

*Pharmacists can suggest new therapies
for seasonal affective disorder*

When patients are **SAD**

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**Dark and Cold and Sad
Bleak till the promise of Spring
Winter depression.**

*—Haiku by Dr. Raymond Lam, Professor and Head,
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Canadians are acutely aware of the change of seasons, as we experience extreme conditions at both ends of the weather spectrum every year. A show of strong mental resolve in the face of adverse environmental conditions is often considered an important virtue in our culture, or at the very least affords us certain bragging rights. This was certainly the case when I attended a reunion of about 15 of my University of Saskatchewan pharmacy classmates who had moved to southwestern Ontario after graduation. Conversation invariably turned to that old standby—the weather. We took great pleasure in mocking our new Ontario neighbours as they bundled up in their winter parkas as the mercury dipped slightly below freezing. But something about our new environment did unnerve us—where the heck was the sun? We longed for the multi-coloured beauty of the prairie sunsets. We pined for the nearly blinding brightness of the -45°C days. And we had all made that new essential purchase—an umbrella.

While we dramatically moaned and groaned about our newfound “winter blahs,” fortunately none of us appeared to have suffered any real hardship from acclimatizing to our new surroundings. Admittedly, however, the term “seasonal affective disorder” was tossed around more than once. We did gain some appreciation for the effect of light on mood, and recognized that the change of

TABLE 1 DSM-IV-TR CRITERIA FOR SEASONAL PATTERN SPECIFIER²

“With seasonal pattern” can be applied to the pattern of major depressive episodes in bipolar I disorder, bipolar II disorder, or major depressive disorder, recurrent in the following situations:

- A. There has been a regular temporal relationship between the onset of major depressive episodes in bipolar I or bipolar II disorder or major depressive disorder, recurrent, and a particular time of the year (e.g., regular appearance of the major depressive episode in the fall or winter). Cases should be excluded when there is an obvious effect of seasonal-related psychosocial stressors (e.g., regularly being unemployed every winter).
- B. Full remissions (or a change from depression to mania or hypomania) also occur at a characteristic time of the year (e.g., depression disappears in the spring).
- 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 non-seasonal major depressive episodes have occurred during the same period.
- D. Seasonal major depressive episodes (as described above) substantially outnumber the non-seasonal major depressive episodes that may have occurred over the individual’s lifetime.

seasons can affect people. But what does it really mean to have seasonal affective disorder (SAD)?

What is SAD?

THE EFFECT OF CHANGES IN THE SEASONS and weather on health and mood have been recognized since the time of Hippocrates, but the term “seasonal affective disorder” did not fully enter the lexicon until 1984, when Rosenthal first described the condition and the positive effects of light therapy.³

When most people think of SAD, they tend to imagine a depression that occurs during the dark cold months of

winter. Although “winter depression” is its most common form, SAD is in fact defined as any affective disorder, including unipolar and bipolar depression, which occurs in a specific season, including summer.¹

A survey of 454 patients with SAD in a Vancouver clinic found that 89 per cent had unipolar depression, 8.5 per cent had bipolar type II (spring/summer hypomanic episodes), and 2.5 per cent had bipolar type I (spring/summer manic episodes).¹ Thus, rather than being considered a disorder on its own, “with seasonal pattern” is in fact a course specifier that describes the pattern with which episodes occur in an individual (Table 1).²

Diagnosis/symptoms

SYMPTOMS OF SAD ARE GENERALLY similar to those associated with atypical depression, i.e., hypersomnia, increased appetite, weight gain, decreased activity, fatigue, irritability, loss of interest in sex, poor concentration and social withdrawal.¹ Increased appetite is often a key symptom, with an increase in carbohydrate cravings, overeating and even binge eating. In fact, there is some evidence of overlapping features and even co-morbidity with SAD and bulimia nervosa. In one survey, 17 to 26 per cent of patients with SAD were described as having an eating disorder, and a trend of worsening of mood and binge/purging with bulimic patients was noted in the winter.⁴

A diagnosis of SAD can be difficult,

A variety of light therapies are available, including this one using fluorescent light.



as a pattern must emerge over a period of at least two years. The depressive episodes typically start in the fall, with a full remission for at least two months in the summer, starting as early as May.⁵ Besides the seasonal pattern, patients with SAD differ from those with atypical depression in some of the “non-vegetative” symptoms, with less chance of mood reactivity, leaden paralysis and rejection sensitivity.¹

Tools such as the Seasonal Pattern Assessment Questionnaire (SPAQ), a retrospective self-report instrument, can assist with diagnosis, while the clinician-administered Structured Clinical Interview Guide for the Hamilton Depression Rating Scale, SAD version (SIGH-SAD) can measure the severity of an episode.^{5,6}

