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. [now available for free download at www.UBCsad.ca]

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,

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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. Now available for free download at www.UBCsad.ca

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. Frequently Asked Questions about SAD (patient brochure).
2. Suggestions for Coping with Seasonal Depression (patient handout)
3. Notes on Using the SPAQ and HAM-D
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
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
12. Journal Article: Update on the Biology of SAD, by Chang-Ho Sohn and Raymond W. Lam

HELPFUL WEB SITES

University of BC SAD Information Page
www.UBCsad.ca

Society for Light Treatment and Biological Rhythms
www.sltbr.org

Circadian Lighting Association (light device suppliers)
www.cla.org

Center for Environmental Therapeutics
www.cet.org

Canadian Network for Mood and Anxiety Treatments
www.canmat.org

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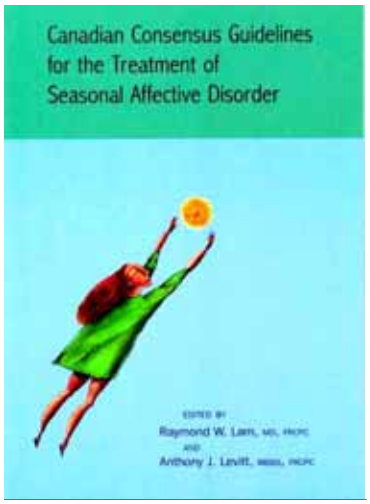

Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder

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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Frequently Asked Questions about Seasonal Affective Disorder (SAD)

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

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?

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 1 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?

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 specially-designed light device results in significant improvement in 60% to 70% of patients with SAD.

How do you use light therapy?

A fluorescent light box is the best-studied light therapy treatment. People 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. Some devices use light-emitting diodes (LEDs) which are longer-lasting and are much smaller and portable than light boxes. 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.

Most light devices use white light. Currently, blue-light devices are NOT recommend because they have not been extensively tested, there is no indication that blue light is better than white light for SAD, and there is no information on long term safety (unlike white light devices). There are some theoretical reasons why blue light may be harmful to the eyes.

What about sun tanning studios?

People are cautioned NOT to use sun 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 and LED lights do not emit ultraviolet wavelengths.

How do I get a light box?

Safe and portable light devices are now commercially available. Ask your doctor, or contact our clinic for more information (or check our web site at www.UBCsad.ca). The cost of a light box is usually between $150 and $300 (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.

Are there side effects to light therapy?

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 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, macular degeneration or diabetes) or taking certain medications (such as thioridazine, lithium or melatonin) should have special eye examinations before considering light therapy.

Are there other treatments for SAD?

Other treatments for depression, including the newer antidepressant medications (e.g., selective serotonin reuptake inhibitors, or SSRIs such as fluoxetine [Prozac], bupropion-XL [Wellbutrin], moclobemide [Manerix], and others) are also effective for patients with SAD and can be used to prevent episodes. Counselling or cognitive-behaviour therapy 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.

What causes SAD and how does light therapy work?

We don't know, exactly, but research shows that light has a biological effect on brain chemicals (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 evidence for a genetic contribution to SAD.

What should I do if I think I have SAD?

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 UBC Hospital (telephone: 604-822-7512), 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.

Can I read more about SAD?

Check our web site at www.UBCsad.ca , or this book:

Winter Blues: Everything you Need to Know to Beat Seasonal Affective Disorder, by Dr. Norman Rosenthal (one of the pioneer researchers in SAD and light therapy). Guilford Press, revised 2005, about $18.00 (Cdn).

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 ½ hour 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; <u>not others</u> 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....

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	**OR**	No particular month(s) stand out as extreme on a regular basis
A. Feel best	O	O	O	O	O	O	O	O	O	O	O	O		O
B. Gain most weight	O	O	O	O	O	O	O	O	O	O	O	O		O
C. Socialize most	O	O	O	O	O	O	O	O	O	O	O	O		O
D. Sleep least	O	O	O	O	O	O	O	O	O	O	O	O		O
E. Eat most	O	O	O	O	O	O	O	O	O	O	O	O	**OR**	O
F. Lose most weight	O	O	O	O	O	O	O	O	O	O	O	O		O
G. Socialize least	O	O	O	O	O	O	O	O	O	O	O	O		O
H. Feel worst	O	O	O	O	O	O	O	O	O	O	O	O		O
I. Eat least	O	O	O	O	O	O	O	O	O	O	O	O		O
J. Sleep most	O	O	O	O	O	O	O	O	O	O	O	O		O

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: ____ ____ ____ **Visit No.:** [1]❑ [2]❑ [3]❑ [4]❑ [5]❑ [6]❑ [7]❑

Patient No.: _____ **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. Worse in: AM PM
2 = Severe.

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 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., LED lights, 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, tanning lamps or halogen 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 6:00 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, macular degeneration, or diabetes), or worries about eye damage, please see your doctor.
12. Some people experience mild headaches, nausea, dizziness 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.

Mood Disorders Centre, UBC Hospital
Vancouver Coastal Health

Tel: 604-822-7512, www.UBCmood.ca
Director: Dr. Raymond W. Lam

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, antidepressant medications) are also effective. Self-diagnosis or self-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 harmful 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.

Most light devices use white light. We do NOT recommend blue-light devices because they have not been extensively tested, there is no indication that blue light is better than white light for SAD, and there is no information on long term safety (unlike white light devices). There are some theoretical reasons why blue light may be harmful to the eyes.

We have no direct financial interest in any companies listed below, nor can we take any responsibility for their products.

British Columbia Suppliers

Shoppers Drug Mart carries a range of light devices. www.shoppersdrugmart.ca

Clinical Sleep Solutions,
www.clinicalsleep.com
Vancouver and other cities
Tel: 1-866-432-9271

VitalAire, www.vitalaire.com
Unit 201-9087B-198th Street
Langley, BC V1M 3B1
Tel: (604) 881-0214

Canadian Direct-Order Suppliers

Up-Lift Technologies, Halifax, NS
www.day-lights.com
Tel: (902) 422-0804 / 1-800-387-0896

Northern Light Technologies, St. Laurent PQ
www.northernlight-tech.com
Tel: 514-335-1763 / 1-800-263-0066

Litebook Company, Medicine Hat, AB
www.litebook.com
Tel: 1-877-723-5481

Apollo Light Systems, Orem, UT (CSA approved)
www.apollolight.com
Tel: 1-800-545-9667

Bio-Brite Inc., Bethesda, MD (CSA approved)
www.biobrite.com
Tel: 1-800-621-LITE

International Direct-Order Suppliers

Circadian Lighting Association
www.claorg.org

March 1, 2007

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-TR), the standard medical classification system published by the American Psychiatric Association, SAD is listed as a *seasonal pattern* course specifier for:

CODE NO.	DIAGNOSIS
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
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Department of Psychiatry, University of British Columbia
Medical Director, Mood Disorders Centre
UBC Hospital, Vancouver Coastal Health
www.UBCmood.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

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. Available at www.UBCsad.ca

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

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	For Optimal Management:
Diagnosis			
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?			
Total:			**All 8 items should be checked YES**
Management – Light Therapy			
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?			
10. Checked for side effects to light therapy?			
11. Checked response to light therapy?			
12. Used a rating scale to check response?			
13. Advised when to stop light therapy in the spring?			
14. Advised when to restart light therapy next season?			
Total:			**At least 10 items should be checked YES:**
Management – Antidepressants (if applicable)			
1. Checked whether antidepressant medication needed?			
2. Used an SSRI (fluoxetine, sertraline) as first-line medication?			
3. Checked side effects/response to antidepressant?			
4. Advised when to stop antidepressant?			
Total:			**All 4 items should be checked YES**
Management – Combined Light Therapy/Antidepressant (if applicable)			
1. Used monotherapy before using combination therapy?			
2. Used combined light therapy/antidepressant?			
3. Checked side effects/response to light therapy/antidepressant?			
Total:			**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.

