

# **Evidence-Based Management of Seasonal Affective Disorder (SAD)**

## **Clinician Resource Package**

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## **INTRODUCTION**

Dr. Anthony Levitt and I have given a very successful continuing education course on the management of seasonal affective disorder (SAD) at recent annual meetings of the American Psychiatric Association and the Canadian Psychiatric Association. This practical, half-day course is designed so that participating clinicians can be comfortable with the diagnosis of SAD and clinical uses of light treatment. The course is based on the Clinical Guidelines for the Treatment of Seasonal Affective Disorder (1). Published in 1999, these guidelines were developed by a group of Canadian clinician-researchers using a rigorous, standardized, evidence-based clinical guidelines process and peer-reviewed by international experts. They are now recognized internationally as the definitive guidelines for the diagnosis and management of SAD, and were used in other, more general clinical guidelines for the treatment of depressive disorders.

As part of this course, we developed a resource package for the clinician with useful tools to use in their clinical practices. We have decided to make this resource package available for wider distribution. Please feel free to use any of these tools in your clinical practice as needed. However, we would appreciate an acknowledgment or citation to us if they are used in presentations or copied for educational events or other clinical settings. And, please let us know if you have ideas about other resources that we can include in the package.

Regards,

**Raymond W. Lam, MD, FRCPC, FAPA**

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### **References**

1. Lam RW, Levitt AJ (eds). Clinical Guidelines for the Treatment of Seasonal Affective Disorder. Vancouver, Clinical & Academic Publishing, 1999.

## **COURSE OBJECTIVES**

At the conclusion of this course, the participant should be able to:

1. Diagnose seasonal affective disorder (SAD)
2. Use light therapy in clinical practice to treat SAD and other conditions
3. Identify and deal with management issues in the use of light therapy and medications for SAD.

## **RESOURCES**

1. Information about how to obtain the full Guidelines, edited by Drs. Lam and Levitt, and the book Seasonal Affective Disorders and Beyond, edited by Dr. Lam, APA Press, 1998.
2. Frequently Asked Questions about SAD (patient brochure).
3. Suggestions for Coping with Seasonal Depression (patient handout)
4. Seasonal Pattern Assessment Questionnaire (screening questionnaire for SAD).
5. Hamilton Depression Rating Scale, SAD version (outcome scale)
6. Patient Instructions: How to Use the 10,000 Lux Light Box.
7. Patient Information: Where to Get a Light Device  
– For more companies, check on the internet, [www.sltbr.org/corporate.htm](http://www.sltbr.org/corporate.htm)
8. Sample Insurance Reimbursement Letter
9. Audit Form for practice management.
10. Journal Article: Diagnosis and Management of SAD, by Raymond W. Lam
11. Journal Article: Pathophysiology of SAD, by Raymond W. Lam and Robert D. Levitan

## **HELPFUL WEB SITES**

University of BC SAD Information Page

[www.psychiatry.ubc.ca/mood/sad](http://www.psychiatry.ubc.ca/mood/sad)

Society for Light Treatment and Biological Rhythms

[www.sltbr.org](http://www.sltbr.org)

Circadian Lighting Association (light device suppliers)

[www.cla.org](http://www.cla.org)

Center for Environmental Therapeutics

[www.cet.org](http://www.cet.org)

Canadian Network for Mood and Anxiety Treatments

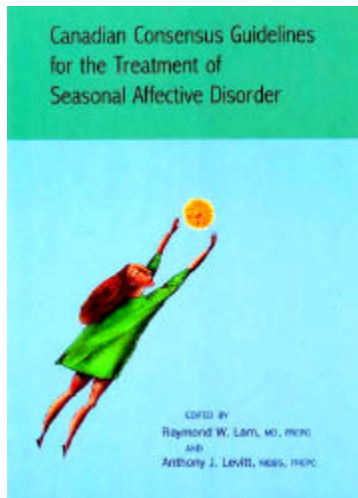
[www.canmat.org](http://www.canmat.org)

Depression Information and Resource Centre, Toll-free

[www.psychdirect.com](http://www.psychdirect.com)

## LITERATURE REFERENCES

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- Lam RW: Seasonal affective disorder: Diagnosis and management. *Primary Care Psychiatry* 1998; 4:63-74. (Attached to this package)
- Lam RW (ed). *Seasonal Affective Disorder and Beyond. Light Treatment for SAD and Non-SAD Conditions*. Washington, American Psychiatric Press, 1998.
- Lam RW, Goldner EM, Solyom L, Remick RA. A controlled study of light therapy for bulimia nervosa. *Am J Psychiatry* 1994; 151:744-50.
- Lam RW, Gorman CP, Michalon M, Steiner M, Levitt AJ, Corral MR, Watson GD, Morehouse RL, Tam W, Joffe RT. Multicenter, placebo-controlled study of fluoxetine in seasonal affective disorder. *Am J Psychiatry* 1995; 152:1765-70.
- Lam RW, Levitan RD. Pathophysiology of seasonal affective disorder. A review. *J Psychiatr Neuroscience* 2000; 25:469-480. (attached to this package, but also available for free download at [www.psychiatry.ubc.ca/mood/sad](http://www.psychiatry.ubc.ca/mood/sad))
- Lam RW, Levitt AJ (eds). *Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder*. Vancouver, Clinical & Academic Publishing, 1999.
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- Tam EM, Lam RW, Levitt AJ. Treatment of seasonal affective disorder: a review. *Can J Psychiatry* 1995; 40:457-66.
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## Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder

*Edited by Raymond W. Lam and Anthony J. Levitt  
Clinical & Academic Publishing, Vancouver, 1999  
160 pages, CAN\$19.95, ISBN 0-9685874-0-2*

Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder is the first comprehensive clinical guide for the diagnosis and treatment of seasonal affective disorder (SAD), a type of clinical depression that affects between 2% and 3% of the Canadian population. Drs. Raymond W. Lam and Anthony J. Levitt, leading clinician-researchers in SAD, organized a Canadian Consensus Group to develop clinical guidelines for the treatment of SAD. Using a rigorous consensus process, this group reviewed the world scientific literature and formulated evidence-based recommendations for the diagnosis and treatment of SAD. Draft guidelines were extensively discussed, reviewed by international experts in the field, and then ratified by the Canadian Consensus Group. This book is the final result.

The consensus guidelines are organized into four major sections:

- Diagnosis, Epidemiology, and Pathophysiology
- Light Treatment
- Medication Treatment
- Management Issues

The question-and-answer format of the guidelines makes them readily accessible to busy clinicians. Summary tables of recommendations and conclusions allow rapid access to the most important information. A rating of level of scientific evidence is included after every recommendation so that areas of controversy or limited data are highlighted. A full bibliography of over 650 references, updated to June 1, 1999, is also included as a resource for researchers.

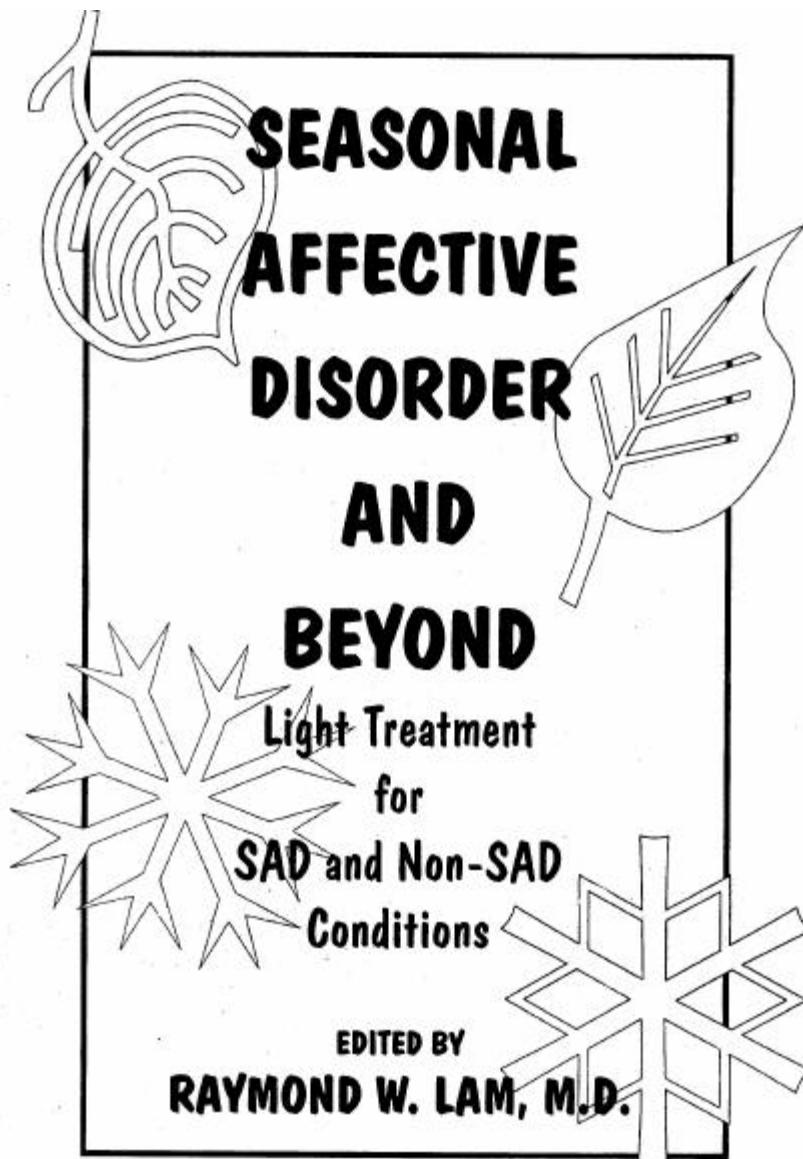
These guidelines will be clinically useful to family doctors, psychiatrists, psychologists, nurses, and other health professionals who treat depression and SAD. Researchers and students will find the concise reviews of the literature highly informative. Knowledgeable consumers and family members will also discover practical information and answers to many of their questions about SAD.

