured by electroencephalogram, melatonin suppression, and cerebral blood flow. *Br J Psychiatry* 1993;163:327-31.
 103. Oren DA, Moul DE, Schwartz PJ, Wehr TA, Rosenthal NE. A controlled trial of levodopa plus carbidopa in the treatment of winter seasonal affective disorder: a test of the dopamine hypothesis. *J Clin Psychopharmacol* 1994;14:196-200.
 104. Levitan RD, Jain UR, Katzman MA. Seasonal affective symptoms in adults with residual attention-deficit hyperactivity disorder. *Compr Psychiatry* 1999;40:261-7.
 105. Laufer MW, Denhoff E, Solomons G. Hyperkinetic impulsive disorder in children's behavior problems. *Psychosom Med*

- 1957;19:38-49.
106. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis [published erratum appears in *JAMA* 1992;268:200]. *JAMA* 1992;267:1244-52.
 107. Zametkin AJ, Nordahl TE, Gross M, King AC, Semple WE, Rumsey J, et al. Cerebral glucose metabolism in adults with hyperactivity of childhood onset. *N Engl J Med* 1990;323:1361-6.
 108. Cohen RM, Gross M, Nordahl TE, Semple WE, Oren DA, Rosenthal N. Preliminary data on the metabolic brain pattern of patients with winter seasonal affective disorder. *Arch Gen Psychiatry* 1992;49:545-52.
 109. Magnusson A, Axelsson J. The prevalence of seasonal affective disorder is low among descendants of Icelandic emigrants in Canada. *Arch Gen Psychiatry* 1993;50:947-51.
 110. Magnusson A, Stefansson JG. Prevalence of seasonal affective disorder in Iceland. *Arch Gen Psychiatry* 1993;50:941-6.
 111. Madden PA, Heath AC, Rosenthal NE, Martin NG. Seasonal changes in mood and behavior. The role of genetic factors. *Arch Gen Psychiatry* 1996;53:47-55.
 112. Oren DA, Jacobsen FM, Wehr TA, Cameron CL, Rosenthal NE. Predictors of response to phototherapy in seasonal affective disorder [published erratum appears in *Compr Psychiatry* 1992;33:419]. *Compr Psychiatry* 1992;33:111-4.
 113. Lam RW. Morning light therapy for winter depression: predictors of response. *Acta Psychiatr Scand* 1994;89:97-101.
 114. Jang KL, Lam RW, Livesley WJ, Vernon PA. Gender differences in the heritability of seasonal mood change. *Psychiatry Res* 1997;70:145-54.
 115. Rosenthal NE, Mazzanti CM, Barnett RL, Hardin TA, Turner EH, Lam GK, et al. Role of serotonin transporter promoter repeat length polymorphism (5-HTTLPR) in seasonality and seasonal affective disorder. *Molecular Psychiatry* 1998;3:175-7.
 116. Enoch MA, Goldman D, Barnett R, Sher L, Mazzanti CM, Rosenthal NE. Association between seasonal affective disorder and the 5-HT2A promoter polymorphism, -1438G/A. *Mol Psychiatry* 1999;4:89-92.
 117. Levitan RD, Masellis M, Kennedy JL, Kennedy SH, Kaplan AS, Vaccarino FJ, et al. Polymorphism in serotonin genes in seasonal affective disorder and bulimia. *Biol Psychiatry* 1999;43(Suppl 8):271.
 118. Ozaki N, Rosenthal NE, Pesonen U, Lappalainen J, Feldman-Naim S, Schwartz PJ, et al. Two naturally occurring amino acid substitutions of the 5-HT2A receptor: similar prevalence in patients with seasonal affective disorder and controls. *Biol Psychiatry* 1996;40:1267-72.
 119. Sher L, Goldman D, Ozaki N, Rosenthal NE. The role of genetic factors in the etiology of seasonal affective disorder and seasonality. *J Affect Disord* 1999;53:203-10.
 120. Murray GW, Allen NB, Trinder J. Construct validation of seasonality in Australia. [abstract] *International Congress on Chronobiology Abstracts* 1999. p. 27.