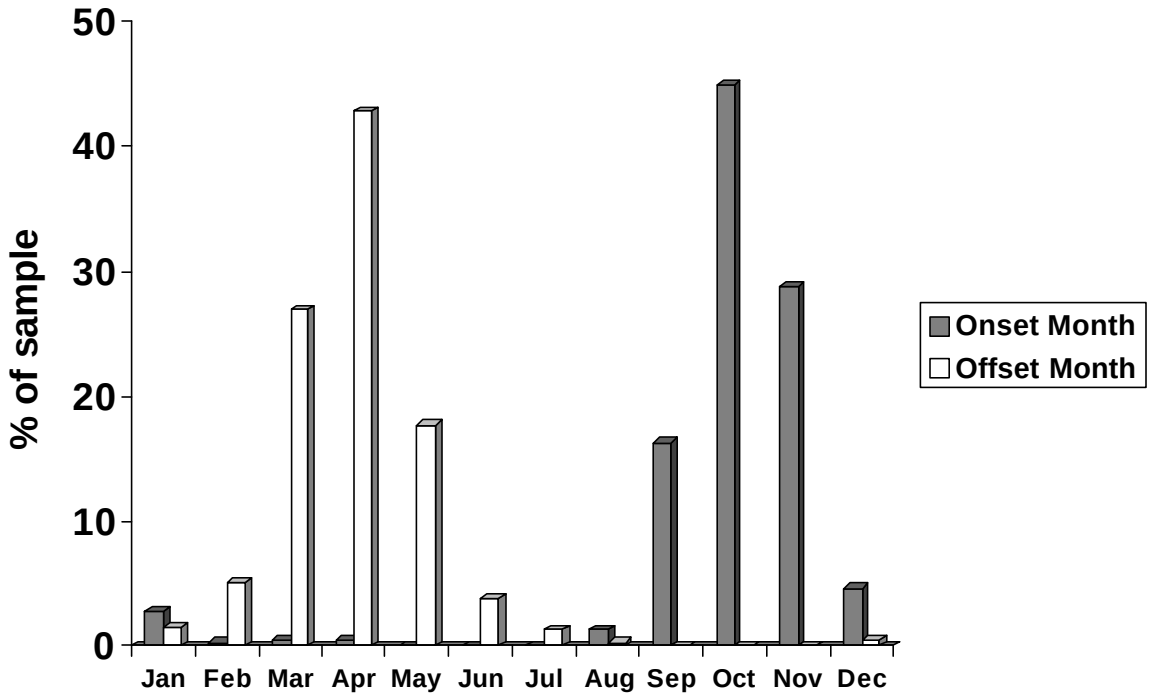
Episode Specifiers	Course Specifiers
With psychotic features	With seasonal pattern
With melancholic features	With postpartum onset
With atypical features	With rapid-cycling
With catatonic features	

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 ± 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 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
(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/

Centre for Environmental Therapeutics

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

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,[1] is considered a clinical subtype of major depression. The criteria for "winter seasonal pattern" in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, which are similar to other definitions of SAD, specify a recurrent pattern of major depressive episodes during winter and remission of symptoms during summer, in the absence of seasonal psychosocial stressors. Using these criteria, the prevalence of SAD has been estimated at less than 1% in the US[2] and at 1% to 3% in Canada.[3] Much of the interest in SAD has been sparked by its response to exposure to bright, artificial light, known as light therapy or phototherapy. Clinical consensus guidelines have recommended light therapy as a first-line treatment for SAD,[4] based on the evidence of numerous studies showing efficacy, including large

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randomized controlled trials[5,6] and meta-analyses.[7,8]

SAD and light therapy were identified from basic studies of circadian and seasonal rhythms in animals. Kripke et al[9,10] had proposed circadian-rhythm hypotheses for nonseasonal depression and first published reports showing that bright light exposure could improve mood in patients with depression. Many seasonal rhythms are mediated through changes in melatonin, a neurohormone secreted by the pineal gland during the subjective night. Melatonin secretion is controlled by the endogenous circadian clock, but it can also be suppressed by exposure to light. In 1980, Lewy et al[11] 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[12] and to the first systematic studies involving patients with SAD.[13] Thus, the theories of the pathophysiology of SAD are intimately tied to the mechanisms of light therapy. This paper reviews the major biological hypotheses for SAD and light therapy, focusing on circadian rhythms, neurotransmitter function, and genetics, and defines important future directions for research.

Circadian rhythms in SAD

Photoperiod and melatonin

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

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

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

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

Circadian phase shift

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

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

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

Another study found that patients with SAD had significantly delayed melatonin rhythms, and the melatonin cycle phase advanced with both morning light alone and morning light in combination with evening light.[36] Morning bright light also significantly phase-advanced cortisol, temperature, and melatonin rhythms in patients with SAD, although the sleep–wake cycle also advanced.[37] The circadian activity–rest cycle was also found to be significantly delayed in patients with SAD.[38]

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

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

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

In the phase-delay hypothesis, evening or mid-day light exposure should not have significant antidepressant effects in SAD. Although morning light is usually statistically superior to evening light in controlled comparisons[6,35] and in most[7,46] but not all[47] meta-analyses, there are large individual studies showing that evening light is more effective than placebo[6] and as effective as morning light.[5,48] In a morning–evening comparison study, the phase position of 6-sulphatoxymelatonin, the

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

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

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

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

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

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

Neurotransmitter function in SAD

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

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

Serotonin

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

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

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

In more recent studies, a tryptophan depletion protocol has been used to examine a possible vulnerability factor for SAD related to the serotonergic system. Plasma tryptophan levels can be reduced to 20% of normal within 5 hours by administering an oral tryptophan-free mixture of large, neutral amino-acids.[61] Positron-emission tomographic studies have shown that serotonin synthesis is reduced markedly in response to this depletion protocol.[62] Two separate studies have shown that patients with SAD in remission after light therapy experience a clear relapse of depressive symptoms with tryptophan depletion.[63,64] In the latter study, "atypical" symptoms such as carbohydrate craving were especially sensitive to the depletion protocol, suggesting an important role for serotonergic mediation of this symptom cluster in particular. These results also point to a serotonergic mechanism for light therapy in SAD. The effects of tryptophan depletion during summer remission, however, are less consistent: one report showed relapse,[65] while another did not.[66] Taken as a whole, tryptophan-depletion studies offer significant evidence that serotonin plays a role in SAD. However, the fact that patients with nonseasonal depression also show sensitivity to tryptophan depletion[67] 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 crossover design, finding similar efficacy for the 2 treatments.[68,69] There was some evidence that relapse after withdrawal from treatment was slower following tryptophan discontinuation.[69] In one sample of patients with SAD that was either partially or completely nonresponsive to light therapy, adding tryptophan (3 g per day) produced a robust response in nine of 14 patients (64%).[70] Given the role of tryptophan in brain serotonin activity, these results support the hypothesis that serotonin plays a role in the pathophysiological features of SAD.