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For information and orders: [www.psychiatry.ubc.ca/mood/sad](http://www.psychiatry.ubc.ca/mood/sad) or [www.amazon.com](http://www.amazon.com)



In 1984, Dr. Norman Rosenthal and his colleagues published a seminal research paper on seasonal affective disorder (SAD), unveiling what they were convinced was the healing power of light therapy for people suffering from the illness. Since then, many scientific and medical communities have come to believe that the therapeutic use of light holds great promise for not only SAD, but also a variety of other disorders.

This wide-ranging book combines in a single, cohesive reference new findings with a complete summary of the available literature on light therapy. Seventeen contributors, leading clinicians studying the effects and uses of light treatment, discuss the impact of light and light therapy on conditions such as SAD, premenstrual depression, circadian phase sleep disorders, jet lag, shift work disorders, insomnia, and behavioural disturbances.

Challenging conventional thinking about light therapy, several contributing authors make convincing cases for its positive effects in treating nonseasonal depression, bulimia nervosa, and other illnesses. Finally, members of a joint task force of the Society for Light Treatment and Biological Rhythms and the American Sleep Disorders Association explore the use of light for treating sleep disorders, and a combination of light and melatonin in some cases.

Seasonal Affective Disorders and Beyond is an invaluable reference tool for clinicians, researchers, scientists, students, and consumers who want the latest information and opinion about the therapeutic uses of light, compiles in one succinct, comprehensive volume.

*"This book, edited by Raymond Lam, M.D., one of the leading clinical researchers in the field, is both a practical introduction for the novice psychiatric clinician and a comprehensive, up-to-date overview of the basic mechanisms of light therapy, the pathophysiology of the disorders, and the pitfalls and future prospects of light therapy for the clinical researcher. I recommend it highly for anyone interested in this new and exciting field."*

**J. Christian Gillin, M.D.**  
*Professor of Psychiatry,  
University of California, San Diego*



# SEASONAL AFFECTIVE DISORDER AND BEYOND Light Treatment for SAD and Non-SAD Conditions

*Edited by Raymond W. Lam, M.D., 1998, 328 pp, US\$45.*

*American Psychiatric Press, Inc., Washington DC*

*www.psychiatry.ubc.ca/mood/sad*

## TABLE OF CONTENTS

<i>Raymond W. Lam</i>	Preface
<i>George C. Brainard</i>	The Healing Light: Interface of Physics and Biology
<i>Virginia Wesson, Anthony J. Levitt</i>	Light Therapy for Seasonal Affective Disorder
<i>Michael Terman</i>	On the Specific Action and Clinical Domain of Light Therapy
<i>Edwin M. Tam, Raymond W. Lam, Lakshmi N. Yatham, Athanasios P. Zis</i>	Psychobiological Studies of Light Therapy in Seasonal Affective Disorder
<i>David H. Avery, Michael J. Norden</i>	Dawn Simulation and Bright Light Therapy for Subsyndromal Seasonal Affective Disorder
<i>Daniel F. Kripke</i>	Light Treatment for Nonseasonal Major Depression: Are We Ready?
<i>Barbara F. Parry</i>	Light Therapy of Premenstrual Depression
<i>Raymond W. Lam, Elliot M. Goldner</i>	Seasonality of Bulimia Nervosa and Treatment with Light Therapy
<i>Rod J. Hughes, Alfred J. Lewy</i>	Light and Melatonin Treatment of Circadian Phase Sleep Disorders
<i>Ziad Boulos</i>	Bright Light Treatment for Jet Lag and Shiftwork
<i>Scott S. Campbell</i>	Bright Light Treatment of Sleep Maintenance Insomnia and Behavioral Disturbance
<i>Raymond W. Lam</i>	SAD and Beyond: A Commentary

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## **Frequently Asked Questions about Seasonal Affective Disorder (SAD)**

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### **What is SAD? How is it different from the winter blues?**

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Many people feel mildly “depressed” during the winter, but some people have more severe bouts of feeling down all the time, low energy, problems with sleep and appetite, loss of interest, and reduced concentration to the point where they have difficulty functioning at work or in the home. We say that these people have a clinical depression, to distinguish it from everyday ups and downs. Seasonal affective disorder (‘affective’ is a psychiatric term for mood), or SAD, describes people who have these clinical depressions only during the autumn and winter seasons. During the spring and summer, they feel well and “normal”.

Other common symptoms of SAD include oversleeping, extreme fatigue, increased appetite with carbohydrate craving, overeating, and weight gain. With more severe episodes, people may have suicidal thoughts.

### **How common is SAD?**

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Researchers believe that SAD results from the shorter daylength in winter. Recent studies estimate that SAD is more common in northern countries because the winter day gets shorter as you go farther north. Studies in Ontario suggest that 1% to 3% of the general population have SAD. This means that up to 120,000 people in British Columbia (1.2 million in Canada!) may have difficulties in the winter due to significant clinical depression. Another 15% of people have the “winter blues” or “winter blahs” – winter symptoms similar to SAD, but not to the point of having a clinical depression.

### **What treatments are available for SAD?**

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Research has shown that many patients with SAD improve with exposure to bright, artificial light, called light therapy, or phototherapy. As little as 30 minutes per day of sitting under a special fluorescent light box results in significant improvement in 60% to 70% of SAD patients.

### **How do you use light therapy?**

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A fluorescent light box is the best-studied light therapy treatment. Patients usually purchase a light box and use it in their own homes. The usual “dose” of light is 10,000 lux, where lux is a measurement of light intensity. Indoor light is usually less than 400 lux; a cloudy day about 3,000 lux; and a sunny day is 50,000 lux or more. Using the 10,000 lux light box for about 30 minutes a day is usually enough for

a beneficial response. A light box with a lower lux rating usually requires more time for a response. For example, 5,000 lux light boxes usually require 45-60 minutes of daily exposure, while 2,500 lux light boxes require 1-2 hours of exposure.

Other light devices are also commercially available. Light visors and other head-mounted units can offer more portability than light boxes. Dawn simulators are devices that gradually increase the lights in the bedroom to “simulate” a summer dawn in the winter. While these devices can be beneficial for some people, there is less evidence to show that they are effective for SAD compared to light boxes.

People are cautioned NOT to use tanning studios to treat SAD because there is NO evidence that they are helpful. The effect of light therapy is through the eyes, not through skin exposure, and people should not open their eyes in tanning booths because of the harmful effects of ultraviolet exposure. Fluorescent light boxes have filters to block the harmful ultraviolet rays.

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### **How do I get a light box?**

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Safe and portable light boxes are now commercially available. Ask your doctor, or contact our clinic for more information (or check our web site at [www.psychiatry.ubc.ca/mood/sad](http://www.psychiatry.ubc.ca/mood/sad)). The cost of a light box is usually between \$250 and \$500 (Cdn). We do not recommend building your own light box, because of the safety hazards, and the difficulty in getting the correct dose of light.

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### **Are there side effects to light therapy?**

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Side effects of light therapy are usually mild. Some people may experience mild nausea, headaches, eyestrain, or feeling “edgy” when they first start using light therapy. These effects usually get better with time or reducing the light exposure. People who have bipolar disorder (manic-depressive illness) should also consult their doctor before using light therapy.

There are no known long-term harmful effects of light therapy. However, people with certain medical conditions (such as retinal disease or diabetes) or taking certain medications should have special eye examinations before considering light therapy.

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### **Are there other treatments for SAD?**

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Other treatments for depression, including the newer antidepressant medications (e.g., selective serotonin reuptake inhibitors, or SSRIs, bupropion-SR, moclobemide, and others) are also effective for patients with SAD. Counselling and exercise may also help. People with milder symptoms of the “winter blahs” may be helped by simply spending more time outdoors and exercising regularly in the winter (e.g., a daily noon hour walk).

Some people with SAD find that they also feel better by increasing the indoor light in their homes and/or offices, painting their walls in light colours, and sitting near windows for natural light. There is no evidence, however, that these activities alone can treat SAD.

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## What causes SAD and how does light therapy work?

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We don't know, exactly, but research shows that light has a biological effect on brain chemical (neurotransmitters) and function. One theory is that people with SAD have a disturbance in the "biological clock" in the brain that regulates hormones, sleep and mood, so that this clock "runs slow" in the winter. The bright light may help to "reset the clock" and restore normal function. Other theories are that neurotransmitter functions, particularly serotonin and dopamine, are disturbed in SAD, and that these neurotransmitter imbalances are corrected by light therapy and/or antidepressant medications. Still other scientists believe that patients with SAD have reduced retinal light sensitivity or immune function in the winter that is corrected by light therapy. There is also research showing a genetic basis for SAD.

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## What should I do if I think I have SAD?

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Everyone who is significantly depressed should be assessed by their family doctor because some physical problems (e.g., thyroid disease) can show up as depression. People with SAD can be treated by their family doctor, referred to a psychiatrist who is aware of SAD, or (in Vancouver) referred to the Seasonal Mood Disorders Clinic at the UBC Hospital (telephone: 604-822-7321), for further assessment. To find a SAD specialist, check with the nearest university medical school department of Psychiatry. People should not treat themselves with light exposure until after assessment by a qualified health professional.

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## Can I read more about SAD?

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We recommend these books for further reading, available at most bookstores or the public library.

1. *Winter Blues: Seasonal Affective Disorder - What it is and How to Overcome It*, by Dr. Norman Rosenthal (one of the pioneer researchers in SAD and light therapy). Guilford Press, revised 1998, about \$18.00 (Cdn).
2. *Fight the Winter Blues: Don't be SAD: Your Guide to Conquering Seasonal Affective Disorder*, by Celeste A. Peters. Script Publishing, 1994, about \$19.00 (Cdn).
3. *Clinical Guidelines for the Treatment of Seasonal Affective Disorder*, by Drs. Raymond W. Lam and Anthony J. Levitt. Clinical & Academic Publishing, 2000, about \$20.00 (Cdn). Although primarily directed to family physicians, the Question-and-Answer format of these clinical guidelines are accessible to informed general readers. To purchase, check [www.amazon.com](http://www.amazon.com).
4. Also, check out the UBC SAD Information Page on the Internet at [www.psychiatry.ubc.ca/mood/sad](http://www.psychiatry.ubc.ca/mood/sad) or the web site for the Society for Light Treatment and Biological Rhythms at [www.sltbr.org](http://www.sltbr.org).