Epidemiology

THE PREVALENCE OF SAD IN CANADA is estimated to be about three to five per cent.⁷ Another 10 to 15 per cent of Canadians experience the “winter blues,” a milder, subsyndromal form of the disorder; symptoms can be similar to those of SAD patients, but with less impact on daily functioning.⁷ Women are about twice as likely as men to suffer from SAD.⁵ The influence of latitude on SAD is controversial: some studies found an elevated incidence with increased latitude,¹ while others detected no difference.⁸ Latitude is likely one factor, but other factors (e.g., environment, genetics, sociocultural context) and psychosocial variables may also play a role.⁹

Etiology/pathophysiology

DESPITE RESEARCH ON SEVERAL hypotheses, the exact causes of SAD are not fully known. As with many psychiatric disorders, most of the research has focused on why a certain treatment has been found to work—in this case, looking mainly at the mechanism of action of light therapy. Some results have been conflicting, leading some researchers to postulate the “dual-vulnerability” hypothesis, which suggests that SAD results from separate seasonality and depression factors, each of which may have different causes.¹⁰

Most research is now focusing on the interplay of circadian rhythms, melatonin secretion, serotonin dysregulation and

TABLE 2 CANADIAN RECOMMENDATIONS FOR TREATING MAJOR DEPRESSIVE DISORDER WITH SEASONAL PATTERN¹³

First-line treatments	Level 1 evidence (meta-analysis or replicated randomized controlled trial [RCT] that includes a placebo condition)	Bright-light therapy
Second-line treatments	Level 2 evidence (at least one RCT with placebo or active comparison condition)	fluoxetine, moclobemide
Third-line treatments	Level 3 evidence (uncontrolled trial with 10 or more subjects)	bupropion, citalopram, tranylcypromine

TABLE 3 SUMMARY OF CANADIAN RECOMMENDATIONS FOR LIGHT THERAPY⁵

- Preferred device is the fluorescent light box with light intensities of >2,500 lux (usual indoor light is 100 lux)
- Starting “dose” is 10,000 lux for 30 minutes per day
- Alternatively, light boxes emitting 2,500 lux require two hours of exposure per day
- Light boxes should use white fluorescent light with the ultraviolet wavelengths filtered out
- Light therapy should be started in the early morning, upon awakening, to maximize treatment response. Exposure at other times of the day may be helpful for some patients
- Response to light often occurs within one week, but some patients require two to four weeks to show a response

genetic variables.¹⁰ It is thought that shorter days may disturb normal circadian rhythm, which can result in a longer duration of melatonin secretion each night, and decreased levels of serotonin compared to the summer months. The phase-delay hypothesis suggests that patients’ circadian rhythms are delayed relative to the sleep/wake or rest/activity cycle, such that their internal body clock lags behind the actual time on external clocks; symptoms may improve if circadian rhythms can be shifted back to normal or “phase-advanced” with light therapy administered in the morning.¹⁰

Prognosis

THE PROGNOSIS FOR PATIENTS DIAGNOSED with SAD is varied. About one-third of patients continue to have definable seasonal recurrences, requiring treatment to be restarted each fall. Another third develops a more non-seasonal course to their mood disorder, while the final third has either subsyndromal episodes or goes into remission.¹

Management BRIGHT LIGHT THERAPY

The benefits of light therapy have been documented since the second century

A.D., when the Greek physician Aretaeus said that “lethargics are to be laid in the light, and exposed to the rays of the sun (for the disease is gloom).”¹¹ The Canadian guidelines for the treatment of SAD (Table 2), which are based on meta-analyses¹² and more than 60 controlled trials, recommend bright-light therapy as the first-line treatment for SAD.¹³ Research has been conducted on several aspects of light therapy: which type of light to use, the intensity of the light, what time of day light should be administered, and the duration of daily treatment. Summary guidelines for appropriate light therapy are outlined in Table 3. In controlled trials in patients with SAD, response rates with light therapy range from 60 to 90 per cent. While there is no clear definition of what constitutes a “placebo” in a light therapy trial, a light device with a substantially dimmer light is generally considered a plausible placebo.⁵

The side effects of light therapy are generally mild and resolve over time, with decreased daily duration of light use or discontinuation of therapy.¹⁴ Side effects include eyestrain, jumpiness/jitteriness, headache and nausea.¹⁵ Light therapy may induce hypomania or mania in patients with underlying bipolar disorder.¹⁶

Suicidality is generally less common in SAD than in affective disorders; however, there has been some discussion in regards to the effect of light therapy in this area. Case studies of light therapy increasing suicidality¹⁷ and even suicide have been reported.¹⁸ While a retrospective study found that light therapy generally improved suicidal ideation, three patients had a slight increase in suicidality.¹⁹ This serves as a reminder that suicidal ideation needs to be monitored even in a population in which it is somewhat less likely.²⁰

