Release Date: August 12, 2005; **Valid for credit through August 12, 2006**

Target Audience

This activity is intended for psychiatrists, primary care physicians and other specialists who care for patients with SAD.

Goal

To better recognize and treat patients with Seasonal Affective Disorder.

Needs Statement

There is a need to diagnose a common but under-recognized disorder by describing the neurochemical changes that may be responsible for the symptoms of SAD and how these aberrant systems may suggest useful treatment strategies, including light therapy, pharmacologic therapy, cognitive-behavioral therapy, or combination therapy.

Program Overview

Seasonal Affective Disorder (SAD) annually affects an estimated 2%-10% of Americans. SAD is a condition of recurring depressions in fall and winter, typically characterized by lethargy, oversleeping, overeating and weight gain, alternating with non-depressed periods in spring and summer. While the prevalence of SAD varies with latitude, evidence suggests that SAD is underdiagnosed. This program helps clinicians detect and treat this common but under-recognized disorder. An overview of the clinical considerations of SAD, including differential diagnosis and the relationship that SAD has with other mood disorders will be examined. Insights to the pathophysiology of SAD and its implications will be reviewed. Data describing the efficacy of light therapy in SAD, the clinical setting, and various devices used to administer light treatment will be presented. Current research data and general strategies for choosing a medication to treat SAD are compared. Practitioners will gain insight regarding the value of integrating cognitive-behavioral therapy into comprehensive SAD treatment, and efficacy data from randomized trials comparing light therapy, cognitive-behavioral therapy, and their combination, from the various studies reviewed.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Diagnose a common but under-recognized disorder in order to better treat patients who are currently going untreated.
2. Understand the neurochemical changes that may be responsible for the symptoms of SAD, and how these aberrant systems may suggest useful treatment strategies.
3. Understand clinical uses of light treatment and how to recognize the various devices used to administer light treatment.

4. Identify when to use medications to treat SAD and understand the mechanism of action of medications used in the treatment of SAD to choose the right options for patients.
5. Recognize the benefits of integrating cognitive-behavioral therapy into a comprehensive SAD treatment regimen.

Credits Available

Physicians - up to 2.0 AMA PRA Category 1 continuing physician education credits

All other healthcare professionals completing continuing education credit for this activity will be issued a certificate of participation.

Participants should claim only the number of hours actually spent in completing the educational activity.

Accreditation Statements

For Physicians

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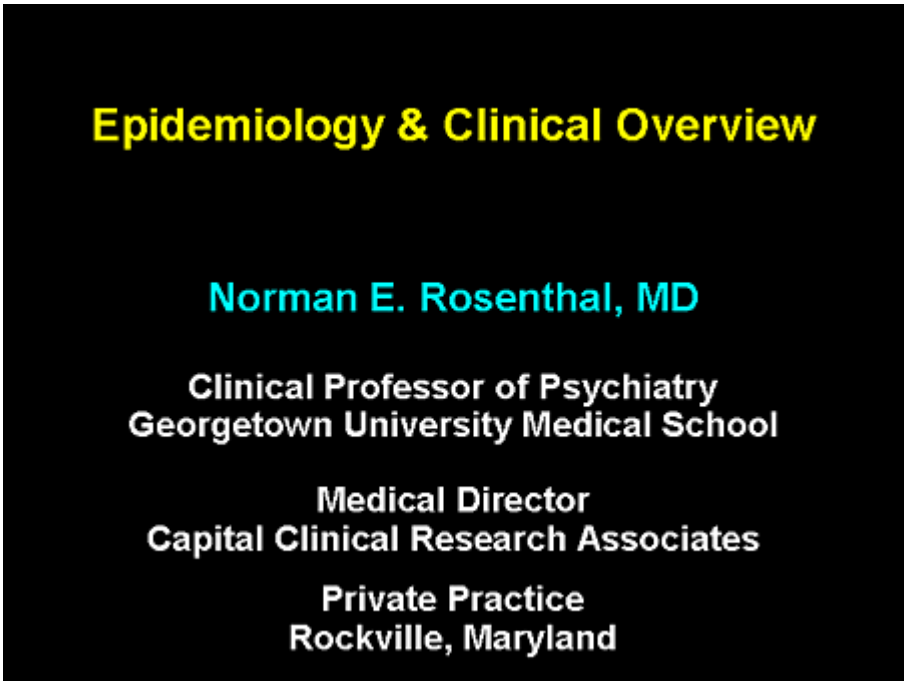
Seasonal Affective Disorder: Diagnosis and Treatment Update

Epidemiology and Clinical Overview

Norman E. Rosenthal, MD

Identification of a New Disorder

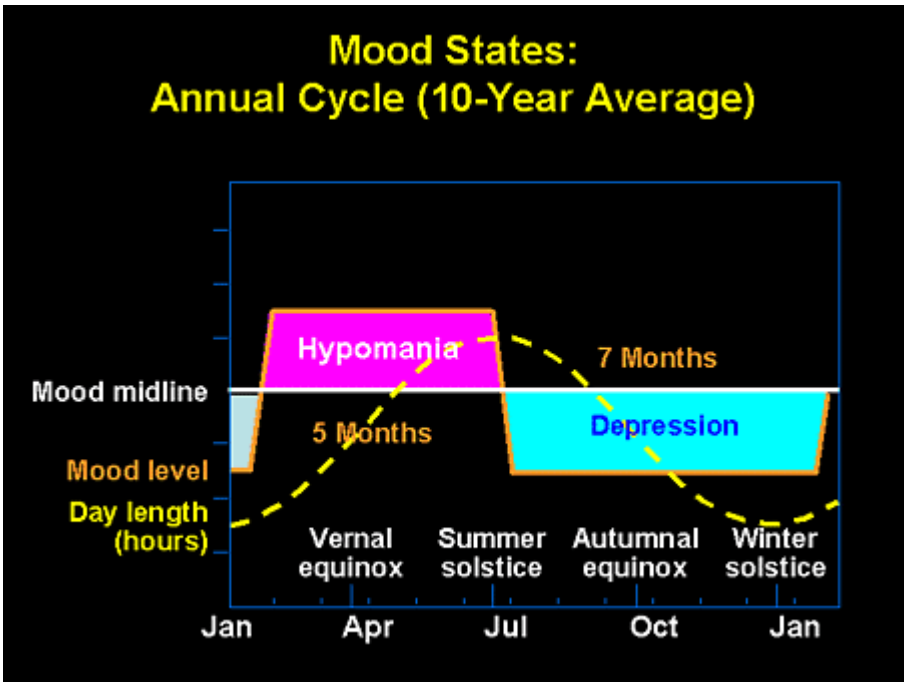


Slide 1. Epidemiology and Clinical Overview

I'm a clinical professor of psychiatry at Georgetown University Medical School, and I was one of the psychiatrists who originally described seasonal affective disorder (SAD) about 20 years ago. I'm going to talk about the clinical picture and epidemiology of SAD.

Slide 2.

This slide shows Herb Kern. At the time, he was a 63-year-old scientist who had stumbled upon the fact that his moods had a curious seasonal occurrence, getting worse in the winter as the days got shorter and better in the summer. As you see, he is logging into his notebooks, one of the many, many notebooks that he kept over the years, where he kept daily records of his mood, which enabled him on reflection to construct the following diagram.

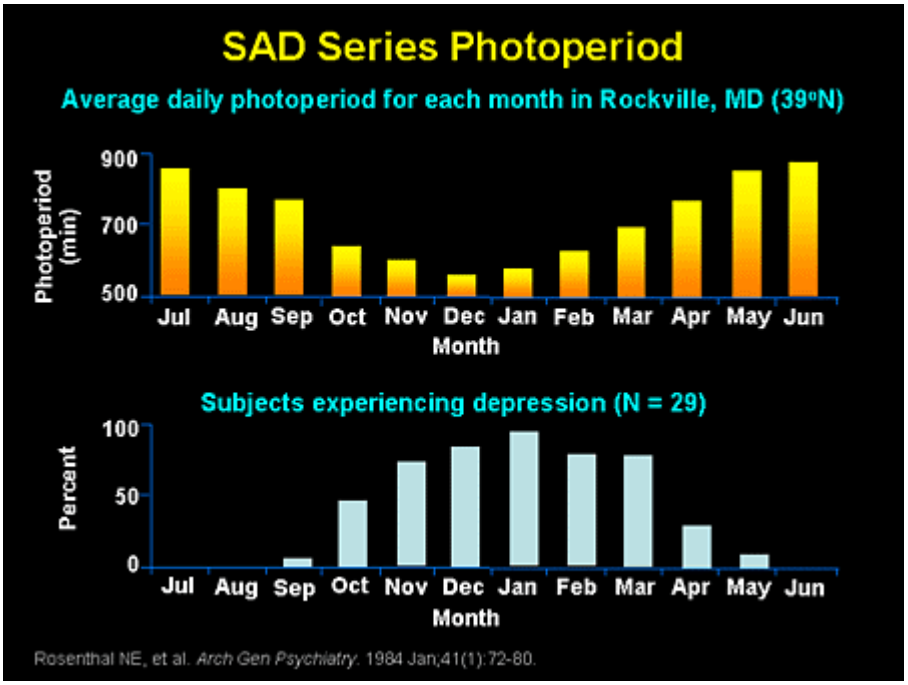


Slide 3. Mood States: Annual Cycle (10-Year Average)

This diagram illustrates Kern's initial schema for 7 months of the year, from the summer solstice, the longest day, until the winter solstice. This is Kern's original conception of how his moods altered with the changing days. As you see, there are 7 months of depression between the summer solstice and past the winter solstice, and as the days got longer, he would move from depression into hypomania. Instead of being sluggish and down and slow, all of a sudden, or rather, I should say, gradually he became galvanized, and as he put it: "The wheels of my mind would begin to spin again."

Kern had initially suggested, and you see in the diagram as illustrated by the dotted line, that perhaps it was the length of the day that was driving his manias or hypomanias and his depressions; it was quite an original concept at the time. He presented this to my colleagues and me at the National Institute of Mental Health (NIMH), and we thought that if we expanded his day length with artificial light, using extra light in the morning and the evening, we might be able to switch him out of his depression and into his hypomania. Sure enough, that's exactly what we did.

But I realized that we needed a population of people if we were going to study this phenomenon in any greater depth, so we advertised, thinking that maybe we would get a handful of responses. On the contrary, we had thousands of responses from all over the country. We featured an article in the *Washington Post*, describing one of the early patients, who said: "I should have been a bear. Bears are allowed to hibernate, but humans are not. We have to get up and off in the morning; we have to get to work and do 100 things when all I feel like doing is curling up like a hibernating bear."



