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Seasonal Affective Disorder: A Clinical Update

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Background. *Seasonal affective disorder (SAD) consists of recurrent major depressive episodes in the fall/winter with remissions in spring/summer.*
Method. *A Medline search was conducted to identify studies relating to clinical management of SAD using the Medical Subject Heading, seasonal affective disorder, and key words, depress* and season*, focusing on studies published in the past 10 years. The Cochrane library of systematic reviews was also searched for relevant studies.*
Results. *A careful history is important to make the diagnosis and differentiate SAD from other similar conditions such as subsyndromal SAD and atypical depression. Seasonal patterns with winter worsening are also recognized in "nonseasonal" depression as well as many other psychiatric conditions, and comorbidity with SAD is common. The pathophysiology of SAD seems to be heterogeneous as research on circadian, neurotransmitter function and genetic hypotheses have shown discrepant results. A dual vulnerability model with differential loading on separate seasonal and depression factors has been proposed to explain these findings. Recent systematic reviews have shown that light therapy is an efficacious and well-tolerated treatment for SAD. There is also evidence for efficacy of pharmacotherapy to treat and prevent SAD. Clinical studies show equal effectiveness with light and antidepressants, so patient preference should be considered in the selection of initial treatment. Dawn stimulation, negative air ions, exercise and cognitve behaviour therapy are under investigation and may also be helpful treatments for SAD.*
Conclusions. *SAD is a common condition with significant psychosocial impairment. Clinicians should be vigilant in recognizing seasonal patterns of depressive episodes because there are effective, evidence-based treatments for SAD.*

Keywords Seasonal affective disorder, Depression, Light, Seasons, Diagnosis

INTRODUCTION

The identification of seasonal patterns for mood disturbances dates back to ancient times, with astute medical observers such as Hippocrates, Pinel, and Kraepelin reporting clear recurrent winter depressive episodes in some of their patients (1). The first systematic description of seasonal affective disorder (SAD) in 1984 (2) led to the development of bright, artificial light, or light therapy, as a treatment. In the past two decades, the concept of SAD has captured media and public interest, while at the same time provoking some skepticism amongst some in the medical community. Recent systematic reviews have demonstrated that light therapy is a safe, well-tolerated and effective treatment for winter depression, but advances in chronobiology and genetics have suggested that the pathophysiology of SAD and the mechanism of light therapy may be more complex than previously thought.

For this review, we identified relevant clinical studies of SAD by conducting an electronic search on Medline using the Medical Subject Heading, seasonal affective disorder, and the key words, depress* and season*. We also searched the Cochrane library of systematic reviews for relevant studies. In this article, we focus on recent findings within the past 10 years and their importance to the clinical management of SAD.

DIAGNOSIS

The first criteria for the diagnosis of winter SAD were described by Rosenthal and colleagues (2). The diagnostic criteria have since been revised and narrowed but they have basically remained the

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Table 1 DSM-IV Criteria for Seasonal Pattern of Major Depressive Disorder (Recurrent Major Depressive Disorder, Bipolar I Disorder or Bipolar II Disorder)

A. There has been a regular temporal relationship between the onset of major depressive episodes and a particular time of the year.
B. Full remissions (or change from depression to mania or hypomania) also occur at a characteristic time of the year.
C. In the last two years, two major depressive episodes have occurred that demonstrate the temporal seasonal relationships defined in criteria A and B, and no nonseasonal major depressive episodes have occurred during the same period.
D. Seasonal major depressive episodes (as described above) substantially outnumber the nonseasonal major depressive episodes that may have occurred over the individual's lifetime.

same: a regular temporal relationship between the onset of major depressive episodes during the fall/winter period, and an occurrence of full remission (or change from depression to mania or hypomania) of symptoms during the spring/summer period.

In DSM-IV, SAD is defined as a specifier of recurrent major depressive episodes (Table 1). This seasonal pattern specifier can be applied to recurrent major depressive disorder (MDD) or to bipolar I or II disorder. Some patients with SAD may experience nonseasonal depressive episodes (e.g., a winter episode that extends into the summer months) during their lifetime, but these must be substantially less common than the seasonal episodes. The DSM-IV criteria also require that the last two seasonal depressive episodes occur in consecutive winters, but this criterion is controversial because it is not evidence-based. Other explanations for seasonal patterns of depressive episodes, such as regularly recurring psychosocial stressors such as winter unemployment and holidays, must be ruled out.