## Helpful Suggestions For Coping With Winter Depression (SAD)

- Discuss symptoms with your physician. You may be referred to a psychiatrist who may diagnose seasonal affective disorder, SAD, or “subsyndromal” SAD, and prescribe special light therapy or other treatments to help relieve your symptoms. Some new antidepressants are also helpful in treating some people with seasonal depression.
- If you have a medical diagnosis of SAD or subsyndromal SAD, and your doctor prescribes light treatment, do not skip or shorten treatment because you’re feeling better...you may relapse. Work with your doctor in adjusting the length of time, time of day, distance, and intensity of lights for your own individualized treatment.
- Educate yourself, family and close friends regarding SAD to gain their understanding and support.
- Get as much light as possible and avoid dark environments during daylight hours in winter.
- Allow natural light to shine through open windows and doors when temperatures are moderate.
- Reduce mild winter depressive symptoms by exercising daily – outdoors when possible to take advantage of natural light.
- If you are unable to exercise outdoors in the winter due to extreme cold, exercise inside. Instead, sit in front of an open south-facing window, in sunlight for short but frequent periods during the day if you are able.
- Rearrange workspaces at home and work near a window, or set up bright lights in your work area.
- When there is alternative seating ask to sit near a window in restaurants, classrooms, cars etc.
- Stay on a regular sleep/wake schedule. People with SAD who get up every morning and go to sleep at the same time, report being more alert and less fatigued than when they vary their schedules.
- Be aware of cold outside temperatures and dress to conserve energy and warmth. Many affected by seasonal changes report sensitivity to extreme temperatures.
- Consider going without sunglasses in the winter except in very bright sunlight or decrease amount of time wearing them.
- Arrange family outings and socials occasions for day times and early evening in winter. Avoid staying up late which disrupts sleep schedule and biological clock.
- Conserve energy by managing time wisely and avoiding or minimizing unnecessary stress.
- Try putting lights on a timer in the bedroom set to switch on ½hour or more before awakening. Some people with SAD report it is easier to wake up when using this technique with lights.
- Some find it helpful to record their biological rhythms during fall and winter. They keep a daily log noting weather conditions and their energy levels, moods, appetite/weight, sleep times and activities.
- Postpone making major life changes until spring or summer when possible.
- Share experiences regarding SAD and treatment with others with SAD for information, understanding, validation and support.
- If you are able, arrange winter vacation to warm sunny climate!

## Notes on the SPAQ and Ham-24 (see following pages)

### Seasonal Pattern Assessment Questionnaire (SPAQ)

- The SPAQ is a widely used screening questionnaire for SAD.
- The Global Seasonality Score (GSS) is the total sum of the 6 items on Question 11. This gives a score from 0 (no seasonality) to 24 (extreme seasonality). The average GSS in community samples is about 5. The average GSS in patients with SAD is about 16.
- The screening criteria for a “diagnosis” of SAD are based on the GSS and the score on Question 17, the degree of problems associated with seasonal changes.
- A GSS of **11** or higher and a score on Q.11 of **moderate** or greater is indicative of SAD.
- As with most screening questionnaires, these criteria tend to overdiagnose SAD. On clinical interview, some people with these criteria will turn out to have subsyndromal features. On the other hand, very few people with a true diagnosis of SAD will be missed using these criteria.

### Summary Sheet for the 24- and 29-item Version of the Hamilton Depression Rating Scale

- The Hamilton Depression Rating Scale (Ham-D) is the most widely used outcome scale for depression studies. The Ham-D is based on a clinical interview with the patient and is rated by the interviewer. The interview asks the patient about symptoms experienced in the past week, compared to a time when they were well.
- There are various versions of the Ham-D, which was originally developed in the 1960’s. The original version (17 items, Ham-17) and a later version (with an additional 4 items, Ham-21) did not include items rating atypical symptoms (like oversleeping, overeating, weight gain, etc). An 8-item atypical symptom addendum was added to rate these symptoms. The resulting 29-item version (Ham-29) is widely used in SAD studies.
- However, the 4 additional items (including the diurnal variation item) on the Ham-21 and 1 item on the Ham-8 are not related to severity of depression. Hence, the Ham-24 (sum of the Ham-17 and Ham-7) is a better indicator of severity than the Ham-29.
- The Ham-24 and Ham-29 scores can be categorized this way:

Category	Ham-24 Score	Ham-29 score
Normal, not depressed	9 or less	11 or less
Mildly depressed	10 to 19	12 to 21
Moderately depressed	20 to 29	22 to 32
Markedly/severely depressed	30 or more	33 or more

## SEASONAL PATTERN ASSESSMENT QUESTIONNAIRE

1. Name \_\_\_\_\_ 2. Age \_\_\_\_\_

3. Place of birth - City / Province (State) / Country \_\_\_\_\_

4. Today's date  
 Month \_\_\_\_\_ Day \_\_\_\_\_ Year \_\_\_\_\_

5. Current weight (in lbs.) \_\_\_\_\_

6. Years of education

Less than four years of high school	1
High school only	2
1-3 years post high school	3
4 or more years post high school	4

7. Sex - Male 1 Female 2

8. Marital Status -

Single	1
Married	2
Sep./Divorced	3
Widowed	4

9. Occupation \_\_\_\_\_

10. How many years have you lived in this climatic area? \_\_\_\_\_

**INSTRUCTIONS**

\* Please circle the number beside your choice.

Example:  
**Sex** Male 1 Female 2

The purpose of this form is to find out how your mood and behaviour change over time. Please fill in all the relevant circles. Note: We are interested in your experience; not others you may have observed.

11. To what degree do the following change with the seasons?

	No Change	Slight Change	Moderate Change	Marked Change	Extremely Marked Change
A. Sleep length	0	1	2	3	4
B. Social activity	0	1	2	3	4
C. Mood (overall feeling of well being)	0	1	2	3	4
D. Weight	0	1	2	3	4
E. Appetite	0	1	2	3	4
F. Energy level	0	1	2	3	4

12. In the following questions, fill in circles for all applicable months. This may be a single month **O**, a cluster of months, e.g. **O O O** , or any other grouping.

At what time of year do you....

	J	F	M	A	M	J	J	A	S	O	N	D		
	a	e	a	p	a	u	u	u	e	c	o	e		
	n	b	r	r	y	n	l	g	p	t	v	c		
A. Feel best	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<p><b>OR</b> No particular month(s) stand out as extreme on a regular basis</p> <p><b>OR</b></p>
B. Gain most weight	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
C. Socialize most	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
D. Sleep least	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
E. Eat most	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
F. Lose most weight	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
G. Socialize least	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
H. Feel worst	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
I. Eat least	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
J. Sleep most	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	

14. How much does your weight fluctuate during the course of the year?

0-3 lbs	1	12-15 lbs	4
4-7 lbs	2	16-20 lbs	5
8-11 lbs	3	Over 20 lbs	6

15. Approximately how many hours of each 24-hour day do you sleep during each season? (Include naps)

Winter	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Over18
Spring	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Over18
Summer	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Over18
Fall	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Over18

16. Do you notice a change in food preference during the different seasons?

No 1      Yes 2      If yes, please specify :

17. If you experience changes with the seasons, do you feel that these are a problems for you?

No 1      Yes 2      If yes, is this problem -

mild	1
moderate	2
marked	3
severe	4
disabling	5

Thank you for completing this questionnaire.

\* Raymond W. Lam 1998 (modified from Rosenthal, Bradt and Wehr 1987).



# HDRS SUMMARY (SIGH-SAD)

Patient Initials: \_\_\_\_ \_\_\_\_ \_\_\_\_

Patient No.: \_\_\_\_\_

Visit No.: 1  2  3  4  5  6  7

Date: (dd/mon/yr) \_\_\_\_ / \_\_\_\_ / \_\_\_\_

## 1. Depressed Mood

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

## 2. Work and Activities

- 0 = No difficulty.
- 1 = Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies.
- 2 = Loss of interest in activities; hobbies or work - either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities).
- 3 = Decrease in actual time spent in activities or decrease in productivity. In hospital rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores.
- 4 = Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted.

## 3. Social Withdrawal

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

## 4. Genital Symptoms

- 0 = Absent.
- 1 = Mild.
- 2 = Severe.

## 5. Somatic Symptoms - GI

- 0 = None.
- 1 = Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
- 2 = Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for G.I. symptoms.

## 6. Loss of Weight

- 0 = No weight loss.
- 1 = Probable weight loss associated with present illness.
- 2 = Definite (according to patient) weight loss.

## 7. Weight Gain

- 0 = No weight gain.
- 1 = Probable weight gain due to current depression.
- 2 = Definite (according to patient) weight gain due to depression.

## 8. Appetite Increase

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

## 9. Increased Eating

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

## 10. Carbohydrate Craving

- 0 = No change in food preference or consumption.
- 1 = Craving or eating more carbohydrates (starches or sugars) than before.
- 2 = Craving or eating much more carbohydrates than before.
- 3 = Irresistible craving or eating of sweets or starches.

## 11. Insomnia - Early

- 0 = No difficulty falling asleep.
- 1 = Complains or occasional difficulty falling asleep - i.e., more than 1/2 hour.
- 2 = Complains of nightly difficulty falling asleep.

## 12. Insomnia - Middle

- 0 = No difficulty.
- 1 = Patient complains of being restless and disturbed during the night.
- 2 = Waking during the night - any getting out of bed rates 2 (except for purposes of voiding).

## 13. Insomnia - late

- 0 = No difficulty.
- 1 = Waking in early hours of the morning but goes back to sleep.
- 2 = Unable to fall asleep again if he gets out of bed.

## 14. Hypersomnia

- 0 = No increase in sleep length.
- 1 = At least 1 hour increase in sleep length.
- 2 = 2+ hour increase.
- 3 = 3+ hour increase.
- 4 = 4+ hour increase.

**15. Somatic Symptoms - General**

- 0 = None.
- 1 = Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability.
- 2 = Any clear-cut symptom rates 2.

**16. Fatigability**

- 0 = Does not feel more fatigued than usual.
- 1 = Feels more fatigued than usual but this has not impaired function significantly; less frequent than in (2).
- 2 = More fatigued than usual; at least one hour a day; at least three days a week.
- 3 = Fatigued much of the time most days.
- 4 = Fatigued almost all the time.