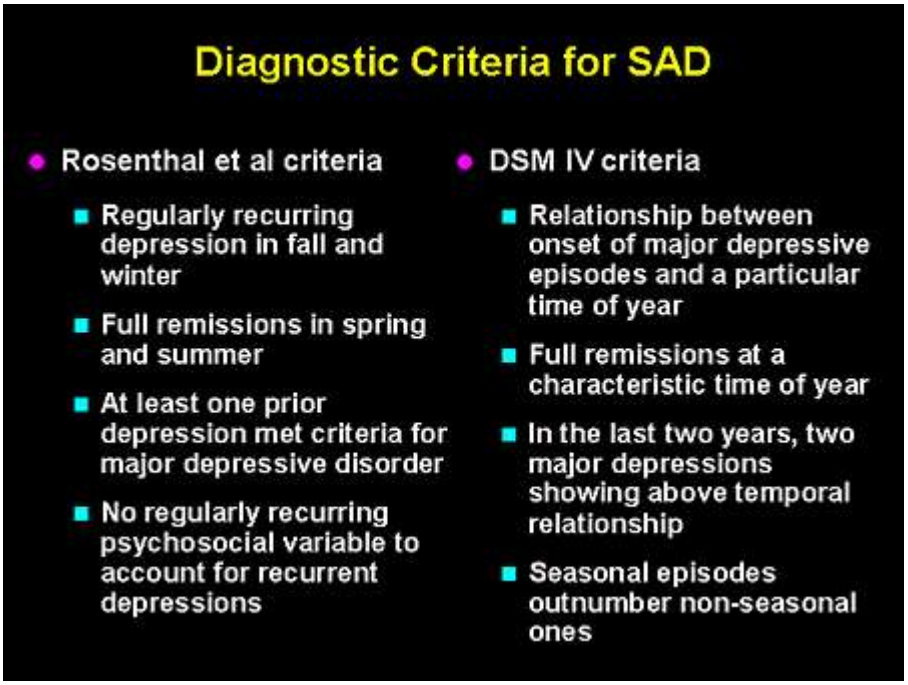
Slide 4. SAD Series Photoperiod

This slide features the first cohort of patients whom we described in our original description of SAD, now over 20 years ago. On the lower panel, you see when our

patients, 29 of them, reported that they suffered from the most symptoms. The peak is in January, tapering off evenly on both sides of the winter solstice. On the upper part of the panel, you see the length of the day in Rockville, Maryland, which is where the study took place. What you see is a nice inverse correlation between these 2 histograms, suggesting to us that it might be the length of the day that was crucially important in creating or evoking these symptoms in our seasonal patients.

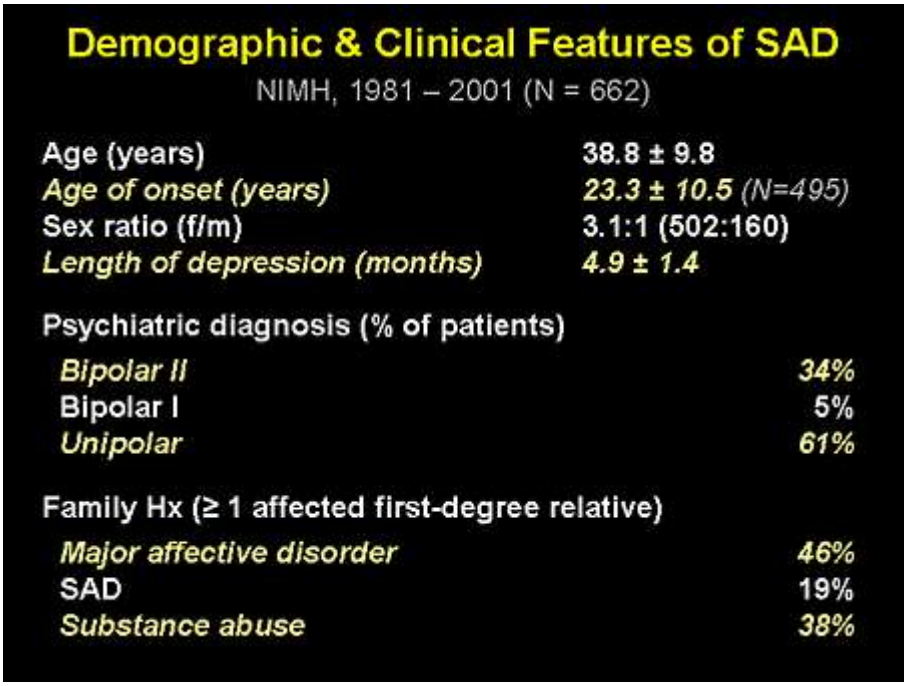
Epidemiology and Clinical Overview
Norman E. Rosenthal, MD

Diagnostic and Clinical Features of Seasonal Affective Disorder



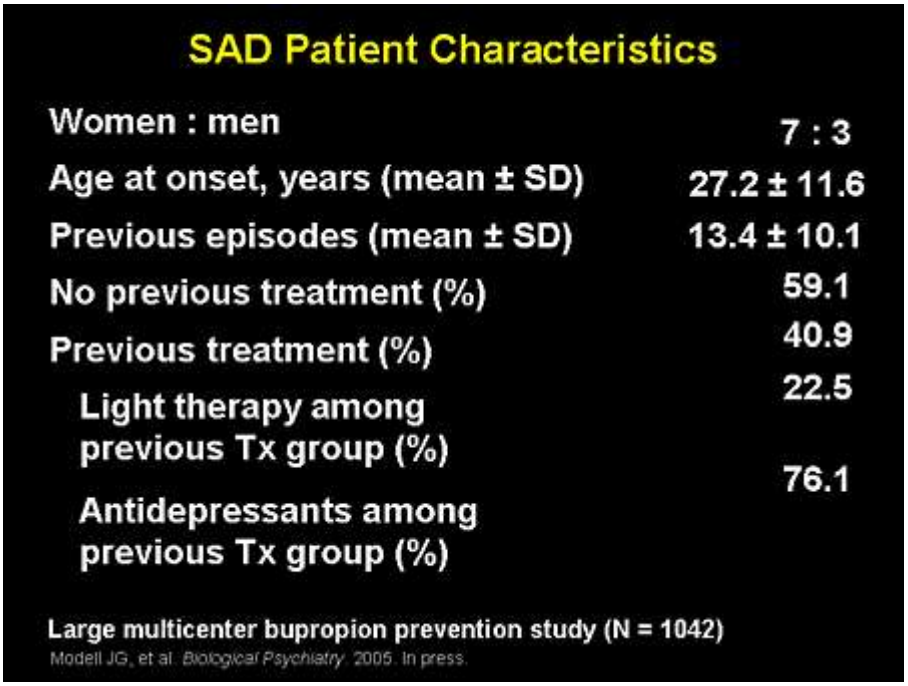
Slide 5. Diagnostic Criteria for SAD

We developed a set of criteria, the Rosenthal et al criteria, for SAD. Patients had to have regularly recurring depressions in fall and winter, full remissions in spring and summer, and at least 1 prior depression that met criteria for major depressive disorder. In addition, there were no psychosocial variables to explain these mood shifts. On the right side of the slide, you see the latest version of these criteria -- very, very similar. I would ask the clinician to be rather creative in applying these criteria. For example, what if patients don't have a full remission in spring and summer? Many of the things that I'm going to tell you are applicable even if patients don't remit completely in the summer, even if they don't meet criteria for a major depressive disorder but are still somewhat depressed. So just be aware of the importance of seasonality.



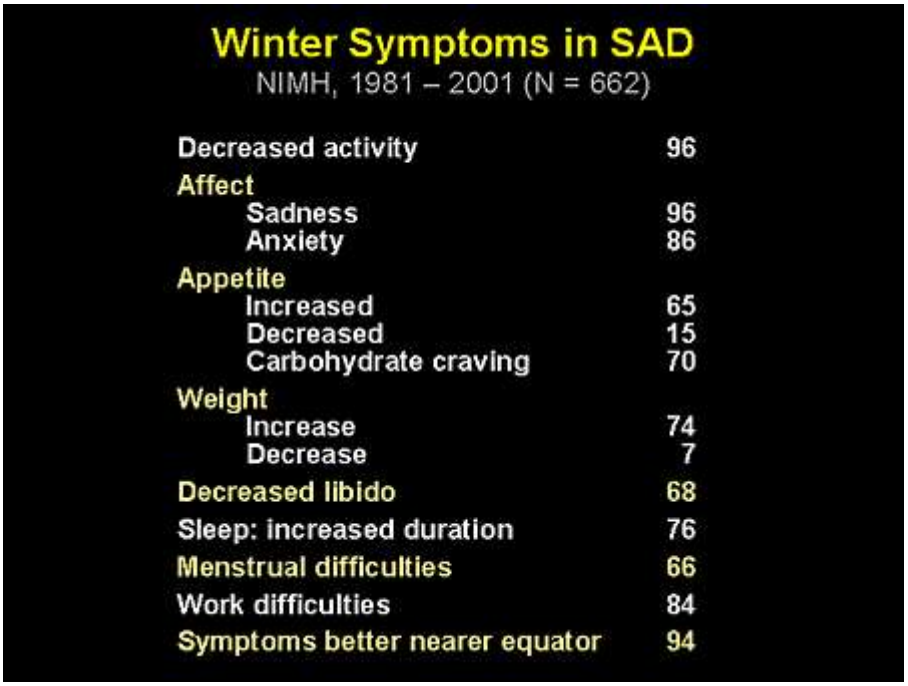
Slide 6. Demographic and Clinical Features of SAD

This slide shows the demographic and clinical features of the 662 patients studied over 20 years at the NIMH. On average, the age of the patients was late 30s, but there was a wide spread in age. Age of onset was early 20s, although when we delved a little further, we found that many of these people had symptoms going all the way back to their childhood or adolescence. The sex ratio, which has held pretty firmly over time, is preponderantly female -- 3.1:1 in this group. And the length of the depression is almost 5 months, an important fact because it highlights that we're not dealing with a trivial 1-or 2-week holiday blues here; we're dealing with a lengthy depression, which, as you will see, has many nasty symptoms that go along with it. Most of our patients were unipolar, but a healthy minority was diagnosed with bipolar II disorder; namely they would have hypomanic symptoms in the summer alternating with their winter depressive symptoms. Family history was fairly common by report, either of depressions, SAD, or substance abuse.