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

trolled studies.[71] Larger studies indicate that the serotonin reuptake inhibitors fluoxetine[72] and sertraline[73] 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[74] and D,L-fenfluramine,[75] although an earlier study with D,L-fenfluramine was negative.[76] Double-blind, placebo-controlled studies indicate that, compared with normal controls, patients with SAD had blunted hormonal responses, and experienced increased subjective activation/euphoria responses, following administration of the postsynaptic 5-HT_{2C} agonist m-chlorophenylpiperazine (m-CPP),[77,78] thereby confirming results from previous non-placebo-controlled studies.[79–81] There was a normalization of the subjective responses following successful light therapy, suggesting that activation/euphoria in response to a post-synaptic serotonergic agent may be a state marker for winter depression, mediated by an alteration in the sensitivity of post-synaptic serotonin receptors.[77] These various findings may be relatively specific for SAD, in that patients with major depression do not show altered responses to m-CPP challenge.[82] m-CPP also has some affinity for other receptors, including 5-HT_{1A} and 5-HT_7; however, no behavioural or neuroendocrine effects were found in a challenge study with ipsapirone, a selective 5-HT_{1A} receptor agonist.[83] Blunted growth hormone responses to the 5-HT_{1D} agonist sumatriptan were also reported in SAD, with normalization after light therapy.[84]

In summary, there are consistent, replicated studies of abnormal neuroendocrine and behavioural responses to serotonergic agents that indicate dysfunction at, or downstream to, 5-HT receptors in SAD. Most of the evidence implicates 5-HT_{2C} or 5-HT_7 receptors, although other receptors such as 5-HT_{1D} may be involved.

Norepinephrine

To determine whether serotonin dysfunction alone can explain the pathophysiology of SAD, Neumeister et al[85] administered both tryptophan depletion and catecholamine depletion protocols, in random order, to patients with SAD in remission after light therapy. Sham depletions were also included in the protocol. Both active depletions caused a temporary relapse of depressive symptoms, demonstrating that catecholamines, in addition to serotonin, likely play a role in SAD.

Clinically, patients with SAD frequently present with core symptoms of hypersomnia and increased eating, in contrast to patients with classic melancholic depression, who exhibit insomnia and weight loss when depressed. One possible interpretation of this difference is that patients with SAD are in a state of central hypo-arousal, while those with melancholic depression are in a state of central hyper-arousal. Several research findings are consistent with this hypothesis. Untreated patients with SAD tended to have lower baseline norepinephrine concentrations than normal controls, and than after light treatment.[77] In this same study, patients with SAD had blunted norepinephrine responses to the serotonin and α_2-noradrenergic agonist m-CPP, both with and without light therapy treatment. Other studies have found an increase in both plasma norepinephrine levels[86] and in turnover of norepinephrine[87] following light therapy. An inverse relation between resting cerebrospinal fluid levels of norepinephrine metabolites and depression scores in patients with SAD has also been reported.[88]

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

Dopamine

Few studies have directly examined dopamine functioning in patients with SAD; however, several lines of indirect evidence point to dopaminergic involvement in this disorder. Low resting prolactin levels have been interpreted as reflecting low functional activity of dopamine, with compensatory up-regulation of D_2 receptors, in patients with SAD.[89,90] This decrease was evident across seasons and was unaffected by subtype of depression (bipolar II versus unipolar) , suggesting that it may be a trait marker for the disorder.[90] This same group has found decreased eye blink rates, which may reflect low dopamine activity, in subjects with SAD,[91] although other groups have not replicated this finding.[92] Additional evidence for dopamine dysfunction in SAD comes from studies that have examined thermoregula-

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

Dopamine is the major retinal transmitter involved in the light response. Oren[95] has speculated that light therapy might work in SAD by stimulating the production of retinal dopamine. There is some evidence from retinal electrophysiological studies for subtle reductions in retinal light sensitivity, which can be reversed with light therapy, in patients with SAD compared with controls.[96–99] In contrast, another study using a dark adaptation threshold procedure has shown supersensitivity to light in winter in patients with SAD compared with control subjects.[100] Still other studies using different electrophysiological methods have not found changes in retinal or ophthalmic function.[101,102] Hence, there is not yet consistent evidence of retinal dopamine or other retinal dysfunction in SAD.

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

It has recently been reported that adults with residual attention-deficit disorder, particularly women with impulsive characteristics, have very high seasonality scores.[104] One of the classic models of attention-deficit disorder proposes that, in particular, the impulsive subtype of this disorder is mediated by a state of central under-arousal; this would explain the robust therapeutic effects of psychostimulants (primarily dopaminergic drugs) in attention-deficit disorder.[105] It has also been speculated that the core symptoms of SAD may reflect a state of low central arousal.[106] It is thus interesting to speculate whether patients with "seasonal" attention-deficit disorder might be in a state of chronic under-arousal mediated by low dopamine activity, compounded by light-deprivation and a further decrease in dopamine activity in the fall/winter months. Interestingly, recent neuroimaging studies have found global decreases in cerebral metabolism in both attention-deficit disorder[107] and in SAD[108] that are consistent with such a model.

Genetics in SAD

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

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

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

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

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

Genetic association studies of SAD have begun to emerge. An association between the short allele of the serotonin transporter promoter gene and the trait of seasonality was reported in a sample of 97 patients with SAD and 71 controls.[115] In a similar study, an association was found between SAD (but not seasonality *per se*) and the 5-HT_{2a} promoter polymorphism –1438G/A.[116] An association between the 218C allele of tryptophan hydroxylase and SAD in a small sample of female patients with increased eating behaviour was also found.[117] In contrast, Ozaki et al reported a lack of association between SAD and naturally occurring amino acid polymorphisms of the serotonin 5-HT_{2A} gene[118] and other 5-HT receptor candidate genes.[119]

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

Future directions

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

The major hypotheses proposed for SAD include phase-shifted circadian rhythms, serotonergic dysfunction, and genetic vulnerability. It should be recognized, however, that these hypotheses may not be mutually exclusive. Recent findings have highlighted important relations between serotonin and circadian rhythms. Direct and indirect serotonergic projections from the midbrain raphe nuclei are involved in the nonphotic signalling to the SCN,[122] and 5-HT agonists can modulate photic responses of SCN cells.[123] Systemic administration of 5-HT agonists may also shift circadian rhythms,[124] but these effects may occur at the level of the raphe nuclei and may be mediated by other neurotransmitters (such as γ-aminobutyric acid) in the SCN.[125] Serotonergic pathways are also likely involved in SCN projections to effector systems, including the hypothalamus, where regulation of neuroendocrine and sleep–wake functions occur. Further studies to link serotonergic dysfunction with dysregulated circadian rhythms in SAD will likely be informative.