**17. Feelings of Guilt**

- 0 = Absent.
- 1 = Self reproach, feels he has let people down.
- 2 = Ideas of guilt or rumination over past errors or sinful deeds.
- 3 = Present illness is a punishment. Delusions of guilt.
- 4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

**18. Suicide**

- 0 = Absent.
- 1 = Feels life is not worth living.
- 2 = Wishes he were dead or any thoughts of possible death to self.
- 3 = Suicide ideas or gestures.
- 4 = Attempts at suicide (any serious attempt rates 4).

**19. Anxiety - Psychic**

- 0 = No difficulty.
- 1 = Subjective tension and irritability.
- 2 = Worrying about minor matters.
- 3 = Apprehensive attitude apparent in face or speech.
- 4 = Fears expressed without questioning.

**20. Anxiety - Somatic**

- 0 = Absent.
- 1 = Mild.
- 2 = Moderate.
- 3 = Severe.
- 4 = Incapacitating.

**21. Hypochondriasis**

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

**22. Insight**

- 0 = Acknowledges being depressed and ill.
- 1 = Acknowledges illness but attributes cause to bad food, climate, over work, virus, need for rest, etc.
- 2 = Denies being ill at all.

**23. Motor Retardation**

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

**24. Agitation**

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

**17-item HDRS Total:** \_\_\_\_\_

(do not include shaded items)

**7-item Atypical Total:** \_\_\_\_\_

(only shaded items)

**24-item HDRS Total:** \_\_\_\_\_

(all items)

**25. Diurnal Variation**

- 0 = None.
  - 1 = Mild.
  - 2 = Severe.
- Worse in:    AM    PM

**26. Reverse Diurnal (Afternoon Slump)**

- 0 = No.
- 1 = yes, of mild intensity.
- 2 = Yes, of moderate intensity.
- 3 = yes, of severe intensity.

**27. Depersonalization/Derealization**

- 0 = Absent.
- 1 = Mild.
- 2 = Moderate.
- 3 = Severe.
- 4 = Incapacitating.

**28. Paranoid Symptoms**

- 0 = None.
- 1 = Suspicious.
- 2 = Ideas of reference.
- 3 = Delusions of reference and persecution.

**29. Obsessive/Compulsive**

- 0 = Absent.
- 1 = Mild.
- 2 = Severe.

**29-item HDRS Total:** \_\_\_\_\_

(all items)

## LIGHT THERAPY: Procedure for Using the 10,000 Lux Light Box

*Note: Note that this information does not substitute for medical consultation. You should always check out information with your own physician. These instructions should **only** be used in conjunction with supervision by a qualified health professional.*

1. These instructions are for fluorescent light boxes that emit 10,000 lux light (lux is a measurement of light intensity). Light boxes with lower lux rating usually require more time for response. For example, 5,000 lux light boxes require 45-60 minutes of daily exposure, while 2,500 lux light boxes require 1-2 hours of exposure.
2. Other light devices are also commercially available (e.g., light visors, dawn simulators). They may be beneficial for some patients, but there is less evidence to show that they are effective compared to light boxes.
3. The light boxes we use contain cool-white fluorescent lights, but full-spectrum fluorescent lights are also effective (although more expensive). The light box should have an ultraviolet filter. **Do not use sunlamps or tanning lamps as these may be harmful to your eyes!**
4. During light therapy, you should keep to a regular sleep schedule (going to sleep and waking up at regular times, for example, 11:00 p.m. to 7:00 a.m.).
5. The light box should be placed on a table or counter so that you can sit comfortably as close as possible to the light.
6. You should sit with your head almost touching the lights to get the required lux (within 12-18 inches of the light). You can read or eat while sitting under the lights, but your eyes must be open for the effect to occur. You cannot sleep during your light exposure! You should **not** stare directly at the lights.
7. Start with 30 minutes of light exposure per day. Start light therapy in the early morning, as soon as possible after awakening (between 7:00 a.m. and 9:00 a.m.).
8. Response usually starts in a few days, and by two weeks the symptoms should be definitely improving. Most people need to continue light therapy throughout the winter until the springtime. When light therapy is stopped, symptoms do not usually reappear for a few days, so most people can stop the treatment for one or two days without much problem (e.g., for a weekend trip).
9. If the symptoms are **not** improving after 10 days, try spending up to 60 minutes per day in front of lights each morning, or divided between the morning and evening. Do not use the light box too near bedtime, as the light exposure can disturb sleep. If this still does not help, contact your doctor.
10. When there is a good response to light therapy, some patients like to experiment with the timing and duration of daily light exposure, e.g., by reducing the daily exposure to 15 minutes, or using the light at a more convenient time of the day (e.g., 7:00 p.m.). We suggest making one change at a time, for 2 weeks. If symptoms start returning, go back to the original dosing schedule.
11. There are no reported harmful effects on the eyes with light therapy as described, but the long-term effects have not yet been studied. If you have eye problems (e.g., retinal disease, cataracts, or diabetes), or worries about eye damage, please see your doctor.
12. Some people experience mild headaches, nausea, or eye strain when using the lights. These symptoms usually occur at the beginning of treatment, and get better in a few days. Otherwise, they can be relieved by reducing the daily exposure time, or by sitting slightly farther away from the lights.
13. Occasionally people report feeling irritable, or euphoric, or being “too high” when treated with light therapy. If this happens, the treatment should be stopped, and you should contact your doctor. If light therapy is restarted, use a shorter exposure time (e.g., 15 minutes per day) or sit slightly farther away from the lights. People with bipolar disorder (manic-depressive illness) should consult with their doctor before using light therapy.

## Light Therapy Devices for SAD

Seasonal affective disorder (SAD) is a type of clinical depression that regularly occurs in the winter, with normal mood in the summer. Light therapy is an effective and safe treatment for SAD. Other treatments for depression (for example, medications) are also effective. Self-diagnosis or treatment of SAD is not recommended because there are other medical causes for depressive symptoms, and because light therapy may be harmful to people with certain medical conditions (for example, eye disease). See your doctor first!

Although light therapy is effective for SAD, we still do not fully understand how the light works and what is the best method for light therapy. There are now many light therapy devices available on the market making claims about light treatment, but light therapy devices are not well regulated in Canada. Therefore, we believe it is wise to be cautious about recommending light therapy devices. Our recommendations are based on the following principles: 1) the light device should be tested and found effective in scientifically valid studies, 2) the light device should have a filter that blocks the ultraviolet rays, 3) the light device should be CSA approved if used in Canada (UL approved in the US), and 4) the light device company should have a track record of reliability.

We recommend fluorescent light boxes because they have been extensively tested with the greatest evidence for effectiveness in scientific studies, and we have experience with these devices. Other light devices, for example light visors and dawn simulators, may be beneficial for some patients but there is less evidence for effectiveness compared to light boxes. We have no direct financial interest in any companies listed below, nor can we take any responsibility for their products.

### **British Columbia Suppliers**

#### **VitalAire**

Unit 201-9087B-198<sup>th</sup> Street  
Langley, BC V1M 3B1  
Tel: (604) 881-0214

#### **MacDonald's Prescriptions**

2188 West Broadway  
Vancouver, BC V6K 2C8  
Tel: (604) 738-0733

#### **Ammundsen Medical Supply**

1062 Homer Street  
Vancouver, BC V6B 2W9  
Tel: (604) 669-9588 / 1-800-663-3366

#### **Polar Sun**

Vancouver, BC  
Tel: 1-888-592-2632

#### **Island Enviro Lighting Ltd.**

44 Linden Avenue  
Victoria, BC V8V 4C8  
Tel: (250) 384-8534 / 1-877-384-8534

For more suppliers, please check our web site:

[www.psychiatry.ubc.ca/mood/sad](http://www.psychiatry.ubc.ca/mood/sad)

### **Canadian Direct-Order Suppliers**

#### **Up-Lift Technologies**

Box 102 CRO  
Halifax, NS B3J 2L4  
Tel: (902) 422-0804 / 1-800-387-0896

#### **Northern Light Technologies**

8971 Henri Bourassa West  
St. Laurent PQ, H4S 1P7  
Tel: 514-335-1763 / 1-800-263-0066

#### **Apollo Light Systems**

Orem, UT (CSA approved devices)  
Tel: 1-800-545-9667

#### **Bio-Brite Inc.**

Bethesda, MD (CSA approved devices)  
Tel: 1-800-621-LITE

### **International Direct-Order Suppliers**

#### **Circadian Lighting Association**

[www.claorg.org](http://www.claorg.org)

February 1, 2002

To whom it may concern:

Seasonal affective disorder (SAD), or winter clinical depression, is an accepted psychiatric diagnosis with standardized diagnostic criteria. In the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the standard medical classification system published by the American Psychiatric Association, SAD is listed as a *seasonal pattern* course specifier for:

<b>CODE NO.</b>	<b>DIAGNOSIS</b>
DSM-IV-296.3x	Major Depressive Disorder, Recurrent
DSM-IV-296.4x	Bipolar Disorder, Manic
DSM-IV-296.5x	Bipolar Disorder, Depressed
DSM-IV-296.6x	Bipolar Disorder, Mixed
DSM-IV-296.70	Bipolar Disorder, NOS

The current recommended first-line treatment for SAD or *seasonal pattern* is light therapy. Light therapy is now a standard medical treatment and is no longer considered experimental. Light therapy has been included as a recommended treatment for SAD in the latest clinical practice guidelines of the American Psychiatric Association, the Canadian Psychiatric Association, and the World Federation of Societies of Biological Psychiatry. Summary references for these clinical guidelines are included below.

In order to administer light therapy, a 10,000 lux fluorescent light box or other light device is required. This light box and treatment should be regarded as a medical necessity and preferable to other forms of treatment.