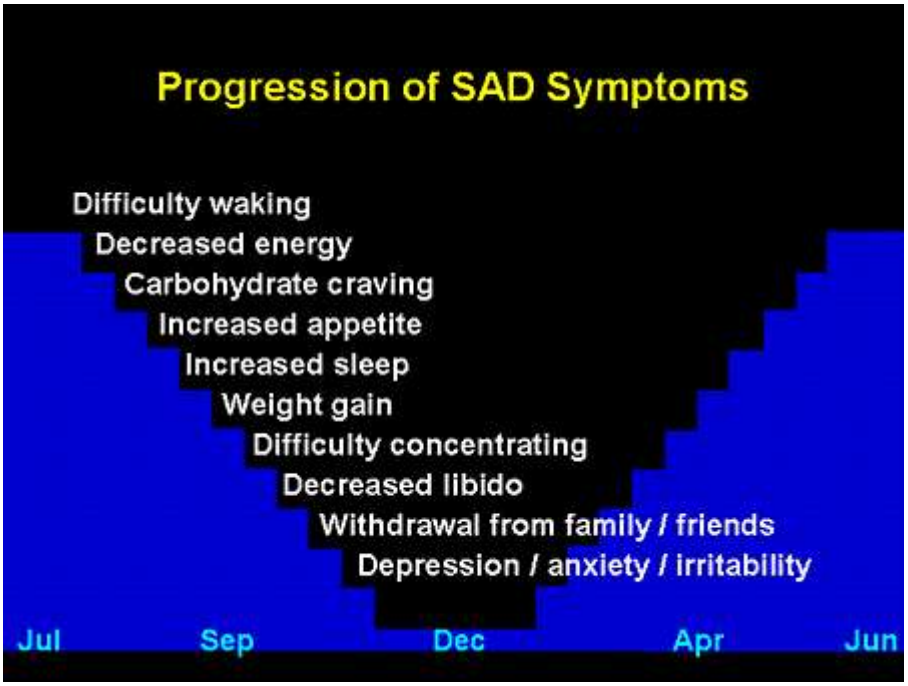
Slide 7. SAD Patient Characteristics

Flashing forward to a very modern study on over 1000 patients -- Modell here is the senior author -- we see very similar characteristics to those of the NIMH group. Women outnumbered men by 7:3; the age of onset was the late 20s; and interestingly, these people complained on average of over 13 winter depressions before they presented to our program. They had, despite these 13 episodes, no previous treatment in almost 60% of cases, so even though the syndrome was described over 20 years ago, it is still not being detected and treated in the majority of cases, let alone episodes. Thousands of episodes have gone missed and untreated, just in this particular group of subjects.



Slide 8. Winter Symptoms in SAD

What are the symptoms of SAD? Decreased activity, that's a given for depression, as are sadness and anxiety, of course. But here come the interesting elements: appetite is increased in about two thirds of the patients, along with a marked carbohydrate craving. Many of our patients say, "It's the only thing I feel like doing; the only thing that will propel me off my couch or out of my bed is a trip to the fridge to gorge on donuts or whatever other junk food I have there." They crave carbohydrates, which actually give them a sense of activation. Needless to say, three quarters, as you see, gain weight. Going on to other symptoms, libido is decreased; of course, sleep is increased. It's an atypical depressive profile. Menstrual difficulties, work difficulties; and here is the most pathognomonic of all the symptoms -- that symptoms are better when they've traveled nearer the equator. If they've taken trips south in the winter, if they've lived in further southern latitudes, this is accompanied by an improvement in symptoms.



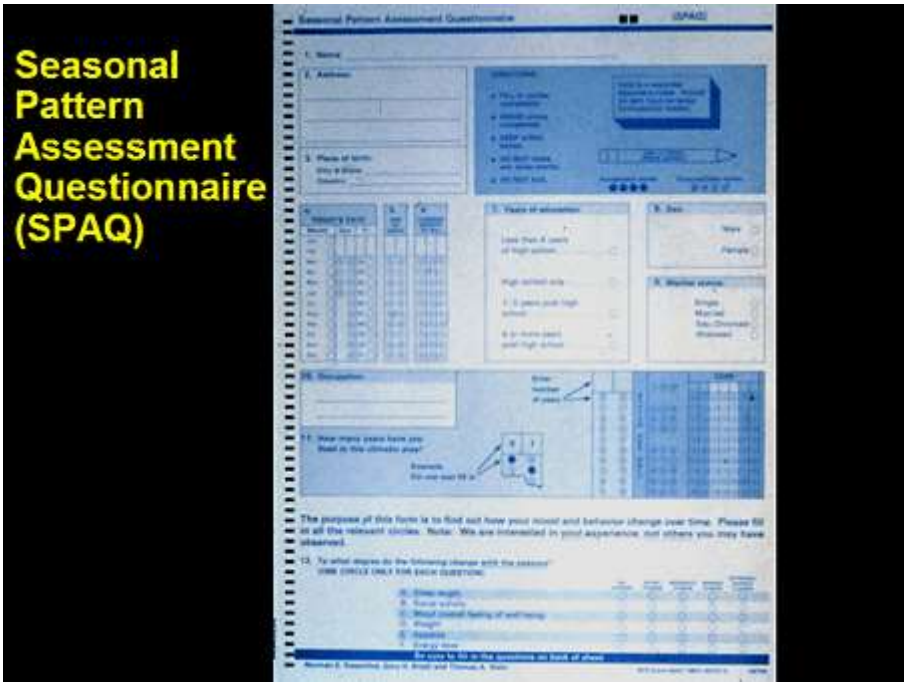
Slide 9. Progression of SAD Symptoms

Now the symptoms don't appear all at once, and what we have in this slide, this sort of staircase, represents the shortening of the days from the summer to the winter solstice. And based on my clinical experience with some scientific backing, what you see is a progression. First they have difficulty waking. Then energy decreases. They crave carbohydrates. Appetite increases. Somewhere in this mix, the daylight savings time change occurs, and you have an hour of more darkness in the afternoon and that sometimes has a marked effect. Sleep increases, weight is gained, they have difficulty concentrating, they have decreased libido, they withdraw from friends and family, and sometimes right at the end of the sequence come depression, anxiety, and irritability. Obviously, these symptoms can occur earlier than this, but the point of the slide is really to emphasize the following points to the clinician. Please, don't wait for these folks to report depression. Pick up those early signs -- the carbohydrate craving, the lower energy, the difficulty waking -- and you will catch these people early and spare them months of misery by treating in a timely manner.

Epidemiology and Clinical Overview

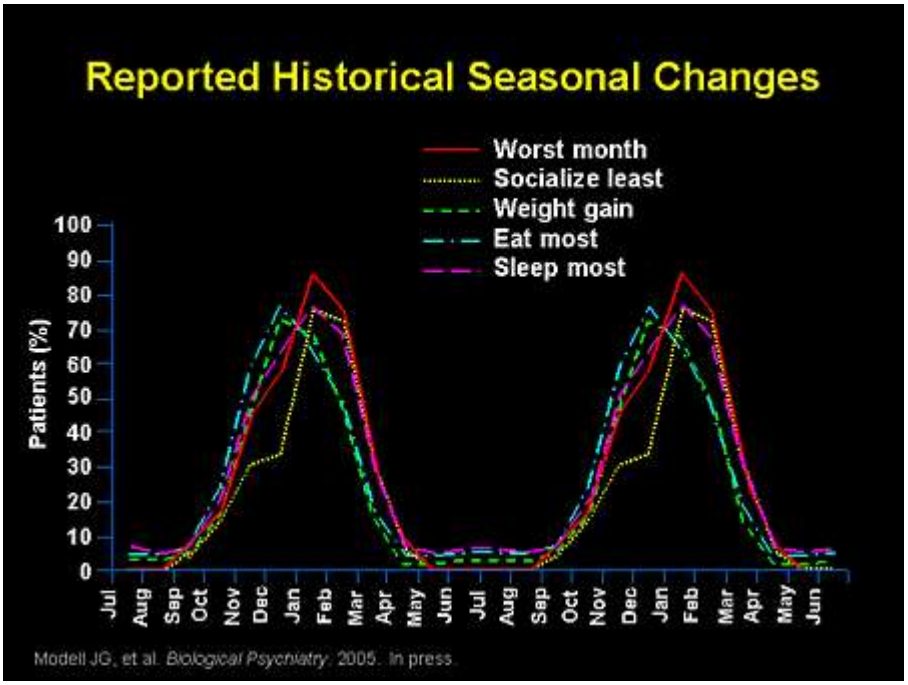
Norman E. Rosenthal, MD

Seasonal Changes in Seasonal Affective Disorder



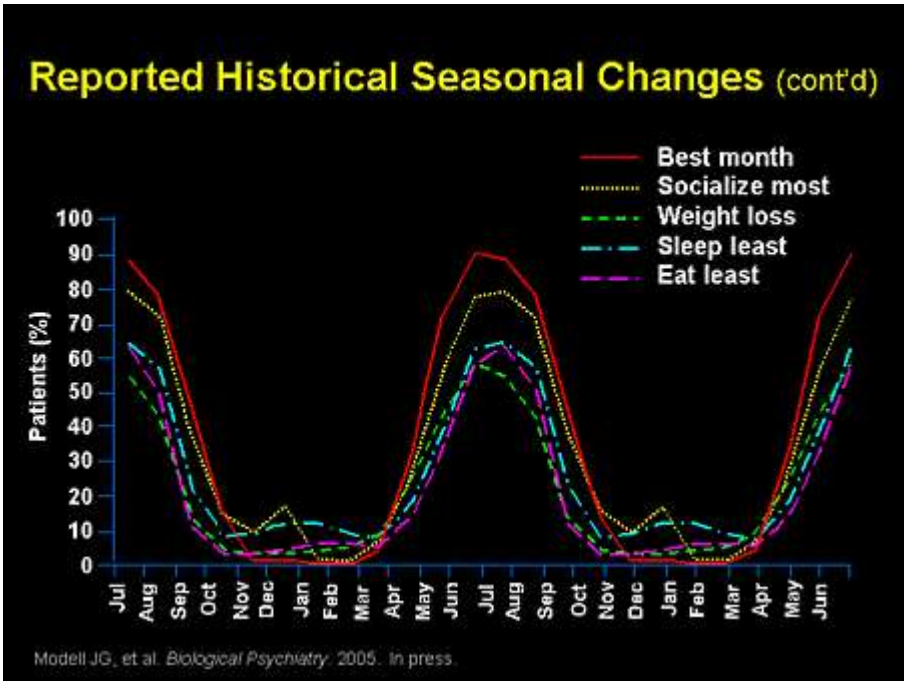
Slide 10. Seasonal Pattern Assessment Questionnaire (SPAQ)

In this slide, we see the Seasonal Pattern Assessment Questionnaire, the SPAQ for short, which my colleagues and I developed at the NIMH. It's an attempt, in a very sort of quick and dirty way, but rather effective in many respects, to assay a person's seasonality. It can be given to any group of people, any population, and has been given to many, many different populations in many different reported studies. It asks about changes in various behaviors with the changing season.



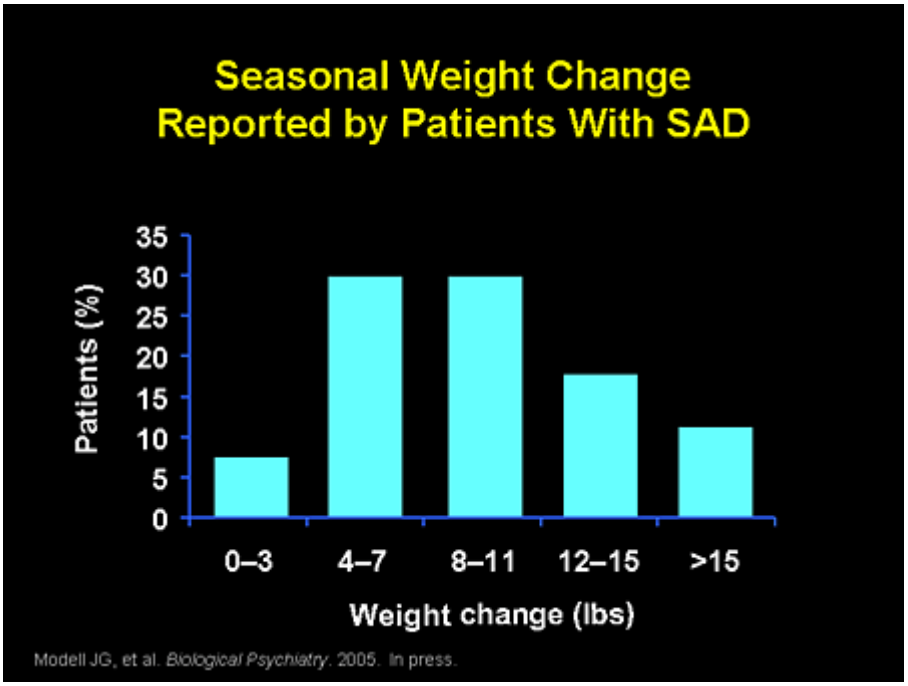
Slide 11. Reported Historical Seasonal Changes

The data in this slide come from that same study of Modell and colleagues, showing how you get parallel spikes during the winter in what is your worst month, when you weigh the most, when you eat the most, when you sleep the most, and when you socialize the least, which you see is slightly delayed related to the other graphs because of the artifact presented by the socializing that comes with the holiday season.