To diagnose SAD, it is important to carefully determine the time of onset and offset of previous depressive episodes, and to ensure that patients have full remission in summer. Many patients with nonseasonal depressions (including dysthymia and chronic MDD) may experience winter worsening of their symptoms, but they can be differentiated from those with SAD because they are still symptomatic in the summer. Up to 20% of patients with SAD will have bipolar I or II disorder (3), so it is also important to identify spring or summer hypomania/mania. A follow-up reassessment in summer can help to identify these bipolar patients, as they may not retrospectively recognize hypomanic symptoms.

SAD versus Seasonality

There is some debate as to whether SAD is a categorical diagnosis or an extreme form of a dimensional seasonality trait. Some people have marked symptoms (especially the vegetative symptoms described below) during the winter, but not to the point where they meet criteria for MDD, or what is termed "subsyndromal" SAD (4). People with subsyndromal SAD may still experience significant distress and impairment of function (5), and they may also respond to the same treatments as SAD (6).

One of the difficulties in making the diagnosis of SAD is that the diagnosis rests on the patient's retrospective history. Despite the presence of physical symptoms, medical examination and laboratory studies are routinely normal in SAD. A helpful clinical characteristic of SAD is a positive mood response to increased (usually outdoor) light exposure and to winter travel to more southerly latitudes. Collateral information from family and/or friends may also help with diagnosis. A prospective spring/summer evaluation for hypomania is very informative in supporting a bipolar diagnosis.

Symptom Profile

Patients with SAD may suffer from general symptoms of depression including diminished pleasure or interest, psychomotor agitation or retardation, loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, indecisiveness, or recurrent thoughts of death. A somatic symptom such as pain is often the presenting complaint at visits to general practice.

The majority of SAD patients report at least one of the "atypical" depressive symptoms associated with SAD such as fatigue, hypersomnia, increased appetite and weight gain, although some patients report reduced appetite, insomnia and weight loss. The increased appetite is typified by carbohydrate craving for sugars and starches that is often described as uncontrollable. Binge type eating can occur, although purging behaviors are uncommon. The increased eating and reduced activity usually leads to significant weight gain. With initial winter episodes patients lose the weight during the summer months when their appetite returns to normal and they are more active. However, with increasing age it becomes more difficult to shed the winter weight gain and there is a gradual year round increase in weight.

The presence of these atypical features has led some investigators to suggest that SAD may be a form of atypical depression, another episode specifier that is characterized by mood reactivity, a marked but temporary improvement in mood in response to favorable external circumstances. However, studies have shown that patients with SAD do not have higher rates of mood reactivity, leaden paralysis or rejection sensitivity than do nonseasonal depressed patients (7). Therefore the overlap between the two subtypes appears to be limited to the atypical vegetative symptoms. Of interest is that these atypical symptoms, particularly the overeating, predict good response to light therapy (8).

Differential Diagnosis

The differential diagnosis of SAD is similar to that of MDD in general. Physical illnesses such as hypothyroidism need to be ruled out, as do other conditions such as phase delayed sleep disorder and anniversary grief reactions. Mixed conditions and

comorbidity should be considered, especially since seasonal patterns are becoming increasingly recognized in other psychiatric conditions including bulimia nervosa, premenstrual depressive disorder, panic disorder, obsessive compulsive disorder, post traumatic stress disorder and attention deficit hyperactivity disorder (9–11). The lifetime prevalence of anxiety disorder (generalized anxiety disorder, simple phobia, social phobia) in patients with SAD is also high, though perhaps not different from that seen in nonseasonal MDD (12). Furthermore, premenstrual depressive disorder has been reported to be much more common in SAD patients than in comparison subjects (13).