Sincerely,

**Raymond W. Lam, MD, FRCPC, FAPA**

Professor and Head, Division of Clinical Neuroscience  
Department of Psychiatry, University of British Columbia  
Medical Director, Mood and Anxiety Disorders Programs  
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Tel: 604-822-7325, Fax: 822-7922, r.lam@ubc.ca

**References**

American Psychiatric Association: Practice Guideline for the Treatment of Patients with Major Depressive Disorder (Revision, April, 2000). American Journal of Psychiatry, Vol. 157, No.4 (Supplement), p.31, 2000. [www.psych.org](http://www.psych.org)

Lam RW, Levitt AJ, editors: Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder. Vancouver, BC; Clinical & Academic Publishing, 1999, ISBN 0-9685874-0-2. Summary available at [www.fhs.mcmaster.ca/direct/depress/sad.html](http://www.fhs.mcmaster.ca/direct/depress/sad.html)

Kennedy SH, Lam RW, Cohen NL, Ravindran AV: Clinical guidelines for the treatment of depressive disorders. IV. Pharmacotherapy and other biological treatments. Canadian Journal of Psychiatry Vol. 46, Supplement 1, pp 38S-58S, 2001. [www.cpa-apc.org](http://www.cpa-apc.org)

Bauer M, Whybrow PC, Angst J, Versiani M, Moller H-J: World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, Part 1: Acute and continuation treatment of major depressive disorder. World Journal of Biological Psychiatry Vol. 3, pp 5-43, 2002.

**Audit Form -- Best Practices Course**  
**Evidence-based Management of SAD: Focus on Light Therapy**

Pull the charts of the last 10 patients whom you have seen in the past 12 months for whom you have made the diagnosis of depressive disorder or seasonal affective disorder.

*Note: **Bold items** refer to follow-up care; all other items refer to initial assessment.*

Behaviour	Yes	No	<b>For Optimal Management:</b>
<b>Diagnosis</b>			
1. Checked for atypical features?			
2. Checked for recurrent seasonal episodes?			
3. Checked for summer remissions?			
4. Checked for regular seasonal psychosocial stressors?			
5. Checked for eating disorders?			
6. Checked for summer hypomania/mania?			
7. Checked for winter worsening of depression?			
8. Checked relevant laboratory tests, e.g., TSH?			
<b>Total:</b>			All 8 items should be checked YES
<b>Management – Light Therapy</b>			
1. Discussed light therapy?			
2. Warned against suntan studio use?			
3. Checked for retinal and systemic risk factors?			
4. Advised light therapy with 10,000 lux light box?			
5. Checked specifications of light box used?			
6. Discussed reimbursement issues re: light boxes?			
7. Advised light therapy for at least 30 minutes per day?			
8. Advised light therapy in early morning?			
9. Advised light therapy daily for at least 2 weeks?			
<b>10. Checked for side effects to light therapy?</b>			
<b>11. Checked response to light therapy?</b>			
<b>12. Used a rating scale to check response?</b>			
13. Advised when to stop light therapy in the spring?			
14. Advised when to restart light therapy next season?			
<b>Total:</b>			At least 10 items should be checked YES:
<b>Management – Antidepressants (if applicable)</b>			
1. Checked whether antidepressant medication needed?			
2. Used an SSRI (fluoxetine, sertraline) as first-line medication?			
<b>3. Checked side effects/response to antidepressant?</b>			
4. Advised when to stop antidepressant?			
<b>Total:</b>			All 4 items should be checked YES
<b>Management – Combined Light Therapy/Antidepressant (if applicable)</b>			
1. Used monotherapy before using combination therapy?			
2. Used combined light therapy/antidepressant?			
<b>3. Checked side effects/response to light therapy/antidepressant?</b>			
<b>Total:</b>			At least 2 items should be checked YES

# Seasonal Affective Disorder: Diagnosis And Management

Raymond W. Lam, MD, FRCPC \*

Over a decade of research has refined and clarified the diagnosis of seasonal affective disorder (SAD), a condition characterized by recurrent major depressive episodes in the fall and winter. Primary care physicians are likely to encounter SAD in their practice because it is a common condition, SAD patients generally have mild to moderate depressions, and they may present with somatic complaints. Numerous studies have shown that exposure to bright, artificial light, termed light therapy (or phototherapy) is a safe and effective treatment for SAD. Although lack of environmental light is widely thought to be a factor in the etiology of SAD, the pathophysiology of SAD and the mechanism of action of light therapy remain elusive. Bright light clearly has significant, predictable effects on human circadian rhythms, but a circadian hypothesis for SAD remains unconfirmed. Other studies have implicated serotonergic dysfunction in the pathophysiology of SAD, and serotonergic medications (e.g., SSRI antidepressants) appear to be effective in the treatment of SAD. The role of light therapy versus medications requires more systematic evaluation, but the choice of treatment depends on various factors such as the severity of the episode, side effects of treatment, cost, and patient compliance. Recent research has begun to explore seasonality and the use of light in other psychiatric conditions, including nonseasonal depression, bulimia nervosa, and premenstrual depression.

*Primary Care Psychiatry 1998; 4:63-74*

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A number of subtypes of major depressive disorder have been identified, based on the cross-sectional clinical features or the course of depressive episodes (Table 1). These subtypes have important differences in clinical course, treatment response, and possibly etiology and pathophysiology. Seasonal affective disorder (SAD) is one such subtype, termed seasonal pattern in DSM-IV. SAD consists of recurrent fall and winter depressive episodes with full remissions (or switch to hypomania or mania) in the spring and summer. Although seasonality of depression has been recognized for centuries, the concept of SAD was first systematically developed and described in 1984 by Rosenthal and his group at the U.S. National Institute of Mental Health [1]. Their studies showed that these patients experienced dramatic and rapid relief of symptoms when exposed to bright, artificial fluorescent light, which they initially called phototherapy (and later was changed to light therapy, to distinguish it from other forms of phototherapy, i.e., for hyperbilirubinemia).

Diagnostic criteria for SAD are similar across the different classification systems (Table 2). The major tasks for diagnosis consists of identifying the specific onset and offset (remission) of depressive episodes, and excluding any depressive symptoms in the summer. For most patients, the usual onset of an episode is in October, and the typical offset is in April (Figure 1).

**TABLE 1. Clinical subtypes (specifiers) of mood disorders identified in the DSM-IV.**

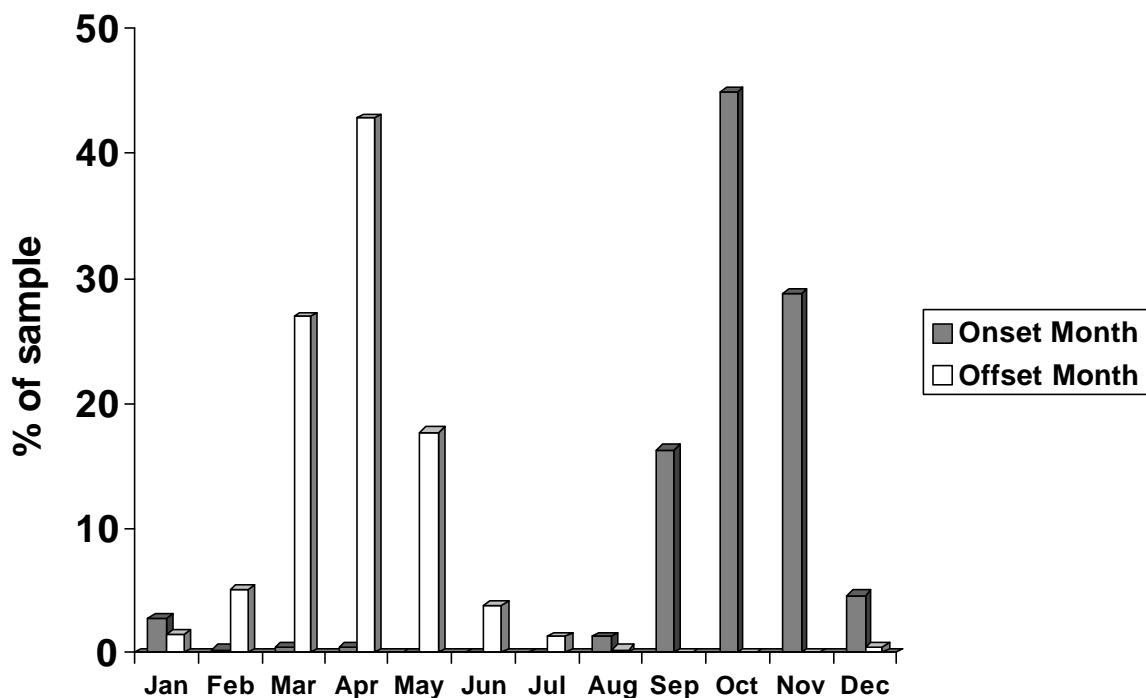
Episode Specifiers	Course Specifiers
With psychotic features	With seasonal pattern
With melancholic features	With postpartum onset
With atypical features	With rapid-cycling
With catatonic features	

Patients may not be reliable about the specific times for their episode onsets and offsets, so collateral information from family and friends is important to ensure that the depressive episodes are strictly seasonal. The seasonal specifier can be applied to either recurrent major depressive disorder, or to bipolar disorder. In our Vancouver clinic sample of 454 SAD patients diagnosed with DSM-III-R criteria (similar to ICD-10 criteria), the majority had unipolar depressions (89%), while 8.5% had spring/summer hypomanic episodes (bipolar disorder, type II), and 2.5% had full-blown mania (bipolar disorder, type I).

**TABLE 2. Diagnostic Criteria for Seasonal Affective Disorder**

DSM-IV Criteria	ICD-10	Rosenthal Criteria
2 or more episodes meet DSM-IV criteria for Major Depressive Disorder  Last 2 episodes must be consecutive	3 or more mood episodes meeting ICD-10 criteria for Major Depression  3 or more episodes must be consecutive	1 or more episodes lifetime meet Research Diagnostic Criteria for Major Depression  2 or more episodes must be consecutive
Onset and remission of episodes must occur regularly in the same seasons	Onset and remission of episodes must occur regularly within particular 90-day periods of the year	Onset and remission of episodes must occur regularly in the same seasons
Seasonal episodes must greatly outnumber any nonseasonal episodes  No nonseasonal episodes in the last 2 episodes	Seasonal episodes must substantially outnumber any nonseasonal episodes	
Exclude seasonal psychosocial stressors		Exclude seasonal psychosocial stressors

**FIGURE 1. Month of onset and month of offset (remission) of symptoms reported by a clinic sample of 454 patients with SAD, diagnosed using DSM-III-R criteria.**



## CLINICAL FEATURES OF SAD

While the diagnostic criteria for the diagnosis of winter depression only include identifying a specific pattern of recurrent depressive episodes, clinic samples have shown that SAD is associated with a specific symptom cluster [1-4]. This cluster consists of the so-called "atypical" vegetative symptoms of depression, including hypersomnia, increased appetite, carbohydrate craving, and weight gain. Table 3 shows the prevalence of these clinical features in the 454 SAD patients assessed at our SAD Clinic. The hypersomnia seen in SAD may present as increased hours of sleep during the winter, often 2 to 4 hours more per night than in summer, or as increased need for sleep and difficulty arising in the morning.