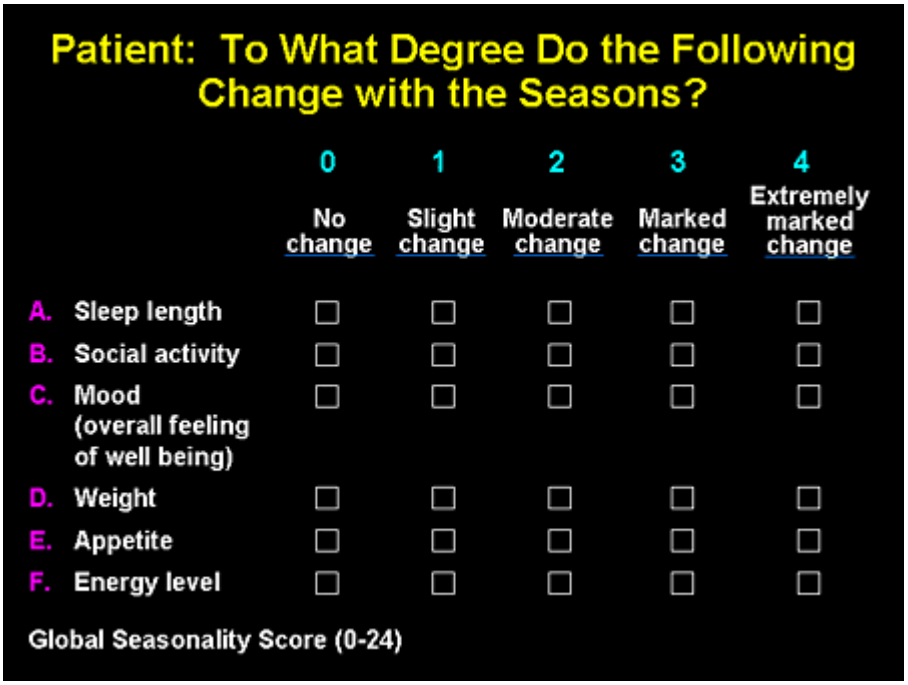
Slide 12. Reported Historical Seasonal Changes (cont'd)

Conversely, when you look at the summer spikes, you see parallel peaks in the best month around July, with socialize most, weigh least, sleep least and eat least all occurring at the same time. So something is happening in the brain in concert that affects these multiple functions that we see disturbed in depression.



Slide 13. Seasonal Weight Change Reported by Patients With SAD

Now when you look at the weight gain, what you see is that many have a marked weight gain; in fact, if you add this up, approximately 50% or more have an 8-lb or more weight gain in the winter, and they don't always lose all of this in the summer, so what happens is you get an increasing problem with weight over the years of SAD. We all have read, of course, all the tremendous health consequences of obesity, so SAD is not only unpleasant in its own right, but it is a risk factor for weight gain and obesity.



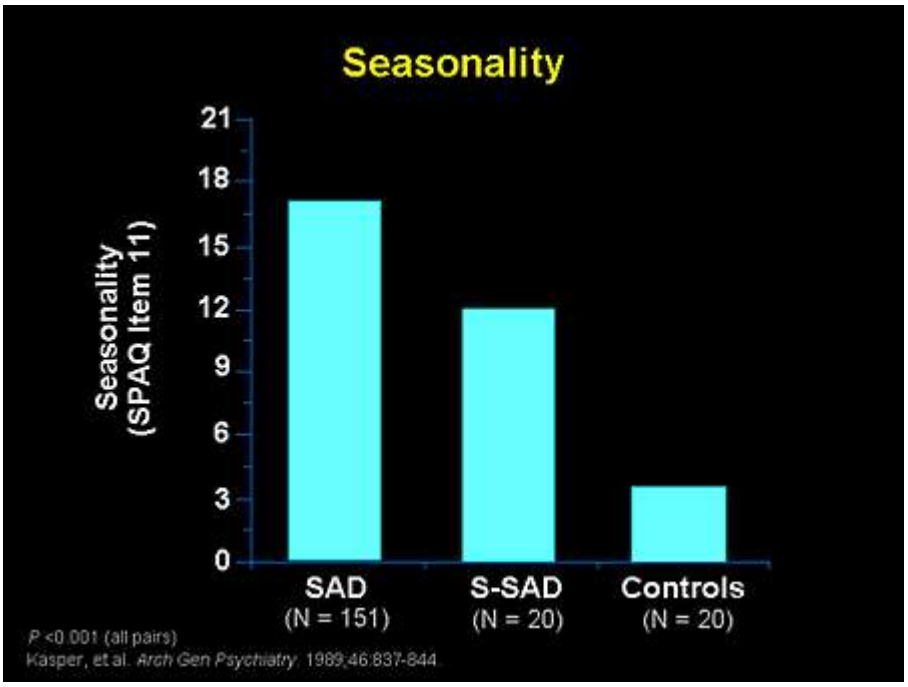
Slide 14. Patient: To What Degree Do the Following Change With the Seasons?

At the bottom of the SPAQ are 6 questions asking to what degree the following change with the seasons: sleep length, social activity, mood, weight, appetite, and energy level. And each of these can be rated from 0 to 4. Then you can add it up and what you get is the global seasonality score, which totals 0 to 24, and it is a very useful index in evaluating the seasonality of an individual.

Epidemiology and Clinical Overview

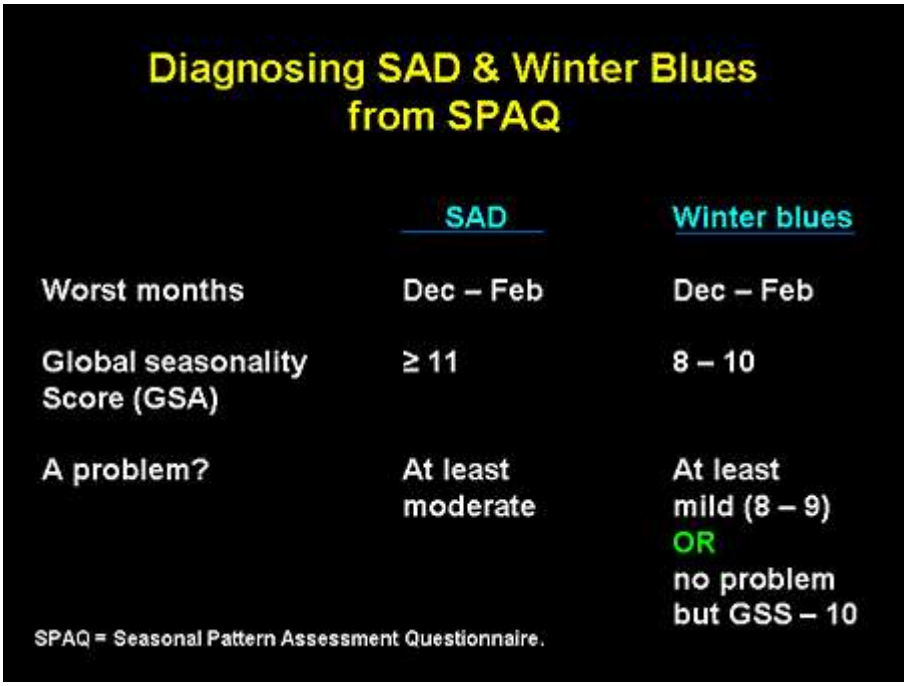
Norman E. Rosenthal, MD

Distinguishing Seasonal Affective Disorder From the Winter Blues



Slide 15. Seasonality

In this slide, we have a histogram showing that the global seasonality score for SAD patients is, on average, 16 or 17 points. On the far right are healthy controls, specifically selected for a lack of seasonality, and you see that by definition almost, they have only 3 points. But in the middle is a very interesting population of people who don't have fully fledged SAD but are nonetheless affected by the winter. They are less creative, less productive in the winter. They wouldn't go to a doctor, it's not that bad, but if you prod them and ask them, they say: "You know, I'm just not the same in the winter as I am in the summer." We have called these people subsyndromal SAD (sub-SAD) or, more commonly, "suffering from the winter blues." And as you see, they have on average an 11-point, 12-point score.



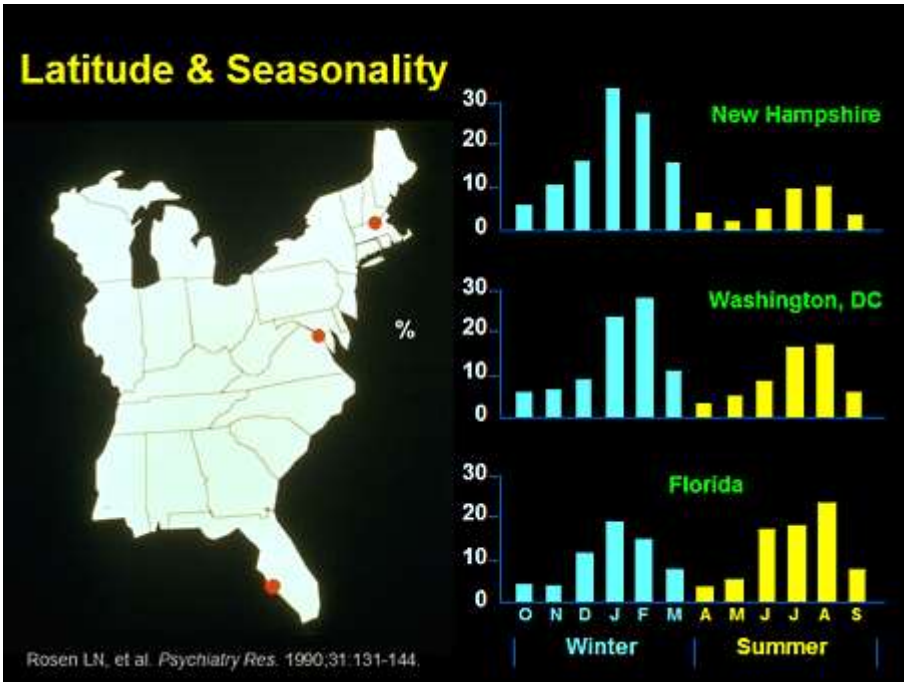
Slide 16. Diagnosing SAD and Winter Blues From SPAQ

We've developed case-finding criteria from the SPAQ whereby you can score the SPAQ. Incidentally, I should let you know that the SPAQ was done as part of our work in the US government, so it is in the public domain; anybody can use the SPAQ, and many people should use the SPAQ because it's just awfully handy and very easy to use and score. If you want to try and assess if people are suffering from SAD or the winter blues, their worst months -- there's an item that asks which are the worst months -- should fall between December and February, almost by definition. The global seasonality score in the case of SAD should be 11 or more, although between you and me, it can sometimes be less than that. Winter blues would be about 8 to 10, and then for SAD, there's an item that asks to what degree this is a problem, and it should be at least a moderate problem to be considered a disorder. On the other hand, if they have simply a case of the winter blues, they should have a mild problem on the lower range of the global seasonality score, namely 8 to 9, but if they've got 10, even if they say there's no problem, we would still categorize them as having the winter blues. These case finding criteria have been used in numerous studies in many countries; the SPAQ has been translated into many languages.