EPIDEMIOLOGY

Many epidemiological studies have reported prevalence rates for SAD as high as 10% (14), but most of these studies were not conducted in general population samples and were based on the Seasonal Pattern Assessment Questionnaire (SPAQ), a retrospective self-report questionnaire that assesses seasonality rather than the diagnosis of SAD (15). The more rigorous studies of large community samples using diagnostic interviews and DSM criteria have found prevalence rates for SAD of 0.4% in the United States (16) and 1.7% to 2.9% in Canada (17;18). SAD appears linked to photoperiod (the light/dark cycle) since the prevalence of SAD is correlated with latitude (i.e., more northerly latitudes have shorter winter days) (19) but not to other environmental factors such as temperature, sunshine hours, cloud cover, snowfall, etc., especially in North American studies (for reviews, see (14,20))

ETIOLOGY

The major theories explaining the pathophysiology of SAD have recently been reviewed (21,22) and include circadian, neurotransmitter function, and genetic hypotheses. The most prominent of the circadian rhythm hypotheses is the phase shift hypothesis (23), which suggests that SAD is associated with an abnormal phase delay of the internal circadian rhythms relative to the external clock. In this hypothesis, light therapy timed in the morning would exert a corrective phase-advance of circadian rhythms. Support for the phase-shift hypothesis includes recent studies suggesting an optimal circadian timing for light therapy (24) and beneficial effects of circadian phase-shifting doses of melatonin in patients with SAD (25). However, studies using rigorous methodologies for examining circadian rhythms have not found evidence for circadian dysregulation in patients with SAD (22) and many treatment studies have not found correlation of therapeutic response with circadian phase-shifts following treatment (e.g., (26)).

Research examining the monoamine hypothesis has focused on serotonin as there is clear seasonal variation in brain and peripheral serotonin in healthy people, e.g., serotonin turnover and hypothalamic serotonin transporter sites are lower in winter than in summer (27,28). Several studies show that tryptophan depletion can reverse the antidepressant effect of light therapy, suggesting that the therapeutic effect of light involves a serotonergic mechanism (29,30). However, other reports implicate catecholamines in the pathogeneses of SAD, e.g., retinal light sensitivity (which is dependent on retinal dopamine function) is lower in SAD patients than in healthy controls (31) and catecholamine depletion can also reverse the effects of light therapy (32).

Genetic studies have also focused on monoamine-related genes in SAD and seasonality. Promising candidate genes include 5 HT2A (33–35), 5-HT2C (36) and the dopamine-4 receptor (DRD4) (37). G protein (38,39) and clock-related genes (40) have also been investigated. However, these small-sample association studies are at risk for false-positive results, and as yet there are few replicated findings in the field.

These discrepant results are likely related to heterogeneity in the pathophysiology of SAD and may be explained by a dual vulnerability model that was first proposed by Young et al. (41) and subsequently expanded upon by Lam et al. (6). According to this hypothesis, seasonality and SAD may be phenotypically expressed via differential loading on separate seasonal and depression factors with different mechanisms. For example, the seasonal factor may have a circadian mechanism while the depression factor may be related to monoamine dysregulation. Alternatively, the depression factor may reflect psychological vulnerability (41), such as neuroticism. A recent study (42) suggested that vulnerability to distress symptoms in response to seasonal physiological changes is associated with neuroticism, so that individuals with high levels of seasonality but too high of a loading on the depression factor (neuroticism) may not show a pattern of SAD because their higher level of vulnerability to distress may manifest as non-seasonal depressive episodes.

TREATMENT

Light Therapy

Although light treatment for SAD is closely intertwined with the original description of the syndrome, its efficacy has been questioned. There have been dozens of positive efficacy studies of light therapy, but the results are clouded by methodological weaknesses in study designs. For example, there has been a lack of an accepted standard for adequate dosing of light treatment and for credible placebo conditions.

However, two recent systematic reviews have rigorously addressed the efficacy question. The first used Cochrane Collaboration methodology to review 14 randomized controlled trials (RCTs) of light therapy versus control conditions (43). The second was commissioned by the Council on Research of the American Psychiatric Association (APA) (44). The authors identified 50 RCTs, of which eight studies meeting strict methodological criteria were included in the meta-analysis. Both

meta-analyses found that bright light was superior to credible control conditions, with an odds ratio of 2.83 (indicating almost 3 times better odds of achieving response with light therapy) and an effect size of 0.83 (indicating a medium to large treatment effect), respectively. These results show that the therapeutic effects of light therapy are equal to, or larger than, those found in most antidepressant pharmacotherapy trials.