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

In an elegant closing of the circle, basic studies of mammalian circadian rhythms gave rise to the study of SAD and light therapy; a decade and a half later, basic molecular science will offer sophisticated new circadian hypotheses to be tested. However, attention should also focus on the noncircadian effects of bright light. Further study of noncircadian effects is particularly important, since light therapy is being investigated for other psychiatric disorders that may not involve circadian mechanisms, including nonseasonal depression,[136] premenstrual depressive disorder[137] and bulimia nervosa.[138,139]

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Update on the Biology of Seasonal Affective Disorder

By Chang-Ho Sohn, MD, and Raymond W. Lam, MD, FRCPC

Needs Assessment

A comprehensive review of studies on the pathophysiology of seasonal affective disorder (SAD) was published in 2000. Since then, researchers have documented many new findings that clarify several biological hypotheses in SAD, including studies of circadian rhythms, neurotransmitter function, and molecular genetics. Clinicians will be better able to diagnose and treat patients with SAD by understanding these latest theories of the biology of SAD.

Learning Objectives

At the end of this activity, the participant should be able to:

- Compare and contrast the evidence to support circadian rhythm theories of SAD.
- Describe the data supporting neurotransmitter theories of SAD.
- Summarize the findings from gene association studies of SAD.
- Identify methodological and integrative issues in the biological study of SAD.

Target Audience

Neurologists and psychiatrists

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Read this article, and the two CME-designated accompanying articles, reflect on the information presented, and then complete the CME quiz found on pages 672 and 673. To obtain credits, you should score 70% or better. Termination date: August 31, 2007. The estimated time to complete this activity is 3 hours.

ABSTRACT

The etiology and pathophysiology of seasonal affective disorder (SAD) has been linked to the seasons and to light since its first conceptualization. Aspects of SAD that make it particularly amenable to biological investigation include the predictable recurrent episodes, the rapid response to a nonpharmacologic treatment, the specific neurovegetative features, and the availability of rich animal models of seasonality. This paper reviews new findings for the major biological hypotheses for SAD, focusing on circadian rhythms, neurotransmitters, and molecular genetics. Integrative issues and future directions for the study of SAD, including the heuristic value of a dual-vulnerability hypothesis that conceptualizes seasonality as a dimensional construct and the importance of studying endophenotypes, will be discussed.

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INTRODUCTION

All living organisms are influenced by the seasons. The degree of seasonal change in mood and behavior is termed "seasonality"[1] while seasonal affective disorder (SAD) is usually considered to be at the extreme end of the spectrum of seasonality.[2] In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,[3] winter SAD is concep-

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tualized as a seasonal pattern of recurrent major depressive episodes during the fall/winter in the absence of seasonal psychosocial stressors, with full remission of symptoms in spring/summer. This seasonal pattern can be applied to both unipolar major depressive disorder (MDD) and bipolar disorder.

Based on *DSM* criteria, the prevalence of SAD in epidemiological studies has been estimated at 0.8% to 2.8% in North America,[4,5] but the prevalence of significant seasonality (or "subsyndromal SAD") is likely much higher, with estimates of 15% to 25% in the global population.[6] In addition to seasonality, SAD has two prominent characteristics: so-called atypical depressive symptoms and responsiveness to light treatment. Most patients with SAD experience atypical symptoms including increased need for sleep, carbohydrate craving with increased appetite and weight, and extreme fatigue. These symptoms, which are similar to seasonal changes in behavior shown by many mammals in response to winter, might be a human expression of a basic evolutionary process to achieve maximum conservation of energy during winter.[7] The other important characteristic of SAD is the response to exposure to bright light, known as light therapy or phototherapy.

There are four specific aspects to SAD that make it particularly of interest for biological investigation. The first is the seasonality of the condition. The predictable onset and offset of winter episodes allow the investigation of biological parameters at different stages of the disorder, from acute illness to natural remission and vice versa. The second aspect is the rapid response to light therapy. This nonpharmacologic treatment allows comparison of the treated state to the natural, untreated summer remission state. The third aspect is the specificity of the neurovegetative symptoms of SAD (eg, extreme fatigue, hypersomnia, and increased appetite). These symptoms contrast to those of other types of mood disorders (eg, melancholic depression) and may be especially important when comparing SAD to other psychiatric conditions in which similar symptoms are prominent, such as atypical depression and certain sleep and eating disorders. Finally, there is a rich abundance of animal models of seasonality to develop and test specific biological hypotheses about SAD.

In 2000, Lam and Levitan[8] comprehensively reviewed the pathophysiology of SAD focusing on evidence for and against the major hypotheses: circadian rhythms, neurotransmitter function, and genetics. In the current article, we update the review with new data from the past 5 years of studies of SAD and its response to light therapy. We also highlight some important integrative issues and future directions for the study of SAD and seasonality.

CIRCADIAN RHYTHMS

In humans, the central pacemaker that entrains internal circadian rhythms to synchronize with external time cues (zeitgebers) is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Light, the most powerful zeitgeber, is conveyed to the SCN through the eyes via the retinohypothalamic tract. A complex neural pathway links the SCN to the pineal gland, where melatonin is secreted under influence of both the SCN (a circadian mechanism) and external light exposure (a direct suppression effect). In many animals, melatonin is a mediating hormone between light and seasonal behavior.

Melatonin displays a robust circadian rhythm with high levels secreted at night and low plasma levels present during the day. The circadian rhythm phase of melatonin can be described by the usual time at which the melatonin level begins to rise at night, usually around 8:00 PM, collected under dim light conditions to prevent any direct suppressant effects of light exposure. This is known as the dim light melatonin onset (DLMO).

Light can predictably shift circadian rhythms, with the direction and magnitude of phase shift dependent on when the light exposure occurs in the circadian cycle. For example, bright light exposure in the late evening can delay the circadian rhythm of melatonin (ie, the DLMO occurs at a later time each day, such as 10:00 PM), while morning light exposure results in phase advance of the melatonin rhythm (ie, the DLMO occurs at an earlier time than usual, such as 8:00 PM) (Figure 1). The phase shift of one circadian rhythm (eg, melatonin) can change the time interval to another circadian rhythm (eg, sleep-wake cycle), the so-called phase angle. Figure 1 illustrates an example of phase shift of DLMO causing a change in phase angle with waking time.

Circadian rhythm theories,[2] including photoperiod and phase-shift hypotheses, initiated the study of SAD and the use of light treatment in depression and other psychiatric conditions. These hypotheses remain prominent in the pathophysiology of SAD and seasonality, but there are also other recent circadian findings in SAD,[9,10] such as disturbances in thermoregulation and electroencephalographic slow-wave sleep.

Photoperiod Hypothesis

Rosenthal and colleagues[2] first suggested that the shorter winter photoperiod (light/dark cycle) might induce depression. There have been three lines of investigation to verify the photoperiod theory.[11] The first involves studies correlating the prevalence of SAD with increasing latitude, since photoperiod is directly influenced by latitude (eg, the winter days are shorter at more northerly latitudes). The results of numerous epidemiological studies have been inconsistent, in part due to methodological limitations of the various studies. The most rigorous studies[4,11] did not find correlations of prevalence of SAD with latitude, although the range of latitude studied was small. Reviews[6,12] summarizing the more methodologically sound studies have shown that there does appear to be a relationship between SAD and latitude, but this effect is complex and relatively weak.