Epidemiology and Clinical Overview

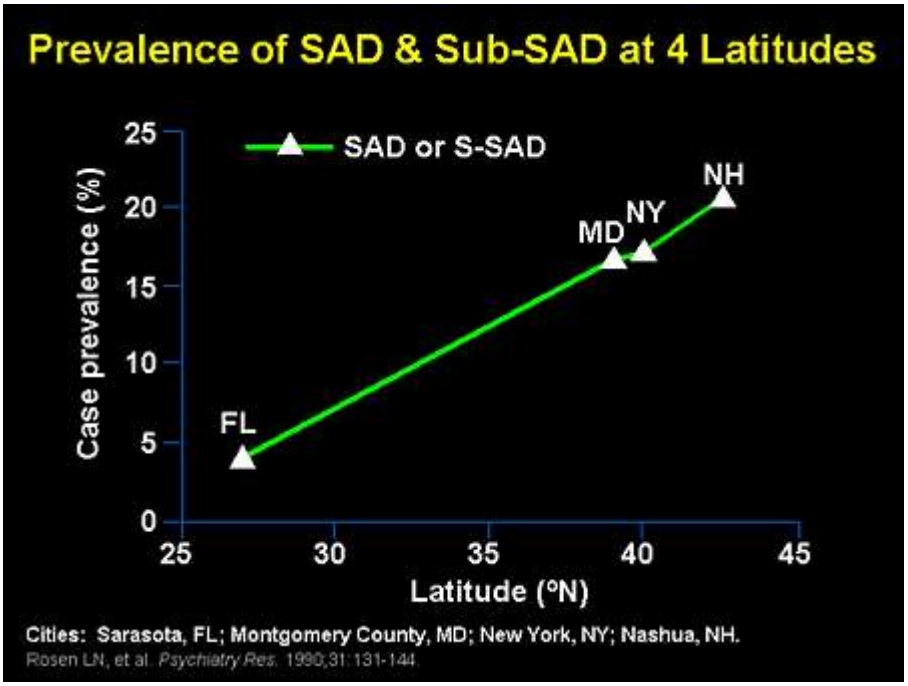
Norman E. Rosenthal, MD

Latitude and Seasonal Affective Disorder



Slide 17. Latitude and Seasonality

Here is 1 study from the United States by Rosen and associates at 3 different latitudes: New Hampshire, which is 42 degrees north; Washington, DC, which is 39 degrees; and Sarasota, Florida, which is 23 degrees, I think. I can't remember exactly. And what you see is that when they're asked which are their worst months, most people in New Hampshire, in the north, say: "Winter is awful." And this is a normal population, by the way. When I say most people, it's 30%; it's not most of the whole population, but of those who have a worst month, most say that it's winter. In Washington, it still is rather nasty in the winter, but the summer is beginning to get a little nasty as well, and in Florida, the nastiness factor shifts and summer is a little worse than winter.



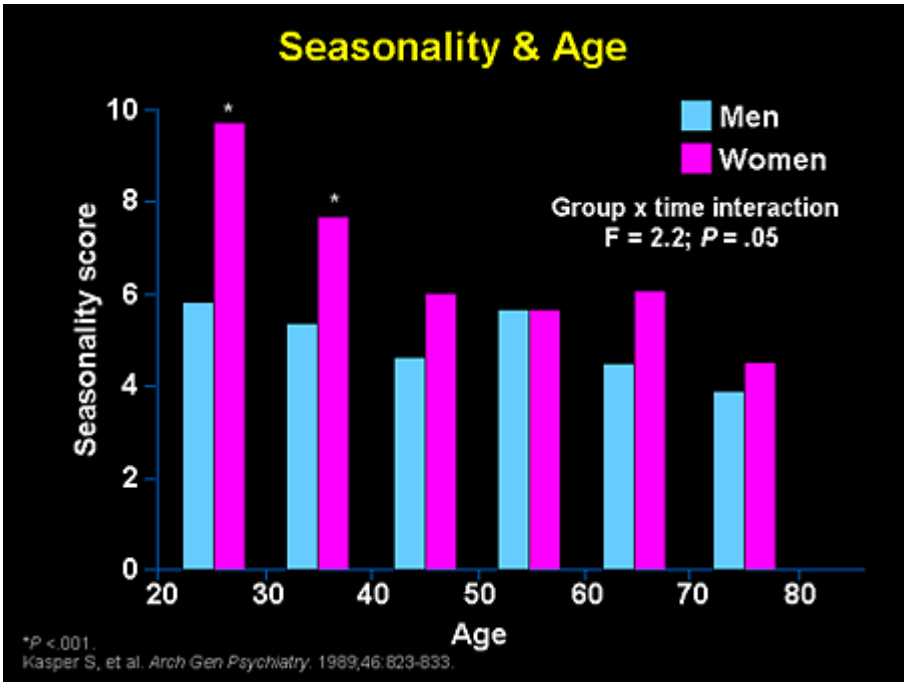
Slide 18. Prevalence of SAD and Sub-SAD at 4 Latitudes

When we added it together, the SAD and sub-SAD populations at 4 latitudes -- now you see New York has sneaked in there between Maryland and New Hampshire -- we found a very nice correlation between latitude and case prevalence. It was a better correlation than when we split it between SAD and sub-SAD, but the statistics for SAD are fairly low in Florida, about 1.5%; and fairly high in New Hampshire, almost 9%; and somewhere in the middle in Maryland, maybe 5%, 5.5%. So it's really quite a common condition, if you think about it, and if you add SAD and sub-SAD, and you may as well because they might be helped by many of the same interventions, we estimate that maybe 1 in 5 people is affected by one or other of these conditions in the northern United States.

Epidemiology and Clinical Overview

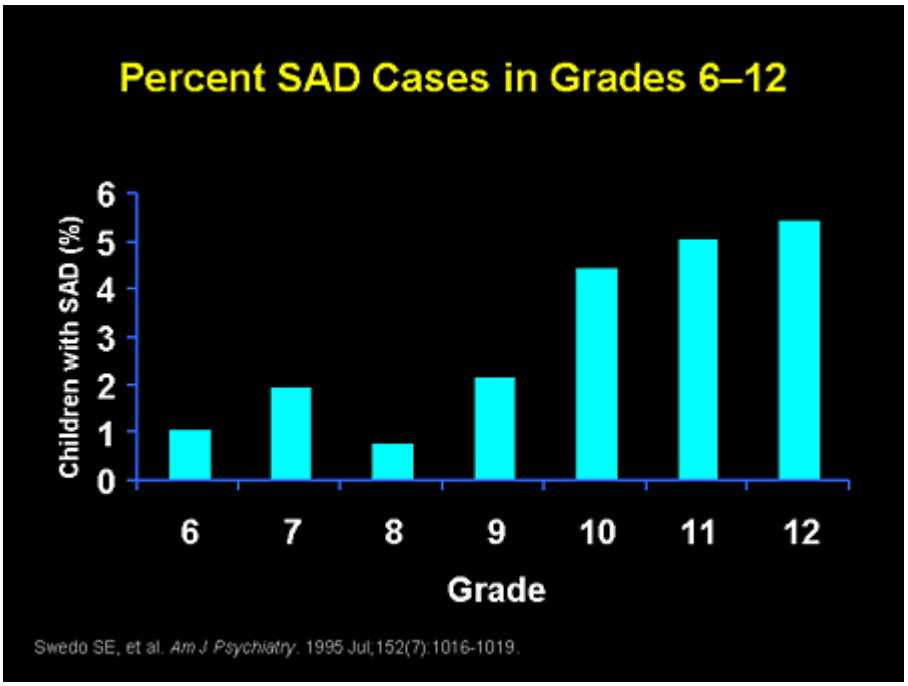
Norman E. Rosenthal, MD

Age and Seasonal Affective Disorder



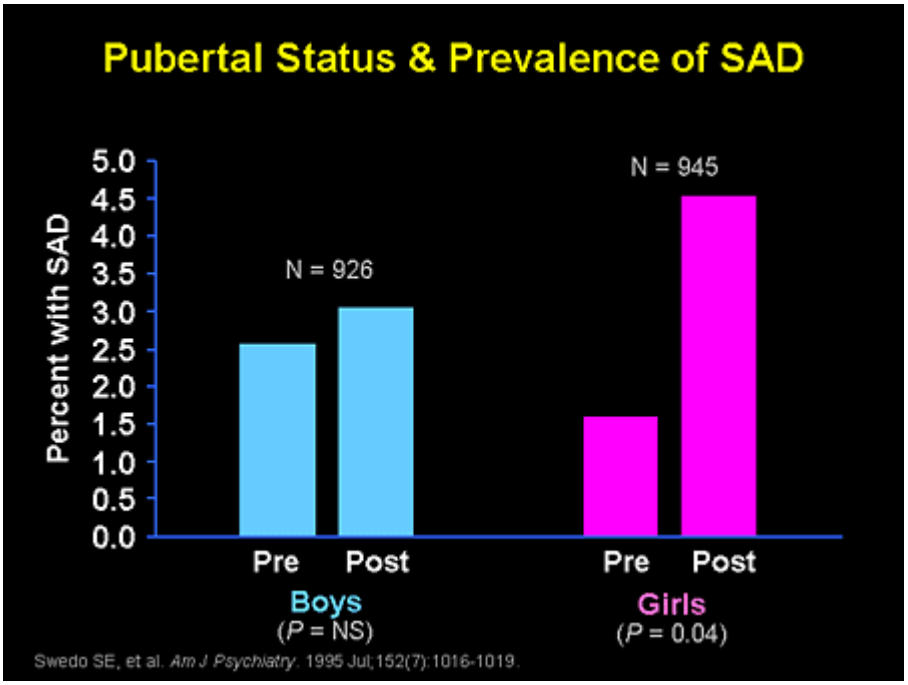
Slide 19. Seasonality and Age

Now here's an interesting relationship that emerged from our study of Maryland County, where Dr. Kasper was the lead author. What he found when he looked at men and women was that women were more seasonal than men, particularly in their 20s, 30s, and 40s -- in other words, during the years when they were reproductively active. After menopause, however, the ratio flattens out somewhat, and this was the first hint that the menstruating years might have something to do with the prevalence or the pathogenesis of SAD.