In clinical practice the preferred device for light therapy is the fluorescent light box that produces light intensities of greater than 2,500 lux. Lux is a unit of illumination intensity that corrects for the phototopic spectral sensitivity of the human eye. For comparison, indoor evening room light is usually less than 100 lux while a brightly lit office is less than 500 lux. In contrast, outdoor light is much brighter: a cloudy grey winter day is around 4,000 lux and a sunny day can be 50,000 to 100,000 lux or more. Newer light devices under investigation use light-emitting diodes (LEDs) that allow much smaller and more portable fixtures.

Table 2 summarizes a standard protocol for light therapy that is recommended in clinical practice guidelines (45) and that in naturalistic clinical use has resulted in response rates of 65% or higher (6). Patients should be instructed to properly position themselves and maintain a correct distance to the light source. They have to be awake with their eyes open during light exposure, but they are not required to look directly at the light source, i.e., they can read or eat during the light treatment. The standard "dose" of light is 10,000 lux for 30 minutes per day. There appears to be a relationship between intensity and duration of exposure, so that light boxes rated at 2,500 lux require 2 hours of daily exposure for the same response. Light therapy is usually administered in the early morning as soon as possible upon arising, e.g., at 7:00 am or earlier, because most studies and meta-analyses have found that early morning exposure is superior to other times of the day (46).

The onset of action of light therapy is usually rapid with significant clinical improvement found in studies of 1 or 2 weeks' duration. However, individual patients may require 2–3 weeks to show clear responses to light therapy. When light therapy is discontinued, most patients will relapse after a similar period of a couple of weeks. Patients are therefore advised to use light therapy regularly during their symptomatic winter season until the time of their usual spring summer remission. Once patients have remitted they can often experiment with individual dosing required to stay well. Thus, they may be able to maintain their response while reducing the daily time of exposure to 15 or 20 minutes, or by using the light box on weekdays only. In subsequent years, patients may need to begin light treatments in the early autumn before the onset of symptoms to avoid any gradual impairment of function (47).

Side effects to light therapy are generally mild and transient and include headache, nausea, eyestrain, blurred vision and agitation (Table 3) (46). Bright light exposure in the later evening may also interrupt onset and maintenance of sleep. As

Table 2 Bright Light Therapy: Summary of Method

- 10,000 lux white, fluorescent light; no ultraviolet wavelengths
- 30 minutes/day in the early morning, upon arising
- Stay awake, with eyes open; not necessary to stare at the light, so may eat and/or read
- Determine response after 2–3 weeks
- After remission, individualize dosing during the rest of the winter season
- Initiate treatment in early autumn in following years to avoid relapses
- In patients with retinal risk factors, obtain baseline eye examinations and monitor during treatment
- In patients with bipolar I disorder, maintain on a mood stabilizer

Table 3 Reported Adverse Effects of Light Therapy (10,000 Lux Fluorescent Light Box, 30 Minutes/Day) for SAD. Only Side Effects Reported in More Than 5% of Treated Patients Are Shown

Study:	Kogan & Guilford, 1998 (62)	Terman & Terman, 1999*(63)	Lam et al. 2006*(57)
Length of treatment	4 to 10 days, N = 70	10 to 14 days, N = 83	8 weeks, N = 48
Emergent Side Effect	%	%	%
Gastrointestinal			
Abdominal discomfort/pain		10	6
Nausea/vomiting	7	16	4
Diarrhea		13	4
Constipation		2	8
Appetite/weight			
Decreased appetite		19	15
Increased appetite		15	8
Weight loss		19	2
Weight gain		10	
Central nervous system			
Headache	21	8	17
Fatigue/weakness	6	3	8–17
Increased sleep		9	13
Decreased sleep		7–14	23
Overactive/excited/agitated	6	9–10	
Anxiety	3	5	13
Sexual dysfunction			
Decreased sexual interest		7	15
Increased sexual interest		18	
Difficulties with orgasm		6	
Difficulties with erection		5	5
Eyes/Ear/Nose/Throat			
Eye or vision problem	19	4–6	
Mouth sores		8	
Nasal congestion		12	
Dry mouth/throat		4–8	19
Chest			
Shortness of breath		6	
Coughing		15	
Breast tenderness		6	
Other			
Muscle/bone/joint pain		8	13
Fever/chills		7	
Sweating/Flushing			6
Feeling faint			6