Since melatonin is only secreted in the dark, the duration of melatonin secretion acts as a signal for photoperiod for many mammalian circadian systems.[13] Previous studies[8] of melatonin as a hormonal indicator of photoperiod showed conflicting results in SAD. Recently, Wehr and colleagues[14] measured the duration of melatonin secretion in constant dim light in 55 patients with SAD and matched healthy control subjects. While there were no significant differences in the duration of melatonin secretion between the two groups in winter, the patients with SAD had a significant seasonal variation with longer melatonin duration in winter than in summer. This suggests that only people with SAD respond to photoperiod in a manner similar to other mammals, while healthy people seem to have lost this seasonal time signal. Potential mechanisms to explain this finding include seasonal differences in the experience of natural or artificial light exposure,[15,16] differences in retinal sensitivity to light,[17-19] or differences within the neural pathways of the circadian system (eg, abnormal clock genes).

The third line of investigation involves the mechanism of light treatment, specifically whether photoperiod extension by artificial light is necessary to treat SAD.[2] One meta-analysis[20] of light therapy studies found that morning-plus-evening light (a photoperiod extension schedule) was superior to single exposures at other times of the day. Other meta-analyses,[21-23] however, indicate that morning light exposure is superior to evening light, which initially seems to refute the photoperiod extension hypothesis. An alternative interpretation is that morning light may still act to extend the photoperiod by truncating early morning melatonin secretion and reducing the overall melatonin duration.

Phase-Shift Hypothesis

In contrast to photoperiod, the phase-shift hypothesis as first proposed by Lewy and colleagues[24] states 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. According to this hypothesis, light therapy exerts its effect by correcting the abnormal phase delay. Morning light exposure that results in phase advance of circadian rhythms should therefore show superior effectiveness to that of evening light, which induces a further phase delay.

The phase-delay hypothesis has proven to be one of the most robust theories of SAD, but also, because of some conflicting findings, the most controversial. In part, this is due to the difficulty in studying circadian rhythms in humans due to masking effects of external zeitgebers including light exposure, sleep, and activity. As previously reviewed,[8] no phase differences were observed in patients with SAD in 24-hour rhythms of melatonin, cortisol, prolactin, thyrotropin, and body temperature,[25-27] although these rhythms may be influenced by masking effects. Studies[28-31] using the DLMO, a marker of circadian phase that is relatively

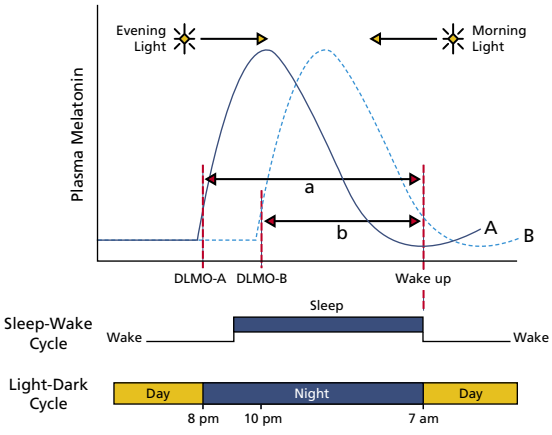

FIGURE 1. Schematic diagram of circadian rhythms of melatonin and sleep-wake cycles*

* Phase of the melatonin cycle (A) is represented by DLMO-A, while the phase of the sleep-wake cycle is represented by the wake-up time. The phase angle between the melatonin and sleep-wake cycles is represented by the time interval between DLMO-A and wake-up time (a). Light exposure in evening results in a phase delay of the melatonin rhythm (B), as measured by DLMO-B. If wake-up time remains constant, then the phase-delayed melatonin rhythm results in a smaller phase angle with the sleep-wake cycle (b). A phase-delayed rhythm can be corrected using morning light exposure, which causes a phase-advance of circadian rhythms.

DLMO-A=dim light melatonin onset for melatonin rhythm A; DLMO-B=dim light melatonin onset for melatonin rhythm B.

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free from masking effects,[28] have more consistently found evidence for phase delays in SAD.[29-31]

Other studies using specific techniques to study endogenous circadian rhythms in SAD have had mostly negative results.[30-35] In studies using constant routine protocols that rigorously control for masking effects, one study[32] found phase delays in body temperature, DLMO, and cortisol rhythms in 6 female patients with hypersomnic SAD studied in winter, while the other did not find any significant phase differences.[33] Forced desynchrony studies,[34,35] in which 20-hour sleep-wake cycles are imposed on subjects thereby unmasking the endogenous circadian rhythm, also found no differences in 7 patients with SAD compared with controls studied in winter and summer. However, one patient did show significant phase-delayed circadian rhythms,[36] suggesting that there may be inter-individual variation in SAD. Given that examining endogenous circadian rhythms requires technically demanding and/or resource-intensive methods, only small numbers of patients are usually studied. Hence, patient selection is particularly important in these small-sample studies and may explain some of the negative findings.

Similarly, there have been conflicting results in the effects of light therapy on phase changes in SAD. The phase-shift theory rests on two necessary components of treatment—that a corrective phase advance of circadian rhythms should occur and that the phase advance should be correlated with the antidepressant effect. In support of the first component, most studies and meta-analyses[21-23] have shown that morning light exposure results in the phase advance of circadian rhythms and is more effective than light at other times of the day. However, there are conflicting results for the second component: a correlation between the phase advance and antidepressant effect. [31,32,37,38] For example, some previous studies[31] have found that clinical improvement was correlated with degree of phase advance while others have not.[32,37,38]

Recent light therapy studies,[39] however, have provided more evidence to support the phase-shift hypothesis. Terman and colleagues[39] sampled the DLMO in 42 patients with SAD before and after light therapy. They found that the magnitude of phase shifts depended on the phase angle from the DLMO to the time of light exposure, with responses to morning light increasing with the size of the phase advance. An optimal time for administration of morning light was found to be 8.5 hours after the DLMO or 2.5 hours from the midpoint of sleep duration.

Another study[40] involved 26 patients with SAD who had rectal core body temperature monitoring during a light therapy protocol. In this study, the degree of phase advance in core body temperature was only weakly correlated with antidepressant response, although there appeared to be an optimal phase angle for response occurring when the wake time was ~3 hours from the nocturnal temperature minima.

Melatonin, administered at an appropriate time in the evening to achieve a circadian phase-advance, can also be used to examine the phase-shift hypothesis. A pilot study[41] showed that low-dose melatonin administered in the evening was effective in SAD, but a subsequent larger study (N=100 patients with SAD)[42] found no overall treatment differences between morning and evening dosing of melatonin and a placebo pill condition. However, a post hoc analysis[42] showed that the patients who were most phase delayed at baseline responded to a corrective phase advance by melatonin and that the best responses occurred when patients achieved an optimal phase angle in which the DLMO occurred ~14 hours from wake time.[42]

In summary, there is substantial evidence to support that some, but not all, patients with SAD have phase-delayed circadian rhythms that can be corrected by appropriately timed circadian interventions (melatonin or bright light exposure) with resultant improvement in depressive symptoms. However, there is also evidence indicating that other people with SAD have beneficial effects of light therapy independent of circadian phase-shifting effect.