As with any treatment modality, non-compliance with light therapy can be caused by side effects or the patient's feeling that treatment can be discontinued once a response is achieved. In addition, lack of convenience and time constraints can affect compliance with light therapy. While patients can engage in some activity (e.g., reading, eating) while undergoing light therapy, they must be 12 to 18 inches from the light source with their eyes open for 30 minutes.⁶

A pilot study investigating patient compliance with light therapy used hidden elapsed time meters to record the total time in minutes that each lightbox had been used. The expected total time was 1,365 minutes, but actual readings ranged from seven to 2,104 minutes. Patients with the treatment lightboxes (10,000 lux) used the devices for a median of 1,073 minutes, while patients using the dim red control lights averaged 571 minutes.²¹

DRUG THERAPY

Despite the vast body of literature on the use of medications in the treatment of depression, very few studies have examined the use of antidepressants and other medications specifically for the treatment of SAD. The few studies that are available have limitations, such as small sample size, short duration of treatment, and a lack of statistical significance in some outcome measures.

Of the various drugs studied, selective serotonin reuptake inhibitors have the most evidence of efficacy. In a five-week study of 68 patients, a positive response was noted in 59 per cent of patients receiving fluoxetine, compared to 34 per cent of placebo recipients.²² An eight-week study in 187 patients revealed a 62

TABLE 4 SAD: USEFUL WEBSITES

The UBC Mood Disorders Centre SAD Information Page

www.ubcsad.ca

This excellent site has information and links for both the public and healthcare providers. The Clinician's Resource Package is an invaluable downloadable resource that includes a copy of the screening questionnaire for SAD, patient brochures on SAD and light therapy, journal articles and a sample insurance reimbursement request letter for light sources.

Canadian Mental Health Association (CMHA)

www.cmha.ca/english/sad

This mini-site from CMHA includes a downloadable SAD pamphlet in a pdf format, as well as sections that include a definition of SAD, frequently asked questions and useful links.

Fact Sheets on Mental Health and Addictions Issues

www.cmha-bc.org/content/resources/primer/primer.htm

Contains 42 fact sheets on various topics, including an excellent two-page sheet on SAD that can be downloaded, photocopied and distributed.

The Society for Light Treatment and Biological Rhythms

www.sltbr.org

This international, nonprofit society is dedicated to fostering research, professional development and clinical applications in the fields of light therapy and biological rhythms.

Canadian guidelines for the treatment of SAD (summary)

www.psychdirect.com/depression/d-treatmentguidelinesSAD.htm

A summary of these guidelines is on the PsychDirect website, a public education site of the Department of Psychiatry & Behavioural Neuroscience at McMaster University, Hamilton, Ont.

Canadian Network for Mood and Anxiety Treatments

www.canmat.org

The CANMAT website includes some patient information on SAD in the "Depressed? Anxious?" section, as well as summary tables of CANMAT treatment guidelines and a link to the full Canadian Psychiatric Association (CPA)/CANMAT Clinical Guidelines for the Treatment of Depressive Disorders (2001).

per cent response rate with sertraline compared to 46 per cent for placebo.²³ In a six-week study of 29 patients, response rates were 66 per cent for fluoxetine compared to 44 per cent with moclobemide.²⁴ A three-week study with moclobemide showed no difference from placebo; however, the treatment period was likely too short.²⁵ Open trials and case studies have shown promise for bupropion²⁶ as well as tranylcypromine;²⁷ however, these results need to be confirmed by further larger studies. To date, no trials comparing antidepressants and light therapy have been published (see the section "Future directions").

The dosage ranges, side effect profiles and onset of effect (six to eight weeks) with these agents is similar to what would be expected for antidepressants used for the treatment of nonseasonal depression.⁵ The only difference is the duration of treatment. Patients with SAD should be instructed to taper and discontinue their

medication at the time they would normally experience symptom remission (i.e., spring or early summer). Tapering is required to minimize possible discontinuation reactions, and must be individualized. Patients can restart treatment in the fall with the onset of mild symptoms, or before any symptoms recur, according to the advice of their physician.⁵

A small trial (N=13) of tryptophan (1.5 mg tid) found that it was equivalent in efficacy to evening light treatment and superior to placebo.²⁸ Propranolol, which suppresses melatonin secretion in the morning, was found to be superior to placebo when given in doses of up to 60 mg every morning (N=33).²⁹ Both of these treatments need to be studied more extensively before they can be recommended.