Slide 20. Percent SAD Cases in Grades 6-12

In this slide, we see the other side of the age spectrum. This was a study we did in middle- and high-school children with Dr. Swedo as the lead author, and what you see is the prevalence of SAD rather conservatively estimated, and here again the study was in Maryland. The prevalence goes higher in grades 10, 11, and 12, so that by the 12th grade, the prevalence is almost the same as what you see in the adult population.



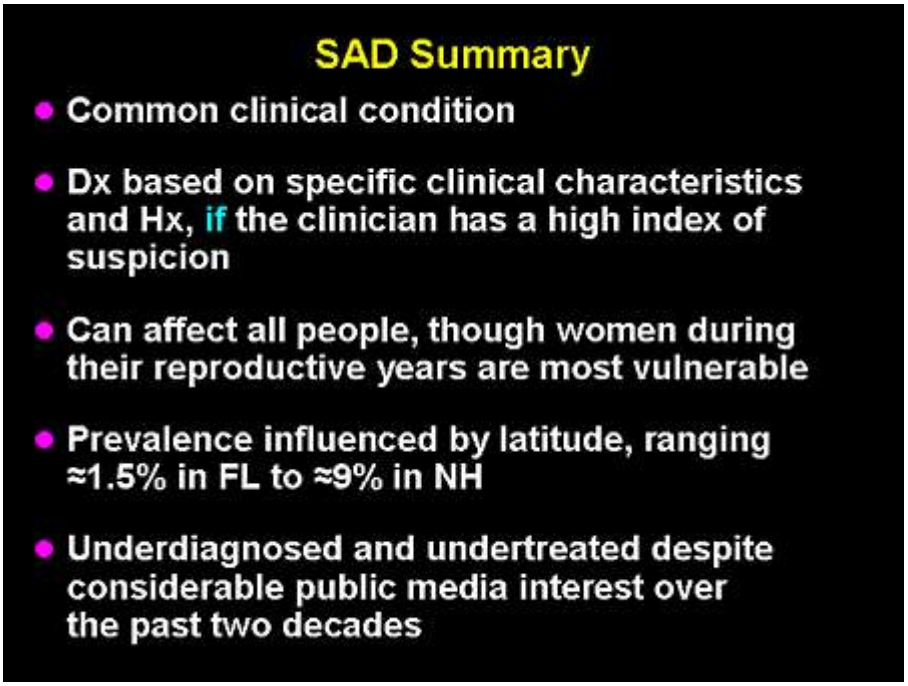
Slide 21. Pubertal Status and Prevalence of SAD

When we looked at the potential role of puberty in prevalence, we asked simple questions like "Have you developed body hair?" and "Have you started menstruating?" and those kinds of questions to sort of evaluate the onset of puberty. In boys, there's rather little influence of puberty on prevalence, whereas in girls, the prevalence triples after puberty. So here you see that at both ends of the reproductive spectrum, the presence of cyclical reproductive hormonal secretion appears to have an influence on prevalence of SAD, presumably by influencing the brain's sensitivity to the changes in the ambient light.

Epidemiology and Clinical Overview

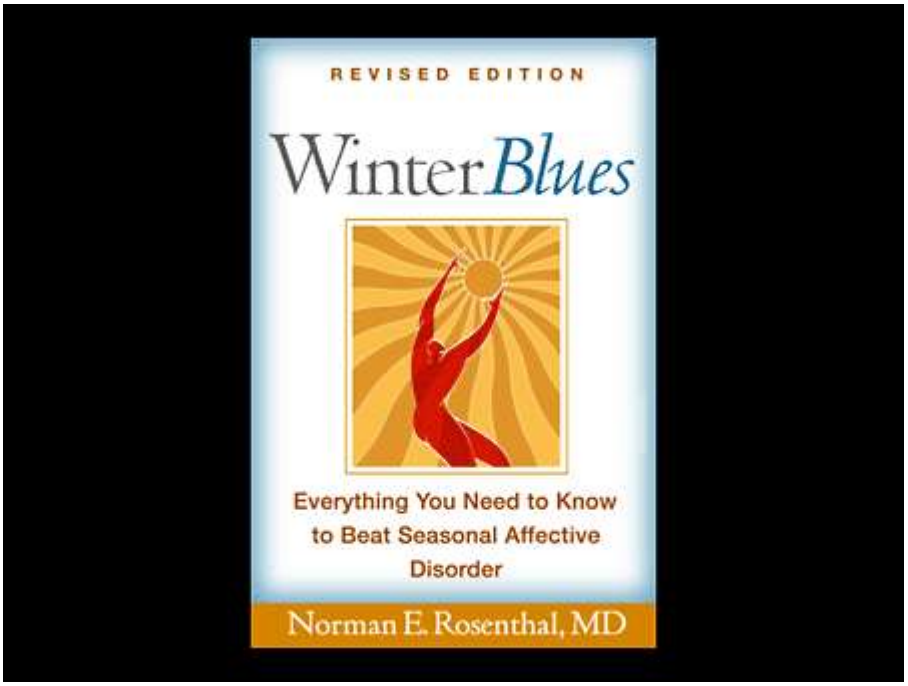
Norman E. Rosenthal, MD

Summary



Slide 22. SAD Summary

So to summarize, SAD is a common clinical condition. Diagnosis is based on specific clinical characteristics and history, but you will only make the diagnosis if you, as the clinician, have a high index of suspicion. Otherwise, with somebody arriving at your doorstep in the autumn and the winter with nonspecific complaints of fatigue and eating too much or gaining weight, you could easily mistake this for chronic fatigue syndrome or the flu or hypoglycemia or hypothyroidism, unless you ask the key questions, the questions you find on the SPAQ. SAD can affect all people, although women during their reproductive years are most vulnerable. The prevalence is influenced by latitude, ranging from about 1.5% in Florida to about 9% in New Hampshire. And there also is some association with latitude elsewhere in the world; for example, you'll have a high incidence in Scotland and a low one in Australia, which is closer to the equator. SAD is underdiagnosed and undertreated. Remember, almost 60% of the recent study of over 1000 patients were untreated despite having had, on average, 13 episodes of SAD -- 13 episodes and they still hadn't been diagnosed despite considerable public media interest over the past 2 decades.



Slide 23.

I sincerely hope that this presentation will help everybody to do a better job in diagnosing and treating this common and eminently treatable condition. It's very useful to have resources for yourself and your patients and one such resource is my book, *Winter Blues: Everything You Need to Know to Beat Seasonal Affective Disorder*, which is currently available and will be out in its new edition as of October 2005.

Epidemiology and Clinical Overview

Norman E. Rosenthal, MD

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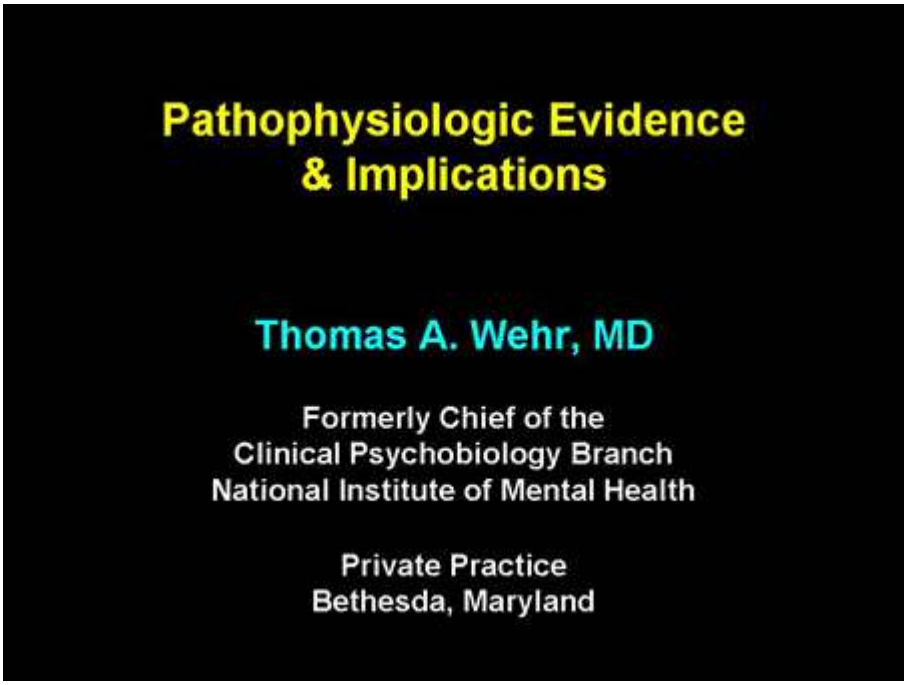
Pathophysiologic Evidence and Implications

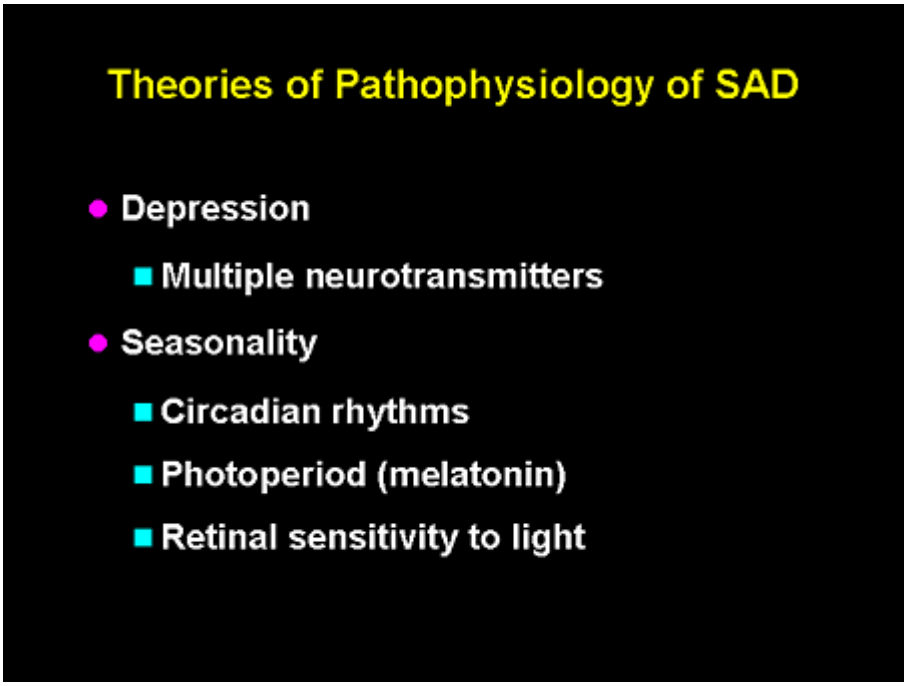
Thomas A. Wehr, MD

Introduction



Slide 1. Pathophysiologic Evidence and Implications

I'm Thomas Wehr, and I'm going to be talking about the pathophysiologic evidence and implications for seasonal affective disorder (SAD). I'm currently in private practice in Bethesda, Maryland; however, I spent over 30 years doing research on this and related topics at the National Institutes of Health in Bethesda.