NEUROTRANSMITTERS

Since SAD is a subtype of major depression, there has been much interest in studying the major neurotransmitters of interest in depression, namely serotonin (5-HT), noradrenaline, and dopamine. There has been special interest in 5-HT, given the abundant evidence that seasonal variation of brain and peripheral 5-HT occurs in healthy people. For example, recent studies found that both 5-HT turnover[43] and availability of hypothalamic 5-HT transporter sites, as measured by single photon emission computed tomography,[44] are lower in winter than in summer.

In SAD, past studies[8] of metabolites of 5-HT and catecholamines in peripheral blood and cerebrospinal fluid were inconclusive. More consistent results were found in neuroendocrine challenge studies, in which blood levels of hormones are measured after administering a drug that acts on specific receptors that control secretion of that hormone. Studies using primarily serotonergic drugs acting on various 5-HT receptors consistently showed evidence for serotonergic receptor dysfunction in

SAD.[45] However, there are problems with interpreting the results of neuroendocrine challenge studies. For example, they are only indirect measures of brain function since they involve the pituitary gland which is outside the blood-brain-barrier. Also, they only provide correlative measures, since there is no way to determine whether any receptor dysfunction is directly related to SAD symptoms, or whether they are merely epiphenomena of the illness.

More recent investigations focus on monoamine depletion protocols in which brain monoamines can be experimentally manipulated to determine whether changes lead to depressive symptoms, thereby giving a more direct means of linking neurotransmitter function to behavior.[46] For example, tryptophan depletion studies are conducted on the understanding that tryptophan is the dietary amino acid precursor for conversion to 5-HT in the brain. When a mixture containing large amounts of amino acids without tryptophan is ingested, the ensuing increase in liver enzyme metabolism can temporarily reduce the blood levels of free tryptophan by ≥80% within 5 hours. Animal studies and neuroimaging studies in humans show that brain 5-HT is reduced by a similar magnitude using this procedure.[47,48] This technique has been widely used in studies investigating mechanisms of antidepressant action and the neurobiology of nonseasonal depression.[49,50]

In the study of untreated, symptomatic patients with SAD,[51] tryptophan depletion did not exacerbate the depressive symptoms in winter, similar to findings in nonseasonal depression. However, in patients with SAD in short-term clinical remission with light therapy, Lam and colleagues[52] first reported that tryptophan depletion induced relapse of depressive symptoms, thereby reversing the effect of light therapy, a finding subsequently replicated by two independent groups.[53,54] Interestingly, atypical symptoms like carbohydrate craving were most sensitive to the tryptophan depletion protocol, implicating the role of 5-HT in the development of these symptoms. During the natural summer remitted state, tryptophan depletion studies produced mixed findings; two studies[55,56] reported significant relapse of symptoms while another[57] did not. A preliminary report[58] also found that patients with SAD who showed relapse with tryptophan depletion in summer were more likely to experience a depressive episode in the following winter, suggesting that tryptophan depletion may predict risk for SAD.

Similarly, depletion of brain catecholamines can be accomplished using α-methyl-para-tyrosine (AMPT), an inhibitor of tyrosine hydroxylase that decreases synthesis of dopamine and noradrenaline.[46,59,60] In a study by Neumeister and colleagues,[54] tryptophan depletion and catecholamine depletion each induced relapse of symptoms in patients with SAD in remission with light treatment, indicating that light therapy may act through several neurotransmitters. Patients in summer remission also showed robust relapses with catecholamine depletion, suggesting that dopamine and/or noradrenaline dysfunction is directly involved in the pathogenesis of winter depression.[61] Of note in this regard is that reboxetine (a selective inhibitor of noradrenaline reuptake) and bupropion (an inhibitor of noradrenaline and possibly dopamine reuptake) may be beneficial treatments for SAD.[62,63]

Other studies[19,64,65] also support dopamine involvement in SAD. Electroretinography (ERG) is a method to assess retinal function in light- and dark-adapted states that involves dopamine as the mediating neurotransmitter. ERG studies[19] found evidence of reduced b-wave amplitude consistent with decreased retinal dopaminergic activity in SAD. A neuroimaging study[64] using $^{[123]}$β-carbomethoxy-3beta-(4-iodophenyl) tropane single-photon emission computed tomography showed decreased availability of striatal dopamine transporter binding sites in symptomatic patients, although another similar study also found evidence of reduced brain 5-HT transporter sites in patients with SAD.[65]

GENETICS

Much of the recent activity in the biological investigation of SAD has involved the pursuit of genetic mechanisms through different approaches including family studies, twin studies, and candidate gene association studies.[66-74] provided evidence for hereditary factors in both SAD and seasonality (Table 1). In family history studies,[66-70] 25% to 67% of patients with SAD had a positive family history of affective illness while 13% to 17% had first-degree relatives with SAD. These rates are significantly higher than expected from population prevalence studies.[71] However, no significant differences in psychiatric disorders among first-degree relatives were found in patients with SAD compared with those with nonseasonal depression.[66,72]

Although there are no twin studies involving SAD, per se, there have been two studies of seasonality (Table 1).[73,74] In Australia, Madden and colleagues[73] conducted volunteer-based twin studies with 4,639 adult twins and reported that genetic effects accounted for 29% of variance in seasonality scores. A similar twin study in Canada[74,75] found greater heritability for seasonality scores, accounting for 45% to 69% of the total variance, perhaps because the phe-

notypic expression of seasonality is greater at higher latitudes. These and the family history findings indicate that SAD and seasonality has robust heritability. Of course, signals from family history and twin studies must be further investigated using molecular genetic analyses, which has been the most active area for SAD research in the past 5 years. Formal genetic linkage studies for complex conditions, such as SAD, are limited by low power and poor feasibility, therefore, the focus has been on case-control association studies of candidate genes (Table 2).

Obvious candidate genes include genes involved in the 5-HT system. Several studies[77-81] examined the 5-HT transporter promoter repeat length polymorphism (5-HTTLPR) after Rosenthal and colleagues[77] and Sher and colleagues[78] first reported that the short variant allele of the 5-HTTLPR was associated with SAD and seasonality. Unfortunately, other studies[79,80] could not replicate this finding. Johansson and colleagues[81] subsequently conducted a pooled analysis of all three studies (including the original sample) that also failed to find an association between 5-HTTLPR and SAD. However, that report did show a difference in 5-HTTLPR genotypes between high and low seasonality groups in a separate population-based sample.[81]

There are several reports of positive findings with the 5-HT_{2A} gene, including increases in the frequency of the 102C allele[82] and the -1438A allele of the 5-HT_{2A} gene,[83] and an association of the 102T/C genotype with childhood attention deficit disorder.[84] However, there are also negative studies involving 5-HT_{2A} genes[79,85] and other 5-HT-related genes (Table 2).[73]