OTHER TREATMENTS

St. John's wort was found to be more effective than placebo in one small trial.³⁰

Other treatments that have shown some efficacy in nonseasonal depression (e.g., cognitive behavioural therapy, interpersonal therapy) may also have benefits in SAD, but they have not been studied. Finally, research is also examining negative ion treatments, dawn simulators (which slowly increase room light while the patient is still sleeping), aerobic exercise and sleep deprivation.^{1,12}

COMBINATION THERAPIES

Combination therapy with light and medications has been mentioned in the literature. One study found that the addition of light therapy hastened the antidepressant effect of citalopram.³¹ A recent report, however, cautions about additive side effects. In two cases where light therapy was added to fluoxetine or sertraline plus lithium treatment, the patients experienced increased side effects, including diarrhea, anxiety, tremor, disorientation, increased sweating and sleeplessness.³² These serotonergic-type side effects resolved when the light therapy was discontinued. It is possible that further investigation of these combinations may lead to using lower dosages of each treatment to reduce time to response and minimize side effects.

CHOICE OF TREATMENT

Light therapy is generally considered the first-line treatment for SAD. Antidepressants can also be used first-line if the depression is more severe, the light therapy is too inconvenient or time-consuming, the patient has retinal disease, or the patient cannot afford the light box (\$300 to \$500) but has a drug plan.⁴

The pharmacist's role

PHARMACISTS CAN ASSIST WITH A NUMBER of aspects of SAD treatment. Patients who frequently complain of hypersomnia, fatigue and flu-like symptoms in the winter can be referred for proper assessment. With medications, pharmacists can counsel on proper initial titration and appropriate duration of therapy, as well as timing (e.g., gradually tapering in the spring and restarting the antidepressant at the appropriate time). Pharmacists can also become involved with light therapy. Dr. Raymond Lam, one of the leading clinical researchers of

SAD, encourages pharmacists to carry light sources in their pharmacies—the “more accessibility the better,” he says.

As with blood glucose monitors, some expertise is required to counsel patients on the proper use of light sources. In addition, since light sources are not well regulated in Canada, some research is required to locate appropriate light sources to stock. Further guidance on minimum requirements for light sources and instructions for use can be found in the Clinician's Resource package on Dr. Lam's SAD website (www.ubcsad.ca).

Pharmacists can also monitor for concurrent medications that may cause photosensitivity reactions, and provide information and support throughout treatment (see the list of useful websites in Table 4).

Future directions

RESEARCH IS CURRENTLY UNDERWAY on several aspects of seasonal affective disorder. Genetics, causes and pathophysiology are being further examined. A large trial comparing light therapy and fluoxetine has been submitted for publication, and other large trials of medications are underway. New technologies are being studied, including more portable and convenient sources of LED (light bright-white light-emitting diodes), such as the Litebook (www.litebook.com).

Summary

SAD IS A MOOD DISORDER THAT IS often mentioned with the approach of long winter nights in Canada, yet it is often misunderstood. Treatment approaches include light therapy and antidepressants, although there is a relative lack of supporting evidence compared to treatments used for non-seasonal depression. Current research, much of which is occurring in Canada, is examining the possibility of multiple causes of seasonality, methods of optimizing and refining present treatment modalities, and finding new approaches to caring for patients.

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Practice Issues

Continued from page 27

The analysis included all patients from the post-marketing study who had received parenteral meperidine, morphine or fentanyl. A computer-assisted chart-abstracting system and trained research nurses were used to obtain data on these patients. Equipotent conversion doses were used: 1 mg of parenteral morphine was considered to be equivalent to 10 mg of parenteral meperidine and to 0.01 mg of parenteral fentanyl.

A total of 8,855 patients were evaluated: 69 per cent received meperidine, 27 per cent received morphine and six per cent received fentanyl. The average four-hour dose in 84 per cent of patients was 4 mg or less of equivalent morphine. Respiratory depression developed in 128 (1.5%) patients. Of these episodes, 53 per cent were considered life-threatening and two deaths were attributable to this side effect. The risk of developing respiratory depression was lower with meperidine and fentanyl than with morphine. The risk of respiratory depression increased

substantially with increasing age.

Nausea and vomiting developed in 2,238 (26%) patients. Meperidine produced less nausea and vomiting than morphine. Patients receiving meperidine had similar odds of nausea and vomiting as those receiving fentanyl. The development of nausea and vomiting increased as the dose increased. Men had less nausea and vomiting than women, while white subjects had more nausea and vomiting than black subjects.

For short-term use, meperidine produced less nausea, vomiting and respiratory depression than morphine. Despite these favourable results, meperidine is not recommended for chronic pain, nor should it be used in patients with renal failure, due to its increased central nervous system side effects.

Cepeda MS, Farrar JT, Baumgarten M, et al. Side effects of opioids during short-term administration: effect of age, gender and race. *Clin Pharmacol Ther* 2003;74:102-12.

If you have a comment about Drug Trials, please email Sandra Knowles at sandra.knowles@sw.ca.