Slide 2. Theories of Pathophysiology of SAD

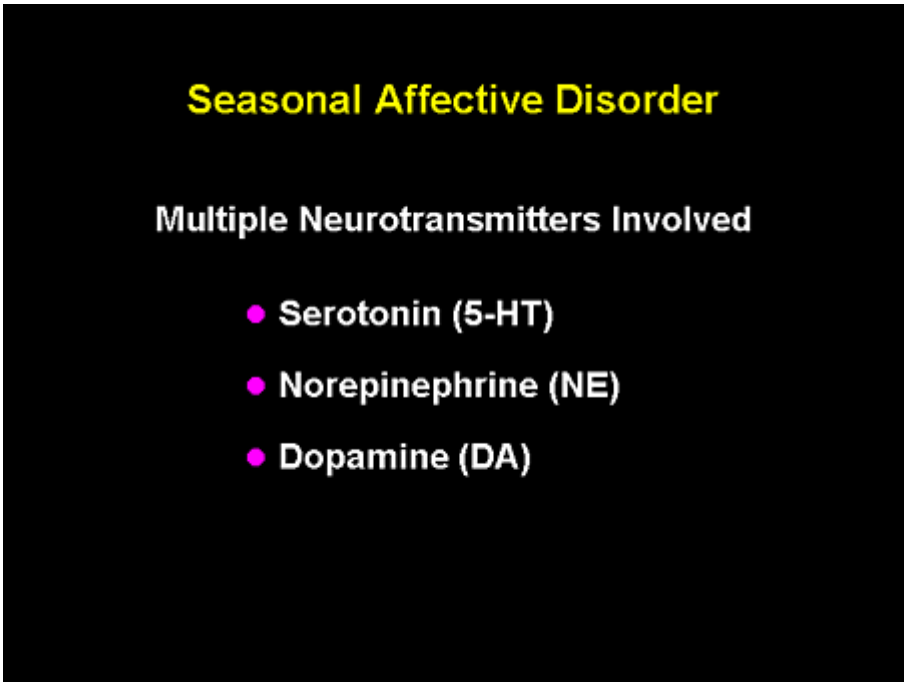
There are many different dimensions to the research that's been done on pathophysiological changes in SAD, and in many respects, they overlap with findings that have been reported for depression in general, even nonseasonal depression. I'm mainly going to focus on neurotransmitter research. However, there also are findings involving neuroendocrinology, genetics, and thermoregulation and other areas that are possibly relevant and potential fruitful lines for future research.

There really are 2 aspects to seasonal depression: there's the depression that people are vulnerable to, and there's another factor that seems to be responsible for the seasonal course that it takes. And so in the second part of my remarks, I'm going to talk about seasonality and the regulation of seasonality and what sort of vulnerability might explain the seasonal pattern of depression in people who have SAD.

Pathophysiologic Evidence and Implications

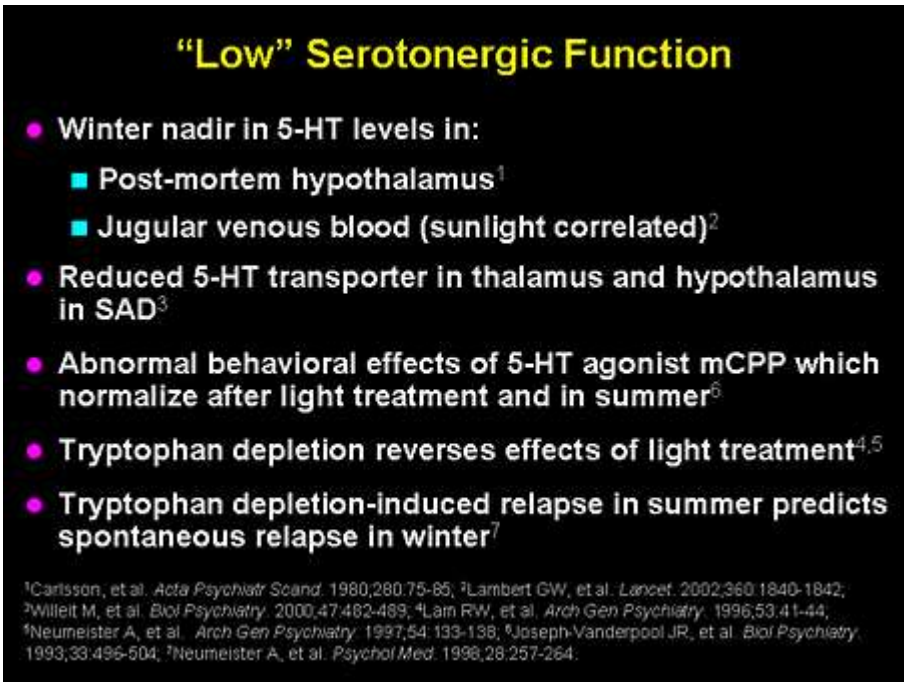
Thomas A. Wehr, MD

Neurotransmitter Involvement in Seasonal Affective Disorder



Slide 3. Seasonal Affective Disorder

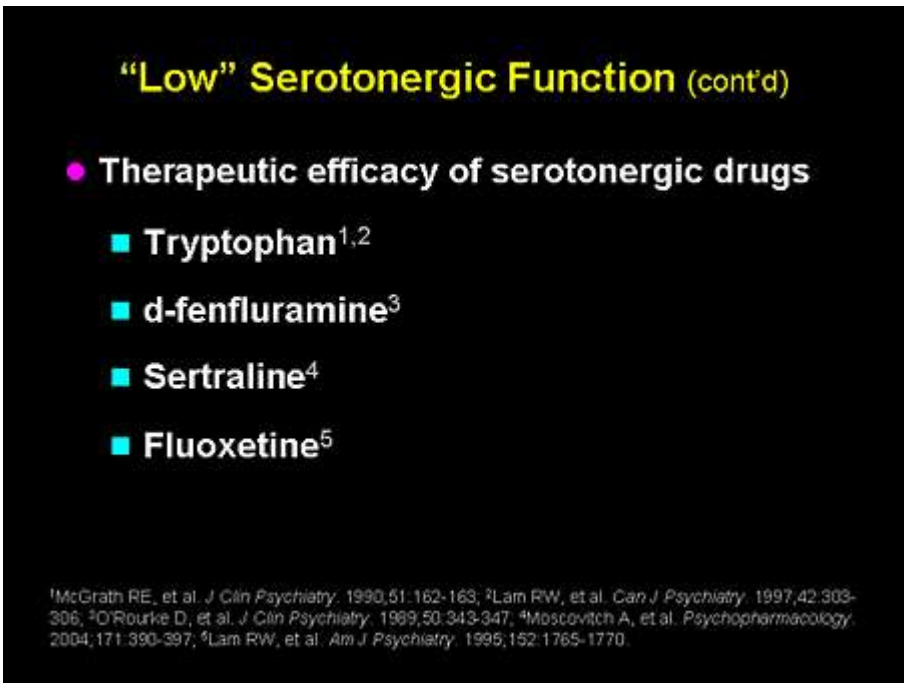
The neurotransmitters that have received the most attention are serotonin, norepinephrine, and dopamine, and foremost among these is serotonin.



Slide 4. "Low" Serotonergic Function

A number of years ago, it was found that serotonin in postmortem human hypothalamus exhibits rather pronounced seasonal variations with a reduction in the wintertime. More recent research has shown that serotonin in jugular venous blood, which mainly is

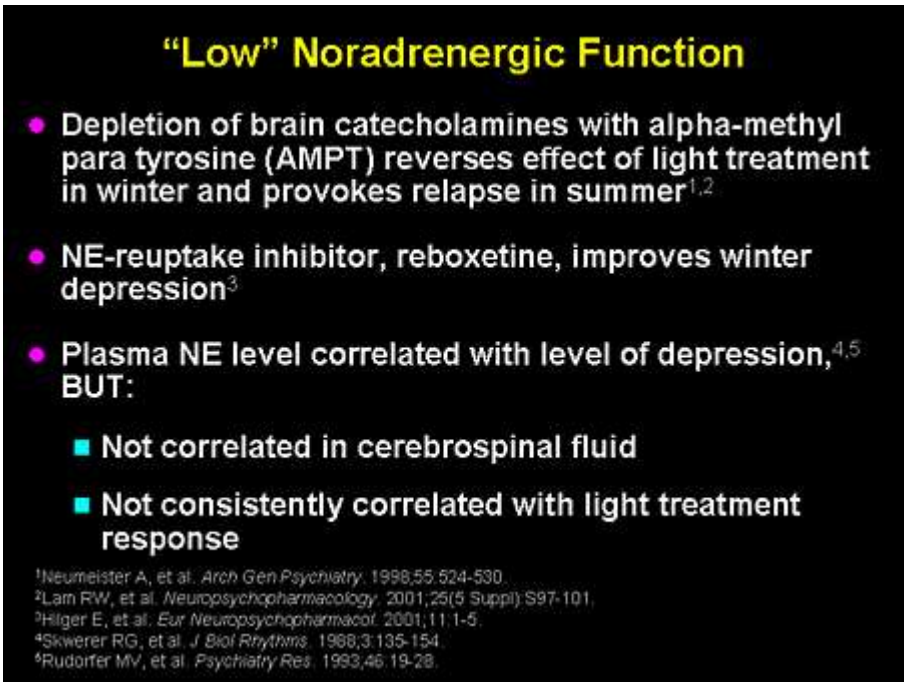
originating in the brain, also shows a similar seasonal variation that can be correlated with variations in sunlight during the period preceding the sampling. So this evidence in healthy human subjects indicates that there are robust seasonal changes in serotonin levels in the human brain and has led to a hypothesis that perhaps winter depression is associated with a reduction in serotonin or serotonergic function. Some further evidence tends to support this; there's neuroimaging evidence of reduced serotonin transporter in the thalamus and hypothalamus in patients with SAD compared with controls. In addition, among challenge tests, it was shown repeatedly that patients with SAD show abnormal behavioral responses to the serotonin agonist mCPP and that these abnormalities normalize after light treatment and in the summer. Finally, newer studies have been carried out in which tryptophan was eliminated from the diet of patients. Tryptophan is the precursor of serotonin; when it's eliminated, the synthesis of serotonin in brain declines, and this experimentally induces a functional deficit of serotonin. Tryptophan depletion has been shown to reverse the therapeutic effects of light treatment in winter depression, so light treatment will not continue to work without the synthesis of serotonin. Furthermore, depletion of serotonin and lowering of central nervous system serotonin levels induce relapses in patients in the summer when they have spontaneously improved, and these relapses predict whether or not they will relapse in the wintertime when the days become shorter.