Despite sleeping more hours, patients remain fatigued and tired during the day, with marked afternoon slumps in mood and/or energy to the point where they may feel compelled to nap.

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 behaviours (e.g., vomiting) are uncommon [5,6]. The increased eating and reduced activity usually leads to significant weight gain. 10% of SAD patients seen in our clinic experience winter weight gains of greater than 20

pounds. Some patients report that they require two wardrobes, with their winter clothes being two or three sizes larger than their summer clothes. 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.

These atypical symptoms have led some investigators to suggest that SAD may be a form of atypical depression [7]. Atypical depression is characterized by mood reactivity, where patients experience marked but temporary improvement in mood in response to favourable external circumstances. The mood reactivity is also associated with at least two symptoms of hypersomnia, hyperphagia with weight gain, leaden paralysis (a severe form of fatigue that is experienced as a physical sensation of heaviness), and interpersonal rejection sensitivity (a long-standing pattern of exquisite sensitivity to rejection, especially romantic rejection). However, studies have shown that SAD patients do not have more mood reactivity, leaden paralysis, or rejection sensitivity than nonseasonal depressed patients [8]. Therefore, the overlap between the two subtypes appears to be limited to the atypical vegetative symptoms.

**TABLE 3. Clinical features reported by a Vancouver (latitude 49°N) clinic sample of 454 patients with SAD, diagnosed using DSM-III-R criteria. In this group, the female to male ratio was 74% to 26%, and the mean age was 37.7 ± 10.8 years.**

Vegetative Symptoms	% of Sample	Other Symptoms	% of Sample	Psychosocial Function	% of Sample
Sleep— Increased	71	Diurnal Variation		Occupational	73
Decreased	26	Morning worse	47	Impairment	
No change	3	Evening worse	26		
Appetite— Increased	57	Anxiety	79	Impaired	93
Decreased	28	Panic Attacks	12	Social	
No change	15			Function	
Weight— Increased	53	Suicidal Thoughts	47	Past	70
Decreased	14	Past Attempts	10	Psychiatric	
No change	33			Contact	
Carbohydrate Craving	77	Feelings of Guilt	82	Hospitalization	12
Loss of Interest	93	Irritability	82		
Loss of Energy	97	Poor Concentration	95		

Cognitive symptoms of depression are also present in SAD, including feelings of guilt and self-blame. SAD patients have similar neuropsychological deficits in memory and concentration as do nonseasonal depressed patients [9]. Interestingly, suicidal ideation and attempts are not as prominent or frequent in SAD compared to nonseasonal depression [10]. In part, this may be because SAD patients recognize the seasonal nature of their mood change and that they will likely improve in a few months with the onset of spring. The fact that an end to their depression is "in sight" may reduce the hopelessness found in nonseasonal depression, when patients never know how long they will be depressed.

Patients with SAD also notice that their symptoms remit when they are at lower latitudes (i.e., closer to the equator) [1]. Thus, it is informative to ask whether they have taken holidays or spent time in a more southerly location during the symptomatic winter months. Patients will often report that their mood improves markedly within a few days at the new latitude. Unfortunately, symptoms usually return within a week or two upon return to their usual locale. Additionally, patients will often notice winter symptoms only when they move to higher latitudes or to an area where there is greater winter cloud cover.

Primary care physicians are likely to encounter SAD patients because the depressions are usually mild to moderate in severity. A study of 303 patients attending a primary care clinic in the winter identified a clinical diagnosis of SAD in 9%, with another 29% having significant winter depressive symptoms without meeting criteria for major depression (subsyndromal SAD) [11]. The functional impairment of these patients, whether SAD or subsyndromal SAD, exceeded that of all the common chronic medical conditions measured. Detection of SAD is important since many patients do not recognize their disorder. In our clinic, 30% of patients diagnosed with SAD had never before sought professional help for their condition, even though they had suffered through, on average,  $10.3 \pm 8.0$  previous winter depressive episodes. The reasons cited for not seeking help include that they believed they had "winter blues", that no treatment was available, that the winter problems were related to physical illness, and that their physicians did not take the symptoms seriously. A degree of vigilance is required since patients often do not associate their winter symptoms with a depression. Therefore, patients seen in the winter should be screened for SAD if they complain of recurrent bouts of the "flu", excessive fatigue, chronic sleepiness, excessive weight gain, or unexplained pain.

## PREVALENCE AND COURSE

Studies of the prevalence of SAD have predominantly relied on questionnaires, such as the Seasonal Pattern Assessment Questionnaire (SPAQ) [12], which assess seasonality rather than clinical diagnoses. The questionnaire studies from the United States indicated that the prevalence of SAD increased with higher (more northern) latitudes, ranging from 1.4% in Florida to 9.7% in New Hampshire [13,14], and 9.2% in Alaska [15]. European and Asian studies, using translated versions of the same questionnaire, found lower rates of SAD at high latitudes, including 3.8% in Iceland [16], less than 1% in Finland [17], and 1% to 2% in Japan [18,19], although a significant correlation of SAD with higher latitude was still observed. This suggests that these questionnaires (or their translations) may not be consistent in identifying diagnoses of SAD [20-22] or that there are other factors that influence seasonality, such as culture or genetics. Other research has found that 15% to 20% of patients with mood disorders have distinct seasonal patterns [23-25]. Since the lifetime prevalence of mood disorders in the general population is about 10%, these data suggest that the prevalence of seasonal depression should be about 1% to 2%. A recent epidemiologic study from Canada supports these figures. In a telephone interview study conducted in the province of Ontario, Canada, 1.7% of the general population were found to have a clinical diagnosis of SAD [26].

Longitudinal follow-up studies of 2 to 11 years suggest that a percentage of patients diagnosed as SAD do not continue to have seasonal major depressive episodes [27-30]. About a third of SAD patients (22% to 42%) continued to have definite, recurrent seasonal depressive episodes. A similar proportion (28% to 44%) had complicated patterns suggesting a more nonseasonal course, although some patients in this group were taking antidepressants constantly throughout the year, so that their seasonal patterns may have been obscured. Another third (14% to 38%) either had subsyndromal episodes, or went into clinical remission. This shifting of episode pattern is also seen in other clinical subtypes of depression, including atypical and melancholic specifiers [31].

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of SAD is similar to that of major depressive disorder. Organic conditions such as hypothyroidism need to be ruled out, as do other conditions such as phase-delayed sleep disorder, anniversary grief reactions, and seasonal occupational or psychosocial stressors.

There is also some debate as to whether SAD is a categorical diagnosis or an extreme form of a dimensional seasonality trait. Some people have marked symptoms during the winter, but not to the point where they meet criteria for major depressive disorder. The term "subsyndromal" SAD has been used to describe these patients [13]. These patients usually have the vegetative features of hypersomnia and hyperphagia, and prominent winter fatigue and lethargy. However, they may not have the cognitive symptoms of depression, such as depressed mood, feelings of guilt, and suicidal ideation. While they do not meet criteria for major depressive disorder, patients with subsyndromal SAD have significant distress and impairment of function [11,13]. Preliminary studies suggest that these patients also show good response to light therapy [32].

Many other patients with nonseasonal depressions, such as dysthymia and chronic major depression, may have winter worsening of their symptoms [33]. These patients can be differentiated from SAD proper because they are still symptomatic in the summer. Patients with bipolar disorder [20] also report marked worsening of mood, sometimes to the point of syndromal depression, but sometimes not, in the winter. Recent findings suggest that these patients also benefit from addition of light therapy to their treatment regimen during the winter.

Finally, seasonality is becoming increasingly recognized in other psychiatric conditions, including anorexia and bulimia nervosa [34-42], premenstrual depression [43], panic disorder [44], obsessive-compulsive disorder [45], and post-traumatic stress disorder [46].

## ETIOLOGY AND PATHOPHYSIOLOGY OF SAD

Research into the etiology of SAD is intimately tied to that of the mechanisms of action of light therapy. Initial theories focused on the light-dark cycle or photoperiodic (relating to the length of the day) mechanisms that mediate seasonal rhythms in animals [1]. These theories hypothesized that patients with SAD were unable to adapt to the shorter winter photoperiod. Thus, the first successful study of light therapy exposed patients to bright (2500 lux) light from 6:00 to 9:00 a.m. and 6:00 to 9:00 p.m., daily, to extend the winter photoperiod and simulate a summer day [1]. However, subsequent studies showed that a pulse of bright light (e.g., 2 hours of 2,500 lux daily) was sufficient for the antidepressant effect. Attention shifted to abnormalities of circadian rhythms, such as phase-delayed [47] or reduced amplitude [48] circadian rhythms that were corrected by appropriately timed bright light pulses. However, studies have not consistently demonstrated that SAD patients have disturbed circadian rhythms compared to normal controls,

or to themselves in summer, or that the clinical effect of light therapy is dependent on normalizing circadian rhythm abnormalities.

Other studies have focused on neurotransmitter or neurohormonal systems, including melatonin, serotonin [49] and dopamine [50,51]. Melatonin is a hormone synthesized from tryptophan and secreted only at night by the pineal gland. Melatonin secretion is controlled by two major influences. It is under circadian control by the biological pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Melatonin secretion can also be directly suppressed by bright light acting through the retina, to the SCN via the retinohypothalamic tract, and from there to the pineal gland via a complicated neural pathway. Seasonal changes in many animal behaviours are mediated by the duration of melatonin secretion, which reflects the photoperiod. Melatonin secretion does not appear to be primarily dysregulated in SAD, and experimental tests of a melatonin hypothesis have been primarily negative [52,53]. However, recent studies of propranolol, a beta-blocker that suppresses melatonin production, suggest that melatonin may still be involved in SAD. Morning doses of propranolol, which would suppress the early morning secretion of melatonin in the same way as bright light, are effective in SAD [54].