It may be more worthwhile to investigate the

TABLE 1. FAMILY HISTORY AND TWIN STUDIES IN SAD

Author(s) (Year)	Type of Study	Sample	Results
Rosenthal et al[75] (1986)	Family history	7 children with SAD	5 of 7 children with SAD had a parent with SAD.
Thompson et al[70] (1988)	Family history	51 patients with SAD	25% and 14% of SAD patients had a positive history in first-degree relatives of affective illness and SAD, respectively.
Lam[68] (1989)	Family history	46 patients with SAD	64% and 13% of SAD patients had a positive history in first-degree relatives of affective illness and SAD, respectively.
White et al[69] (1990)	Family history	61 patients with SAD	66% of SAD patients had family members with nonseasonal depression, SAD or alcohol abuse.
Allen et al[66] (1993)	Family history	34 patients with SAD; 34 matched nonseasonal depressed patients	27% of SAD patients had first-degree relatives with mood disorders. No differences were found in family histories between SAD and nonseasonal depression.
Sasaki et al[76] (1998)	Family history	129 small families from the general population in Japan	No association between children and biological parents in seasonal changes of sleep and eating behaviour.
Stamenkovic et al[72] (2001)	Family history	36 patients with SAD; 36 matched nonseasonal depressed patients	No differences in the lifetime prevalence for psychiatric disorders among the first-degree relatives in both groups (SAD=16.5% and nonseasonal depression=19%).
Madden et al[73] (1996)	Twin	4,639 adult twins from a volunteer-based registry in Australia	Genetic effects accounted for at least 29% of the variance in seasonality scores.
Jang et al[74] (1997)	Twin	339 adult twins from a volunteer-based registry in Canada	Genetic effects in men and women accounted for 69% and 45% of the variance in seasonality scores, respectively.

SAD=seasonal affective disorder.

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genetics of specific endophenotypes of SAD.[86] For example, differences in 5-HTTLPR have been associated with comorbid premenstrual depressive disorder[87] and self-directedness scores on personality testing[88] in some patients with SAD. Furthermore, Levitan and colleagues[89] studied a putative endophenotype of SAD, women with carbohydrate craving and hyperphagia or binge-eating, and its relationship with the 7R allele of the D4 dopamine receptor gene (DRD4). The 7R allele was not associated with the diagnosis of SAD, per se, but instead was associated with a history of childhood attention-deficit disorder and higher body mass index;[89] moreover, this association appeared to be mediated through binge eating behavior.[90]

Another candidate gene comes from the guanine nucleotide-binding (G-protein) system that is involved in postsynaptic signal transduction and which has been of significant interest in nonseasonal depression.[91] There is some evidence for G-protein dysfunction in SAD, as one study[92] found that patients with SAD had decreased levels of Gβ-subunit in peripheral leukocytes. A single nucleotide polymorphism (C825T) in the Gβ3-subunit gene has been shown to influence intracellular response to G-protein-coupled stimuli[93] and an association of the T allele with nonseasonal affective disorder has been reported.[94] In SAD, one study[95] found that patients were more likely than control subjects to carry the T allele of the Gβ3-subunit gene polymorphism, but there was no association of the polymorphism with seasonality scores. Unfortunately, another study[96] did not replicate these findings.

Circadian clock genes are also of significant interest given the prominence of circadian rhythm hypotheses for SAD. In animal studies, mutations in clock and period genes result in altered circadian rhythms.[97-99] Johansson and colleagues[81] conducted a study for potential association between polymorphisms in clock-related genes (clock, period2, period3, and NPAS2 and SAD, seasonality and diurnal preference. They found a significant difference between patients with SAD and control subjects in NPAS2 471 Leu/Ser, indicating a recessive effect of the leucine allele on disease susceptibility.[100] Period3 647 Val/Gly was also associated with scores on self-reported morningness-eveningness (a measure of diurnal preference) with higher scores found in individuals with at least one glycine allele. However, none of the polymorphisms in this study were associated with seasonality in the SAD case-control material.

In summary, there are a number of positive findings in gene association studies involving serotonin-, dopamine-, G-protein- and clock-related genes. Association studies are susceptible to false positive results, so replication of these results will be important. For example, initial enthusiasm for an abnormality in 5-HTTLPR was not confirmed in subsequent pooled analyses.

INTEGRATIVE ISSUES AND FUTURE DIRECTIONS

There has been considerable progress in studying the biology of SAD, but many findings require replication and there continue to be conflicting results that need to be explained. It is now widely recognized that there must be heterogeneity in SAD similar to that seen in nonseasonal depression. One possibility is that the clinical presentation of SAD represents a final common pathway with multiple etiologies that contribute to heterogeneity when examining groups of patients. This may be especially true for circadian hypotheses, since there is great interindividual variability in circadian phase position and phase shifts produced by circadian interventions. Hence, averaging group data, especially in small-sample studies, may not reflect the endogenous circadian rhythms in a subset of subjects. Similarly, circadian treatments given at the same clock time may produce very different phase-changes between individuals, depending on their starting circadian phase at baseline.

Another explanation for this heterogeneity may be related to the inadequacies of the current definition of SAD as a subtype of depression. Considering seasonality as a dimensional construct instead of a categorical diagnosis may be more informative in understanding biological mechanisms. In this regard, a dual-vulnerability hypothesis, first proposed by Young and colleagues[101] and subsequently extended by Lam and colleagues,[102] posits distinct factors associated with seasonality and depression. Differential loading of each factor within an individual may explain some of the different presentations of seasonality. For example, a person with high loadings on a seasonality factor coupled with moderate loadings on a depression factor may present as having SAD, whereas someone with low seasonality and high depression may present with a nonseasonal depressive episode.[102] Other differences in loading on the two factors may result in different clinical presentations such as subsyndromal SAD (high seasonality, low depression) and "seasonal" MDD (ie, winter worsening of nonseasonal MDD [high seasonality, high depression]).

There may be separate biological mechanisms involved with each factor so that, for example, the

seasonality factor may be due to an underlying circadian disturbance while the depression factor may be caused by serotonergic or dopaminergic dysfunction (or, as proposed by Young and colleagues,[101] by cognitive distortions). Since patients with SAD may have different loadings of the two factors, some