*Unlike most clinical trials that depend on spontaneous patient reports, these studies used systematic questionnaires to detect treatment-emergent adverse events.

with any effective antidepressant, light therapy carries a risk for precipitating hypomanic or manic episodes in susceptible individuals. Therefore, patients with bipolar I disorder (with manic episodes) should be on mood-stabilizing medications if light therapy is used.

There are no absolute contraindications to light therapy (although retinopathies are a relative contraindication) and no evidence that light therapy is associated with ocular or retinal damage with current dosing guidelines (48). However, caution should be applied when treating patients at higher theoretical risk for bright light-induced eye toxicity (49). This includes patients with pre existing retinal disease (such as retinitis pigmentosa) or systemic illnesses that involve the retinal (such as diabetes), and those taking photosensitizing medications (such as lithium, phenothiazine antipsychotics, melatonin, and St. John's wort). For these higher-risk patients, an ophthalmologic examination is recommended before starting light therapy as well as regular follow-up exams.

Some hospitals and outpatient clinics in Europe have designed light therapy rooms for patient use, but as most clinical studies use home treatment, which is much more convenient for patients, the necessity of light therapy rooms is not clear. Many web sites now offer helpful advice and resource materials for the clinical use of light (e.g., UBCsad.ca, SLTBR.org, CET.org).

Pharmacotherapy

There have been fewer RCTs on pharmacotherapy for SAD (Table 4). Selective serotonin reuptake inhibitors (SSRIs), especially fluoxetine (20 mg/day, (50) and sertraline (50–200 mg/day, (51)), have the best evidence for efficacy, but likely other antidepressants are also efficacious for acute treatment. A large clinical trial also found that citalopram (20–40 mg/day) was superior to placebo in preventing relapse after one week of treatment with light therapy (52).

In the only antidepressant prevention trial to date, patients with a history of SAD (N = 1042) were randomized to bupropion-XL (300 mg/day) or placebo starting early in autumn and followed throughout the winter (53). Recurrence of winter depressive episodes was significantly lower in the bupropion group (15.7% vs. 28%, respectively). However, it should be noted that the recurrence rate of SAD in this study was low overall, even in the placebo-treated group.

Open-label studies suggest that other medications may also be beneficial in SAD. These include antidepressants such as reboxetine, a selective inhibitor of noradrenaline reuptake (54), and moclobemide, a reversible inhibitor of monoamine oxidase A (55). The wake-promoting agent, modafinil, was also reported to significantly reduce fatigue in patients with SAD (56).

Light versus Antidepressants

One criticism of light therapy research has been the lack of comparisons with antidepressant medications. A recent study directly compared the two treatments in a "double-dummy" design, in which patients with SAD (N = 96) were randomly assigned to 8 weeks of double-blind treatment with either 10,000 lux (active) light treatment plus a placebo capsule, or 100-lux (placebo) light treatment and fluoxetine, 20 mg/day (57). Both groups improved during the 8 weeks with no significant differences between the two in reduction of depression

Table 4 Studies on Pharmacotherapy of SAD. Statistically Significant Differences in Efficacy are Indicated by " > "