Serotonin is of particular interest in SAD because serotonin, of all the neurotransmitters of interest in depression, is the only one to clearly show a seasonal variation in normal metabolism (for review, see [55]). Neuroendocrine challenge studies using nonspecific and specific serotonin agonists have found evidence for serotonergic dysregulation [56-61]. Serotonergic medications are effective in SAD, including serotonin precursors (e.g., tryptophan [62,63]), serotonin reuptake inhibitors (e.g., fluoxetine [64,65], sertraline [66]), and serotonin releasing agents (e.g., d-fenfluramine [67,68]). Finally, tryptophan depletion studies, in which blood tryptophan levels (and presumably brain serotonin levels), are experimentally manipulated, show that the antidepressant effect of light therapy can be reversed if blood tryptophan levels are rapidly reduced [69,70].

Recent behavioural genetics studies have also shown that there may be a genetic basis for SAD. Studies of monozygotic and dizygotic twins, utilizing the SPAQ and multivariate statistical techniques, have shown that seasonality is a heritable trait. A genetic factor accounts for 29% to 83% of the variance in seasonality scores between twins [71,72].

## TREATMENT OF SAD

### Light Therapy

Light therapy (previously known as phototherapy) is recognized as a safe and effective treatment for SAD [73,74]. More than 3 dozen controlled studies have shown efficacy of light therapy with response rates of 60% to 90% [75-77]. The most widely studied protocol is 2500 lux fluorescent light for 2 hours per day, although studies of higher intensity light have shown that 10,000 lux light for 30 minutes per day gives similar response rates [78,79]. Lux is a unit of illumination intensity that corrects for the photopic spectral sensitivity of the human eye. For comparison, indoor evening room light is usually less than 100 lux, a brightly-lit office is less than 500 lux, a cloudy, gray winter day is around 4,000 lux, and bright sunshine can be 50,000 to 100,000 lux or more.

Although light therapy is regarded to be clinically effective, there are still some critiques about the evidence for its efficacy. Like other non-pharmacologic treatments, the studies are not funded by multinational companies, and so sample sizes tend to be small (usually less than 20 patients per condition) and the duration of treatment short (usually 1 to 2 weeks). There is also difficulty in designing a suitable placebo condition. Since the light cannot be "blinded", some deception is usually required to control for non-specific effects of treatment and biases inherent in expectations of response. Not surprisingly, given the small sample sizes, some studies have not found superiority of bright light over putative placebo conditions [80,81]. Other studies have not found that bright light is more effective than dim light of intensity found in ordinary indoor room light [82]. In these studies, the possibility of statistical Type II errors (i.e., missing a true effect) was high.

Two multi-year, large-sample, placebo-controlled studies were recently reported [83,84] that may finally answer the efficacy question. Both showed significant effects of the active bright light condition against plausible placebo controls. Additionally, a recent meta-analysis (where many similar studies are analyzed together using standardized effect sizes) also showed significant effects of bright light over dim or no light controls [85]. Together, these studies should provide sufficient confirmatory evidence that light therapy does have significant clinical benefit over placebo in SAD.

Various studies have investigated clinical parameters of light therapy including intensity of light, wavelength of light, duration of daily exposure, and timing of light exposure within the day. Results of this research are summarized by current clinical guidelines for the use of light therapy [74,86]. The protocol used in our clinic is exposure to 10,000 lux cool-white light produced by a

fluorescent light box, fitted with a ultraviolet filter, for 30 to 45 minutes daily. Light therapy is usually administered in the early morning upon awakening (e.g., 7:00 a.m.) because many studies found that morning light exposure is superior to exposure at other times of the day [83,84,87-89] (but not all, see [56,90,91]). Patients use the light therapy for at least 2-3 weeks to determine response.

Patients usually obtain a light device (see below) and use light therapy at home, although some hospital and outpatient clinics have designed light therapy rooms for patient use. The onset of action of light therapy is rapid, with significant clinical improvement found in studies of 1 or 2 weeks duration. However, relapse usually occurs after a similar period once light therapy is discontinued [92]. Therefore, most patients must 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 [93]. In subsequent years, patients may be advised to begin light treatments in the early fall, before the onset of symptoms, thus avoiding any gradual or insidious impairment of function [94].

Several studies have shown that various atypical depressive symptoms predict positive response to light therapy [95-99]. Similarly, the balance of melancholic symptoms (e.g., insomnia, appetite and weight loss) over atypical symptoms was correlated to poor response to light therapy [100].

Side effects to light therapy are generally mild and transient, and consist of headache, nausea, eyestrain, blurred vision, and feelings of edginess [101,102]. Bright light exposure in the later evening may disrupt onset and maintenance of sleep. Like any effective antidepressant treatment, there is a risk of precipitating a hypomanic or manic episode with light therapy [103,104], and Bipolar I patients (those with a history of manic episodes) should be on mood-stabilizing medications if light therapy is used. Current dosing guidelines for intensity of light should not prove to be harmful to the eyes, and two long-term follow-up studies did not find any ophthalmologic changes with chronic use of light therapy [105,106]. However, caution should be exercised when treating patients at higher risk of bright light induced eye damage, including patients with pre-existing retinal disease (e.g., retinitis pigmentosa), patients who are taking photosensitizing medications (e.g., lithium, antipsychotics, chloroquine), and elderly patients (due to the higher risk for senile macular degeneration, which may be asymptomatic). For those patients, an ophthalmologic examination is

recommended before initiating light therapy, as well as regular follow-up monitoring.

Other light devices also have been studied for winter SAD. Three light therapy studies used a similar portable light visor. These studies, with large sample sizes and rigorous designs, found no differences between bright, medium, and dim intensity light, although the response rates of all conditions were similar to those of light box studies [107-109]. Other head-mounted devices also have not demonstrated a dose-response relationship or a superior response compared to a putative placebo [81,110]. It is possible that less light is required for therapeutic effect using light visors because of the close proximity of the light source to the eye. Physiologic studies using the light visor have shown that biological effects of light can be demonstrated with lower intensity light [111].

“Dawn simulator” devices are also marketed. These devices gradually increase the indirect light in a bedroom, while the patient is sleeping [112], to a final illumination of less than 500 lux, to simulate a summer dawn during the symptomatic winter. Preliminary studies of efficacy are promising [113], but not yet replicated, so dawn simulation remains an experimental treatment.

Light therapy has also been studied for nonseasonal depression, although not as extensively as for SAD. Several studies have shown positive effects with light therapy [82,114-116], although other studies have been negative [117,118]. These studies generally had smaller effect sizes than light therapy studies of SAD, and were all of relatively short duration (1-4 weeks) compared to most antidepressant studies of nonseasonal depression. Thus, further replication or more definitive studies are required before light therapy can be endorsed as effective for nonseasonal depression.

### **Other Treatments For SAD**

Medications have not been studied in SAD as extensively as light therapy. Only 3 placebo-controlled studies have been reported for antidepressants in SAD. Selective serotonin reuptake inhibitors (SSRIs) are the best-studied medications, with multi-centre, placebo-controlled studies showing that fluoxetine and sertraline are effective in SAD. The fluoxetine study (N=68 SAD patients) used a fixed 20 mg/day dose for 5 weeks. Although there was no significant difference in the raw depression scores, the clinical response rate of fluoxetine was superior to that of placebo (59% vs. 34%, respectively) [64]. The sertraline study (N=170 SAD patients) used doses of 50 to 200 mg/day for 8 weeks. Sertraline was superior to placebo in both the depression scores and the clinical response rates

(62% vs. 46%, respectively) [66]. A study of moclobemide (N=31 SAD and subsyndromal SAD patients) used low doses of 300 mg/day for only 3 weeks, and found no differences between drug and placebo [119].

Although not placebo-controlled, a 6-week comparison study of moclobemide versus fluoxetine (N=29 SAD patients), found no significant difference in response rate (64% vs. 44%, respectively) [65]. Other smaller controlled studies of tryptophan (N=11 SAD) [62], d-fenfluramine (N=29 SAD patients in 2 studies) [67,68], and hypericum (an extract of St. John's Wort, N=20 SAD patients) [120] suggest that these treatments, if the positive results can be replicated, may be effective for SAD.

A number of case series studies suggest that other antidepressants may also be beneficial for SAD, including bupropion (N=15) [121], tranylcypromine (N=14) [122] and alprazolam (N=6) [123].

Although psychological treatments like cognitive-behavioural therapy and interpersonal psychotherapy have been demonstrated to be effective in nonseasonal depression, there are as yet no studies of such treatments in SAD.

In summary, the first-line medication treatment for SAD is with SSRI medications such as fluoxetine and sertraline, followed possibly by moclobemide, then with other medications such as d-fenfluramine, tryptophan, bupropion and tranylcypromine.

### **HOW TO CHOOSE A TREATMENT FOR SAD**

There are no published studies comparing the efficacy of light therapy versus medications for SAD. Thus, the choice of treatment for SAD requires individual risk/benefit assessment. There are more studies demonstrating efficacy of light therapy than there are of medications, but the studies of SSRI antidepressants are much larger than any individual light therapy study. Clinically, light therapy seems to work faster than antidepressants, and generally has fewer side effects. Many patients also prefer a non-pharmacologic treatment for their symptoms. For these patients, light therapy should be the first-line treatment of choice. However, compliance is an issue, since even the newer light therapy protocols mandate spending a half-hour per day or more using the light device. Many patients do not have the interest or motivation required to use light therapy effectively. For those patients, daily medication use is more convenient. For more severely depressed inpatients, antidepressant medications are indicated as first-line

treatment, although light therapy is often useful as an adjunctive treatment.