TABLE 2. GENETIC ASSOCIATION STUDIES IN SAD

Author(s) (Year)	Gene Studied (Polymorphism)	Sample	Results
Ozaki et al[84] (1996)	5-HT_{2A} (T102C, Ala447Val, C516T)	50 patients with SAD; 62 control subjects	No associations found.
Enoch et al[82] (1999)	5-HT_{2A} (-1438G/A)	67 patients with SAD; 69 control subjects	Increase in frequency of the -1438A allele in patients with SAD; No association between -1438G/A and seasonality scores.
Arias et al[81] (2001)	5-HT_{2A} (T102C)	159 patients with SAD and nonseasonal depression; 164 control subjects	Genotype distributions were different between SAD and nonseasonal depressed patients; 102C-allele carriers were more frequent in the patients with SAD.
Levitan et al[83] (2002)	5-HT_{2A} (T102C)	66 women with SAD	T102C genotypes associated with childhood attention-deficit disorder.
Sher et al[71] (1999)	5-HT_{1A} (Gly22Ser, Ile28Val), 5-HT_{1D} (T1350C), 5-HT_{1B} (C861G), 5-HT_{1E} (C531T), 5-HT_{2C} (Cys23Ser)	74 patients with SAD; 80 control subjects	No associations found.
Han et al[103] (1999)	TPH (T1095C)	72 patients with SAD; other patients with psychiatric disorders	No associations found.
Lenzinger et al[104] (1999)	5-HTT gene	18 patients with SAD; matched control subjects	No differences genotypes in patients with SAD; no correlation with depression scores after tryptophan depletion.
Rosenthal et al[77] (1998)	5-HTTLPR (long/short)	97 patients with SAD; 71 control subjects with low seasonality scores.	5-HTTLPR short allele was more prevalent among patients with SAD.
Sher et al[78] (1999)	5-HTTLPR (long/short)	209 healthy subjects	5-HTTLPR short allele associated with higher seasonality scores.
Johansson et al[79] (2001)	5-HTTLPR (long/short), 5-HT_{2A} (-1438G/A, 45His/Tyr), 5-HT_{2C} (23Cys/Ser), TRH (218A/C), White (2457G/A)	82 patients with SAD; 82 matched control subjects	No associations with SAD or seasonality and the genotypes of these genes.
Praschak-Reider et al[87] (2002)	5-HTTLPR (long/short)	44 women with SAD and PMDD; 43 women with SAD without PMDD	Long/short allele-heterozygosity was associated with presence of PMDD in patients with SAD.
Willeit et al[80] (2003)	5-HTTLPR (long/short)	138 patients with SAD; 146 control subjects with low seasonality	No difference in genotype distribution and short allele frequency in patients with SAD. Melancholic depression was associated with the long allele and atypical depression with the short allele

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circadian and neurotransmitter studies may show positive results while others may not. Studying the phenomena of seasonality and subsyndromal variants may thus be informative for SAD. For example, some investigators[105] have shown that seasonality (ie, lowering of mood in winter) is associated with circadian phase delay and that subsyndromal SAD is associated with changes in retinal light sensitivity on ERG,[106] similar to findings in patients with SAD.

A major advantage of studying seasonality is in the multitude of animal models available to study seasonal changes in behavior. An example of capitalizing on an animal model is the study of neuroimmune function. There is substantial evidence from animal studies[107] showing that melatonin mediates seasonal changes in the immune system and seasonal variations in immune function have also been reported in humans.[108,109] Other studies[110] indicate that (nonseasonal) depression and immune function can influence each other bi-directionally via inflammatory cytokines. Thus, it is possible that the symptoms of SAD result from

TABLE 2. GENETIC ASSOCIATION STUDIES IN SAD *(continued from page 642)*

Author(s) (Year)	Gene Studied (Polymorphism)	Sample	Results
Johansson et al[81] (2003)	5-HTTLPR (long/short)	Pooled analysis: 464 patients with SAD; 414 control subjects; 226 individuals from a population-based registry; 46 patients with nonseasonal depression.	Pooled data from previous 3 case-control studies[74,77,76] includes new sample of 147 patients with SAD and 115 control subjects. No association between 5-HTTLPR and SAD was found in the new case-control material or in the pooled analysis of all samples. A difference in 5-HTTLPR was detected between the population-based high and low seasonality groups, when assuming a recessive effect of the short allele.
Thierry et al[88] (2004)	5-HTTLPR (long/short)	56 female patients with SAD; 76 age-matched control subjects	Patients with SAD carrying the short allele had lower Self-Directedness scores on personality testing.
Levitan et al[89] (2004)	DRD4 (7R allele)	108 female patients with SAD with increased eating behavior	7R allele was associated with childhood attention deficit disorder symptomatology and higher maximal lifetime body mass index in patients with SAD.
Levitan et al[88] (2004)	DRD4 (7R allele)	131 female patients with SAD with increased eating behavior	7R allele was associated with greater frequency of binge-eaters in patients with SAD.
Willeit et al[95] (2003)	Gβ3 (C825T)	172 patients with SAD; 143 control subjects	Increase in frequency of the C825T-allele in patients with SAD. The polymorphism was not associated with seasonality.
Johansson et al[96] (2004)	Gβ3 (C825T)	159 patients with SAD; 159 matched control subjects	No association between C825T and SAD or seasonality. Some evidence for an effect on diurnal preference but only in a subset (N=92) of the control group.
Johansson et al[81] (2003)	Clock, period 2, period 3 (647 Val/Gly), NPAS2 (471 Leu/Ser)	159 patients with SAD; matched control subjects	NPAS2 471 Leu/Ser was associated with SAD and Period3 647 Val/Gly was associated with diurnal preference.

SAD=seasonal affective disorder; 5-HT=serotonin; Ala=alanine; Val=valine; Gly=glycine; Ser=serine; Ile=isoleucine; Cys=cysteine; TPH=tryptophan hydroxylase; 5-HTT=serotonin transporter; 5-HTTLPR=serotonin transporter promoter polymorphism; His=histidine; Tyr=tyrosine; TRH=thyroid releasing hormone; PMDD=premenstrual dysphoric disorder; DRD4=D4 dopamine receptor; Gβ3=G-protein β3 subunit; NPAS2=neuronal PAS domain protein 2; Leu=Leucine;

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the seasonal activation of cytokines in anticipation of winter stress.[111] Preliminary studies[112] have shown that people with SAD had significantly higher plasma levels of cytokine interleukin (IL) -6 and a trend to higher soluble IL-2 receptor levels than control subjects. Tryptophan and catecholamine depletion of patients in remission with light therapy also found that changes in cytokine soluble IL-4 correlated with increase in depressive symptoms.[113] Further investigation of the role of cytokines and neuroimmune function in SAD and seasonality will be of interest.

Another method to reduce heterogeneity is to study more specific endophenotypes of SAD, such as patients with distinct neurovegetative features or comorbidity. It may also be possible to link some of these endophenotypes to other psychiatric conditions via common neurophysiological mechanisms, such as modeling differences in 5-HT_{2A} and DR_{D4} gene polymorphisms to the appetite and attention disturbances found in women with SAD and bulimia nervosa.[85]

Progress in research on mechanisms of circadian regulation will also likely provide clues for research in SAD and seasonality. For example, several studies[19,106,114] have found evidence for electrophysiological changes in retinal light sensitivity in SAD, but most of these changes reflect rod and cone photoreceptor function. Recent research[115-117] has shown that photic input to the circadian system is mediated through a separate pathway from that of the visual system, and that traditional visual photoreceptors (eg, rods and cones) are not involved in the transduction of circadian light signals. Instead, novel photopigments, such as melanopsin[115,117] and cryptochrome,[116] have been implicated as circadian photoreceptors. Based on these new findings, research on melanopsin and other circadian photopigments will be of great interest in SAD.

Finally, it is also recognized that the different hypotheses proposed for SAD may not be mutually exclusive. For example, 5-HT can modulate photic response to the SCN and sleep disturbances due to abnormal circadian rhythms may be mediated through serotonergic pathways that depend on postsynaptic G-protein signal transduction. An integrative approach involving circadian rhythms, neurotransmitters and genetics will be more likely to explain the biology of SAD than a single, reductionist approach CNS

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