 121. Lam RW, Tam EM, Yatham LN, Zis AP. Seasonal depression: the dual-vulnerability hypothesis revisited. *J Affect Dis*. In press.
 122. Morin LP. Serotonin and the regulation of mammalian circadian rhythmicity. *Ann Med* 1999;31:12-33.
 123. Ying SW, Zhang DX, Rusak B. Effects of serotonin agonists and melatonin on photic responses of hamster intergeniculate leaflet neurons. *Brain Res* 1993;628:8-16.
 124. Prosser RA, Miller JD, Heller HC. A serotonin agonist phase-shifts the circadian clock in the suprachiasmatic nuclei in vitro. *Brain Res* 1990;534:336-9.
 125. Mintz EM, Gillespie CF, Marvel CL, Huhman KL, Albers HE. Serotonergic regulation of circadian rhythms in Syrian hamsters. *Neuroscience* 1997;79:563-9.
 126. King DP, Zhao Y, Sangoram AM, Wilsbacher LD, Tanaka M, Antoch MP, et al. Positional cloning of the mouse circadian clock gene. *Cell* 1997;89:641-53.
 127. Tei H, Okamura H, Shigeyoshi Y, Fukuhara C, Ozawa R, Hirose M, et al. Circadian oscillation of a mammalian homologue of the *Drosophila* period gene. *Nature* 1997;389:512-6.
 128. Koike N, Hida A, Numano R, Hirose M, Sakaki Y, Tei H. Identification of the mammalian homologues of the *Drosophila* timeless gene, *Timeless1*. *FEBS Lett* 1998;441:427-31.
 129. Katzenberg D, Young T, Lin L, Finn L, Mignot E. A human period gene (HPER1) polymorphism is not associated with diurnal preference in normal adults. *Psychiatr Genet* 1999;9:107-9.
 130. Lucas RJ, Freedman MS, Munoz M, Garcia-Fernandez JM, Foster RG. Regulation of the mammalian pineal by non-rod, non-cone, ocular photoreceptors. *Science* 1999;284:505-7.
 131. Thresher RJ, Vitaterna MH, Miyamoto Y, Kazantsev A, Hsu DS, Petit C, et al. Role of mouse cryptochrome blue-light photoreceptor in circadian photoresponses. *Science* 1998;282:1490-4.
 132. Lucas RJ, Foster RG. Photoentrainment in mammals: a role for cryptochrome? *J Biol Rhythms* 1999;14:4-10.
 133. van der Horst GT, Muijtjens M, Kobayashi K, Takano R, Kanno S, Takao M, et al. Mammalian *Cry1* and *Cry2* are essential for maintenance of circadian rhythms. *Nature* 1999;398:627-30.
 134. Vitaterna MH, Selby CP, Todo T, Niwa H, Thompson C, Fruechte EM, et al. Differential regulation of mammalian period genes and circadian rhythmicity by cryptochromes 1 and 2. *Proc Natl Acad Sci U S A* 1999;96:12114-9.
 135. Okamura H, Miyake S, Sumi Y, Yamaguchi S, Yasui A, Muijtjens M, et al. Photic induction of *mPer1* and *mPer2* in cry-deficient mice lacking a biological clock. *Science* 1999;286:2531-4.
 136. Kripke DF. Light treatment for nonseasonal depression: speed, efficacy, and combined treatment. *J Affect Disord* 1998;49:109-17.
 137. Lam RW, Carter D, Misri S, Kuan AJ, Yatham LN, Zis AP. A controlled study of light therapy in women with late luteal phase dysphoric disorder. *Psychiatry Res* 1999;86:185-92.
 138. Lam RW, Goldner EM, Solyom L, Remick RA. A controlled study of light therapy for bulimia nervosa. *Am J Psychiatry* 1994;151:744-50.
 139. Blouin AG, Blouin JH, Iversen H, Carter J, Goldstein C, Goldfield G, et al. Light therapy in bulimia nervosa: a double-blind, placebo-controlled study. *Psychiatry Res* 1996;60:1-9.