Light boxes are now widely available commercially, at a cost of US\$150 to US\$350. Thus, the cost of a light box is approximately the same as one season of the newer antidepressant medications. For recurrent use, light therapy appears to be more cost-effective. However, insurance plans may not reimburse light boxes, while medications may be covered, and some patients may not be able to afford a light device. Many light device companies have rental programs or money-back guarantees so patients can have a trial of light therapy before purchasing a light device.

Some patients find that a combination of light therapy and medications works best for them, and that the dose of antidepressant can be reduced when light therapy is combined. Unfortunately, there are as yet no studies of combined use of light therapy and antidepressant medications.

## CONCLUSION

SAD is a common depressive condition that results in significant psychosocial dysfunction and disability. Primary care practitioners should be vigilant for the presenting features of SAD and subsyndromal SAD when seeing patients during the winter. SAD is a very treatable condition with a good prognosis. Sample sizes in light therapy studies have been limited, but the efficacy of light therapy in the treatment of SAD has been established by multiple replications in independent laboratories around the world. Medications, notably SSRI antidepressants such as fluoxetine and sertraline, have also been demonstrated to be effective in SAD. Further research is required to elucidate the pathophysiology of SAD and light therapy, and the optimal treatment (light therapy, medications, psychotherapies, or a combination) for individual patients with SAD.

## INFORMATION RESOURCES FOR SAD

### Seasonal Affective Disorder Association

*As a registered UK charity, SADA is a self-help organization that promotes information about the disorder and its treatment.*

Contact: The Secretary, SADA, PO Box 989, London SW7 2PZ

## Society for Light Treatment and Biological Rhythms

*As a non-profit international scientific organization founded in 1988, SLTBR is dedicated to fostering research, professional development and clinical applications in the fields of light therapy and biological rhythms.*

Web site: [www.sltbr.org](http://www.sltbr.org)  
(includes a list of Corporate Members that manufacture and distribute light devices)

## Other Web Sites

### Dr. Lam's SAD Page at the University of B.C.

[www.psychiatry.ubc.ca/mood/sad/](http://www.psychiatry.ubc.ca/mood/sad/)

### Centre for Environmental Therapeutics

*Includes a FAQ (Frequently Asked Questions) and resources about SAD.*

[www.cet.org](http://www.cet.org)

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# 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,<sup>1</sup> 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 US<sup>2</sup> and at 1% to 3% in Canada.<sup>3</sup> 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,<sup>4</sup> based on the evidence of numerous studies showing efficacy, including large

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randomized controlled trials<sup>5,6</sup> and meta-analyses.<sup>7,8</sup>

SAD and light therapy were identified from basic studies of circadian and seasonal rhythms in animals. Kripke et al<sup>9,10</sup> 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 al<sup>11</sup> 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 depression<sup>12</sup> and to the first systematic studies involving patients with SAD.<sup>13</sup> 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.<sup>1</sup> This seemed consistent with early studies showing that the prevalence of SAD increases with more northerly latitude, where the photoperiod is shorter in winter.<sup>14,15</sup> 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.<sup>1</sup> This photoperiod extension method led to significant improvement. However, subsequent treatment studies showed that photoperiod extension alone was not effective for SAD,<sup>16</sup> and that single daily pulses of light were as effective as the morning plus evening pulses of photoperiod extension (summarized by Terman et al<sup>1</sup>). Subsequent prevalence studies of SAD showed little or no effect of latitude,<sup>2,3</sup> indicating that the correlation between photoperiod and SAD is smaller than previously believed.<sup>17</sup>

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.<sup>18,19</sup> Melatonin suppression alone is also not enough to produce a therapeutic response.<sup>20</sup> Atenolol, a long-acting  $\beta$ -blocker that suppresses melatonin secretion, was not effective for SAD.<sup>21</sup> However, a study using a short-acting  $\beta$ -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.<sup>22</sup>

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.<sup>23</sup> 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).<sup>24</sup>

Recent studies, however, have revived the photoperiod hypothesis. The nocturnal duration of melatonin secretion reflects changes in the photoperiod in humans.<sup>25</sup> 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.<sup>26</sup> 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,<sup>22</sup> 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.<sup>27,28</sup> 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,<sup>9,29,30</sup> Lewy et al<sup>31,32</sup> 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.<sup>33</sup> 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.<sup>34</sup> 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.<sup>35</sup> 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.<sup>36</sup> Morning bright light also significantly phase-advanced cortisol, temperature, and melatonin rhythms in patients with SAD, although the sleep-wake cycle also advanced.<sup>37</sup> The circadian activity-rest cycle was also

found to be significantly delayed in patients with SAD.<sup>38</sup>

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.<sup>39,40</sup> 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,<sup>24</sup> and that clinical response is correlated to the degree of phase advance.<sup>41</sup>

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.<sup>42</sup> 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.<sup>43</sup> 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.<sup>44</sup> 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.<sup>45</sup>

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<sup>6,35</sup> and in most<sup>7,46</sup> but not all<sup>47</sup> meta-analyses, there are large individual studies showing that evening light is more effective than placebo<sup>6</sup> and as effective as morning light.<sup>5,48</sup> 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.<sup>48</sup> 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.<sup>49</sup>

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.<sup>50</sup> 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.<sup>51</sup> 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 al<sup>51</sup> 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.<sup>52</sup> 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.<sup>53</sup> 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,<sup>54,55</sup> 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.<sup>54</sup>

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.<sup>56</sup> Another study also found higher plasma levels of free tryptophan in the spring, with lower levels in both the early summer and winter periods.<sup>57</sup> 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;<sup>58</sup> 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.<sup>59,60</sup>

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.<sup>61</sup> Positron-emission tomographic studies have shown that serotonin synthesis is reduced markedly in response to this depletion protocol.<sup>62</sup> Two separate studies have shown that patients with SAD in remission after light therapy experience a clear relapse of depressive symptoms with tryptophan depletion.<sup>63,64</sup> 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,<sup>65</sup> while another did not.<sup>66</sup> 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 depletion<sup>67</sup> 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.<sup>68,69</sup> There was some evidence that relapse after withdrawal from treatment was slower following tryptophan discontinuation.<sup>69</sup> 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%).<sup>70</sup> 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.<sup>71</sup> Larger studies indicate that the serotonin reuptake inhibitors fluoxetine<sup>72</sup> and sertraline<sup>73</sup> 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-hydroxytryptophan<sup>74</sup> and D,L-fenfluramine,<sup>75</sup> although an earlier study with D,L-fenfluramine was negative.<sup>76</sup> 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<sub>2C</sub> agonist m-chlorophenylpiperazine (m-CPP),<sup>77,78</sup> thereby confirming results from previous non-placebo-controlled studies.<sup>79-81</sup> 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.<sup>77</sup> These various findings may be relatively specific for SAD, in that patients with major depression do not show altered responses to m-CPP challenge.<sup>82</sup> m-CPP also has some affinity for other receptors, including 5-HT<sub>1A</sub> and 5-HT<sub>7</sub>; however, no behavioural or neuroendocrine effects were found in a challenge study with ipsapirone, a selective 5-HT<sub>1A</sub> receptor agonist.<sup>83</sup> Blunted growth hormone responses to the 5-HT<sub>1D</sub> agonist sumatriptan were also reported in SAD, with normalization after light therapy.<sup>84</sup>

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<sub>2C</sub> or 5-HT<sub>7</sub> receptors, although other receptors such as 5-HT<sub>1D</sub> may be involved.

### *Norepinephrine*

To determine whether serotonin dysfunction alone can explain the pathophysiology of SAD, Neumeister et al<sup>85</sup> 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.<sup>77</sup> In this same study, patients with SAD had blunted norepinephrine responses to the serotonin and  $\alpha$ -noradrenergic agonist m-CPP, both with and without light therapy treatment. Other studies have found an increase in both plasma norepinephrine levels<sup>86</sup> and in turnover of norepinephrine<sup>87</sup> 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.<sup>88</sup>

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 D<sub>2</sub> receptors, in patients with SAD.<sup>89,90</sup> 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.<sup>90</sup> This same group has found decreased eye blink rates, which may reflect low dopamine activity, in subjects with SAD,<sup>91</sup> although other groups have not replicated this finding.<sup>92</sup> 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.<sup>93,94</sup> 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. Oren<sup>95</sup> 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.<sup>96-99</sup> 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.<sup>100</sup> Still other studies using different electrophysiological methods have not found changes in retinal or ophthalmic function.<sup>101,102</sup> 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.<sup>103</sup> 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.<sup>104</sup> 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.<sup>105</sup> It has also been speculated that the core symptoms of SAD may reflect a state of low central arousal.<sup>106</sup> 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 disorder<sup>107</sup> and in SAD<sup>108</sup> 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.<sup>109,110</sup> 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.<sup>111</sup> 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.<sup>112,113</sup>

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.<sup>114</sup> 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.<sup>115</sup> In a similar study, an association was found between SAD (but not seasonality *per se*) and the 5-HT<sub>2a</sub> promoter polymorphism -1438G/A.<sup>116</sup> 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.<sup>117</sup> In contrast, Ozaki et al reported a lack of association between SAD and naturally occurring amino acid polymorphisms of the serotonin 5-HT<sub>2A</sub> gene<sup>118</sup> and other 5-HT receptor candidate genes.<sup>119</sup>

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.<sup>120</sup> 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.<sup>27,121</sup>

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,<sup>122</sup> and 5-HT agonists can modulate photic responses of SCN cells.<sup>123</sup> Systemic administration of 5-HT agonists may also shift circadian rhythms,<sup>124</sup> but these effects may occur at the level of the raphe nuclei and may be mediated by other neurotransmitters (such as  $\gamma$ -aminobutyric acid) in the SCN.<sup>125</sup> 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*.<sup>126-128</sup> 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.<sup>129</sup> 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.<sup>130</sup> Cryptochromes, which are photoactive protein pigments in the mammalian retina, are potential candidates for the circadian photoreceptive component.<sup>131,132</sup> Although it now appears that cryptochromes have a more complex role in regulation of circadian rhythm,<sup>133,134</sup> and they are likely not the only photopigments involved in processing the light signal,<sup>135</sup> 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,<sup>136</sup> premenstrual depressive disorder<sup>137</sup> and bulimia nervosa.<sup>138,139</sup>

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