Antidepressant(s)	Study design (N = number of patients)	Outcome	Authors
Fluoxetine	vs. placebo, RCT, 5 weeks, N = 68	• Fluoxetine = placebo in reducing depression scores • Fluoxetine > placebo in response rates	Lam et al. (50)
	vs. moclobemide, RCT, 6 weeks, N = 32	• Fluoxetine = moclobemide in reducing depression scores and in remission rates	Partonen and Lönnquist (64)
	vs. bright light, RCT, 8 weeks, N = 96	• Fluoxetine = light therapy in reducing depression scores and in response rates	Lam et al. (57)
	vs. bright light, RCT, 5 weeks, N = 40	• Fluoxetine = light therapy in reducing depression scores • Trend to superiority of fluoxetine in response rates	Ruhrmann et al. (65)
Sertraline	vs. placebo, RCT, 8 weeks, N = 187	• Sertraline > placebo in reducing depression scores and in response rates	Moscovitch et al. (51)
Citalopram	vs. placebo, RCT, 15 weeks, N = 282	• Following 1 week of successful light therapy, citalopram > placebo in preventing relapse	Martiny et al. (52)
Bupropion	vs. placebo, prevention RCT, N = 1042	• Bupropion > placebo in preventing seasonal depressive episode	Modell et al (66)
Bupropion, desipramine, tranylcypromine	Case series, open-label treatment, N = 47	• Improvement with all antidepressants	Dilsaver et al. (67)
Reboxetine	Case series, open-label treatment, N = 16	• Improvement with reboxetine	Hilger et al. (54)
Moclobemide	vs. placebo, RCT, 3 weeks, N = 34	• Moclobemide = placebo in reducing depression scores, but > placebo in reducing atypical symptoms	Lingjaerde et al. (55)
Hypericum (St. John's wort)	vs. light therapy, RCT, 4 weeks, N = 20	• Hypericum = hypericum+bright light in reducing depression scores	Martinez et al. (68)
Modafinil	Case series, open-label treatment, N =13	• Improvement with modafanil	Lundt (56)

scores, clinical response rates (67% for both groups) or remission rates (50% for light treatment and 54% for fluoxetine). Light therapy showed earlier onset of response (at 1 week) and lower rates of some adverse events (agitation, sleep disturbance and palpitations) relative to fluoxetine, but both treatments were well-tolerated overall. In the subgroup of patients with greater severity of depression at baseline, there were again no differences in the efficacy or response/remission rates between light and fluoxetine.

These findings suggest that other factors, including patient preference, should be used to guide decisions about light or drugs as first-choice treatment. And, although there are as yet limited data on the combination, many patients with SAD use both light and antidepressant medication for optimal benefit.

Other Treatments

In addition to bright light and pharmacotherapy, other treatments under investigation may be beneficial for SAD. These include dawn simulation, negative air ionization, exercise and cognitive behaviour therapy (CBT).

Dawn simulation imitates the natural summer dawn signal by gradually increasing ambient bedroom illumination while the patient is sleeping. An electronic dawn simulation device controls a bedside lamp that turns on about 90 minutes before the desired wake time and reaches a final illumination of 250 lux, which continues until the patient arises. In the systematic review by the APA, five dawn simulation studies included in a meta-analysis showed a medium-to-large effect size of 0.73 favoring dawn simulation over placebo conditions (44). However, the total number of patients in the meta-analysis was small and the positive results came from one centre, so these results need further replication.

Negative air ionization is a new treatment and the mechanism of action is still poorly understood. In patients with SAD (N = 158), the antidepressant effects of high-density negative ions were not significantly different from those of bright light (58); therapeutic effects have also been observed in patients with chronic (nonseasonal) depression (59). Another study compared the effects of physical exercise and bright light in age-matched groups of female patients (60). The women with winter depression (N = 27) responded equally well to both exercising and light, while exercising was superior to light in patients with nonseasonal depression (N = 18).

A 6-week pilot study of 23 patients with SAD compared a standard light therapy protocol, a novel, SAD-tailored, group CBT intervention, and the combination (61). All conditions demonstrated significant but similar reductions in depressive symptoms and good remission rates. However, during the subsequent winter naturalistic follow-up, patients who had CBT, particularly in combination with light therapy, had better outcomes as measured by symptom severity, remission rates, and relapse rates.

CONCLUSIONS

The diagnosis of SAD can be made by taking a careful history of recurrent winter depressive episodes and ruling out other diagnoses. Although the etiology and pathogenesis of SAD remain unclear, the high prevalence of SAD (0.4% to 2.9%) makes it a significant health problem, particularly in northern countries. Light therapy is an evidence-based, effective, well-tolerated treatment for SAD, while antidepressant medications also have demonstrated efficacy. For many patients, the choice of light or drug (or the combination) will depend on personal preference. Research in progress on newer treatments, including smaller and more efficient light devices, dawn simulation, negative ions, exercise, and CBT, may expand the options for people with winter depression.

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