Slide 5. "Low" Serotonergic Function (cont'd)

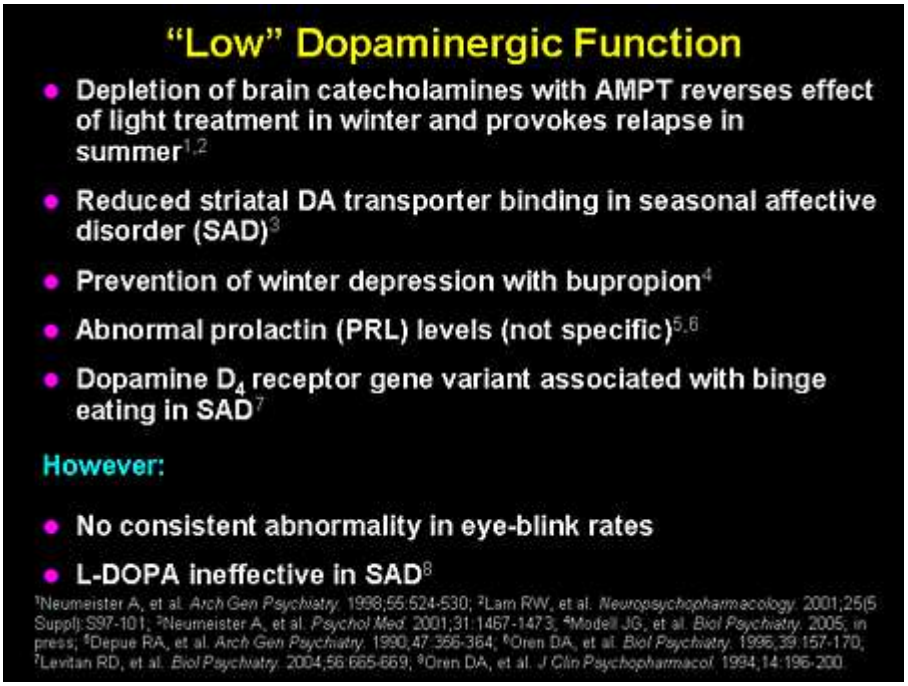
In addition, a number of serotonergic drugs have been shown to have some therapeutic efficacy in the treatment of winter depression. Tryptophan, the precursor of serotonin, has been used to show this effect. Dexfenfluramine, which releases serotonin and stimulates serotonin receptors, also has been shown to have some therapeutic effects, and then the selective serotonin reuptake inhibitors sertraline and fluoxetine in 2 studies have shown some antidepressant effects in patients with winter depression. So there's a considerable

amount of evidence that points to a possible deficiency of serotonergic functioning in winter depression.



Slide 6. "Low" Noradrenergic Function

There have been relatively fewer studies of the catecholamine neurotransmitters norepinephrine and dopamine. However, it has been shown that depletion of brain catecholamines by administering alpha-methyl-para-tyrosine (AMPT) will reverse the therapeutic effects of light treatment in winter and can provoke relapses into depression in patients with SAD who have relapsed in the summertime. In addition, the norepinephrine reuptake inhibitor reboxetine has been shown to improve winter depression, and plasma norepinephrine levels have been shown to be correlated with the level of depression in patients with SAD. However, these correlations were not found in cerebrospinal fluid, and they're not consistently related to the effects of light treatment on winter depression.



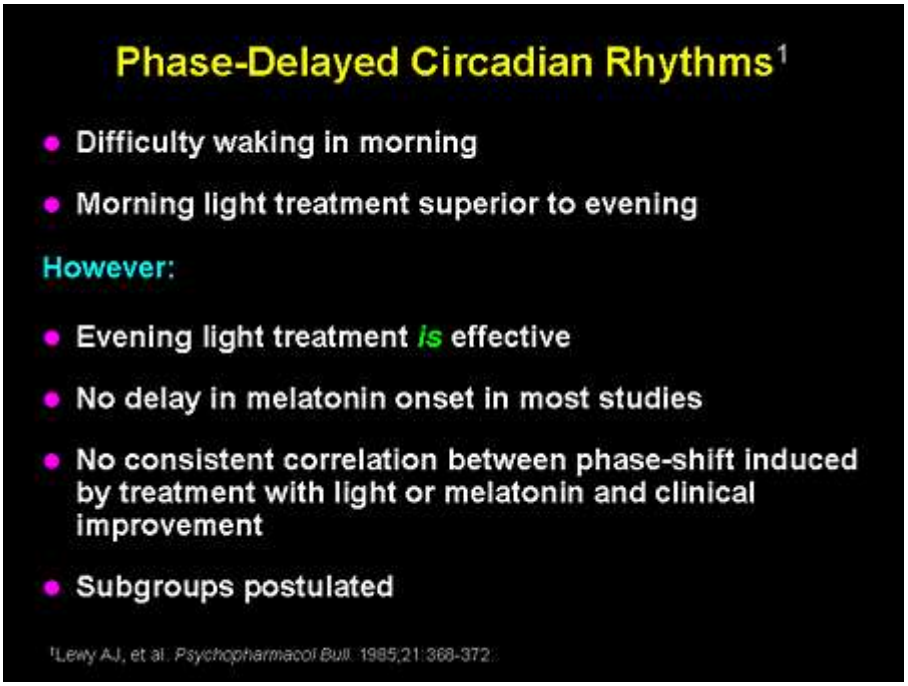
Slide 7. "Low" Dopaminergic Function

Depletion of brain catecholamines with AMPT, in addition to depleting norepinephrine, will deplete dopamine. This, as I mentioned, has been shown to reverse the antidepressant effects of light treatment in the winter and to provoke relapses in patients who have improved spontaneously in the summer. In addition, there is a recent report of a reduction in striatal dopamine transporter binding in SAD in a neuroimaging study, and it's recently been shown that winter depression in a number of cases can be prevented by administration of bupropion, which inhibits the reuptake of dopamine. Abnormal levels of prolactin have been described in winter depression; this might reflect the dopamine abnormality, although it's not specific because serotonin vasoactive intestinal peptide and other factors can be involved. And finally, a recent report described a genetic variant in the dopamine D4 receptor that was associated with binge eating in SAD patients, and this particular symptom is highly characteristic of winter depression. However, other measures of dopaminergic activity have not shown any differences between patients and controls; this would be eye-blink rates and a therapeutic trial of L-dopa, which is the precursor for dopamine, was not effective in the treatment of winter depression.

Pathophysiologic Evidence and Implications

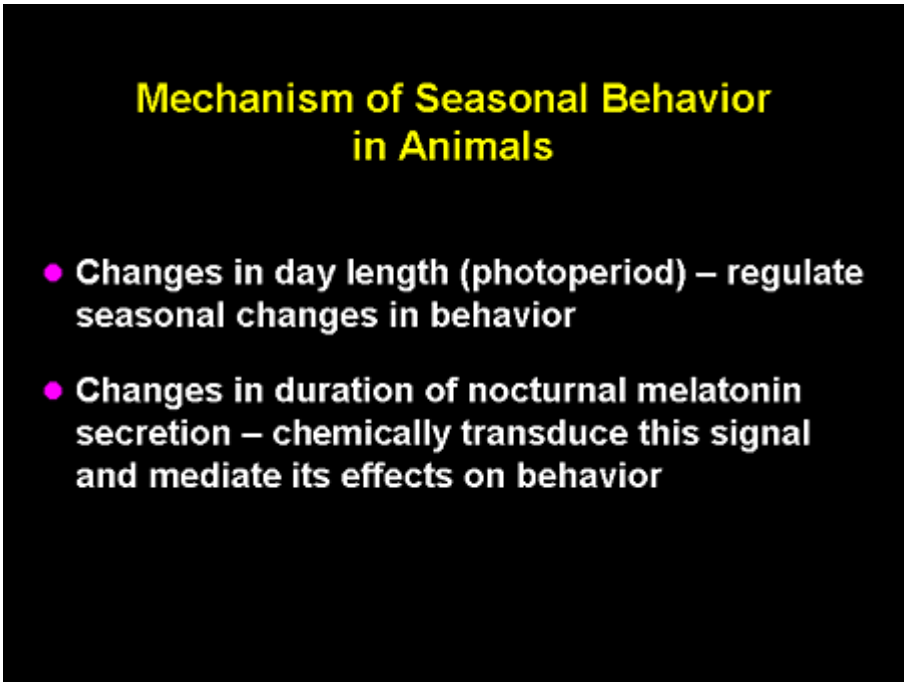
Thomas A. Wehr, MD

Models of Seasonal Affective Disorder



Slide 8. Phase-Delayed Circadian Rhythms

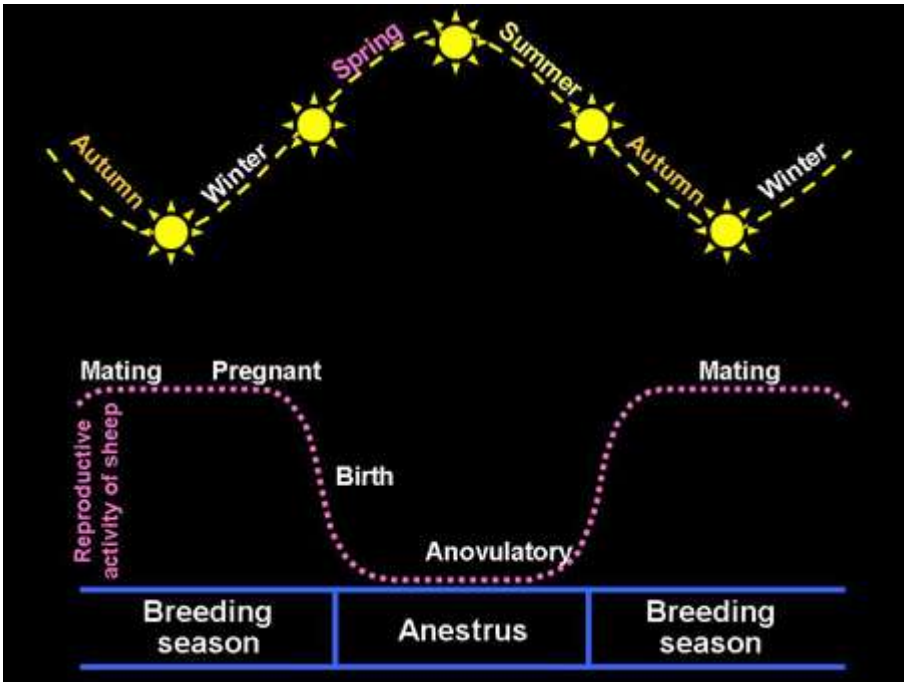
Another pathophysiologic mechanism that's been hypothesized to explain some of the symptoms of winter depression involves circadian rhythms. Since a characteristic of winter depression is difficulty waking in the morning, and since morning light treatment has been shown to be superior to evening light treatment -- morning light treatment being more likely to move waking to earlier in the morning -- it has been hypothesized that circadian rhythms are pathologically delayed in winter depression and that this pathological delay is corrected by morning light treatment, which advances circadian rhythms. However, over time, this theory has not received consistent support because, for example, evening light treatment, which would delay circadian rhythms, also has been shown to be effective in the treatment of winter depression, though less effective than morning light treatment. In the large number of studies that have been done to date, there has been no pathological or abnormal delay in the onset of melatonin secretion, an important marker of circadian rhythms in patients with winter depression compared with controls. And there has been no consistent correlation between the phase shifts in circadian rhythms that are induced by treatment with light or by treatment with melatonin and the degree of clinical improvement that the patients experience.



Slide 9. Mechanism of Seasonal Behavior in Animals

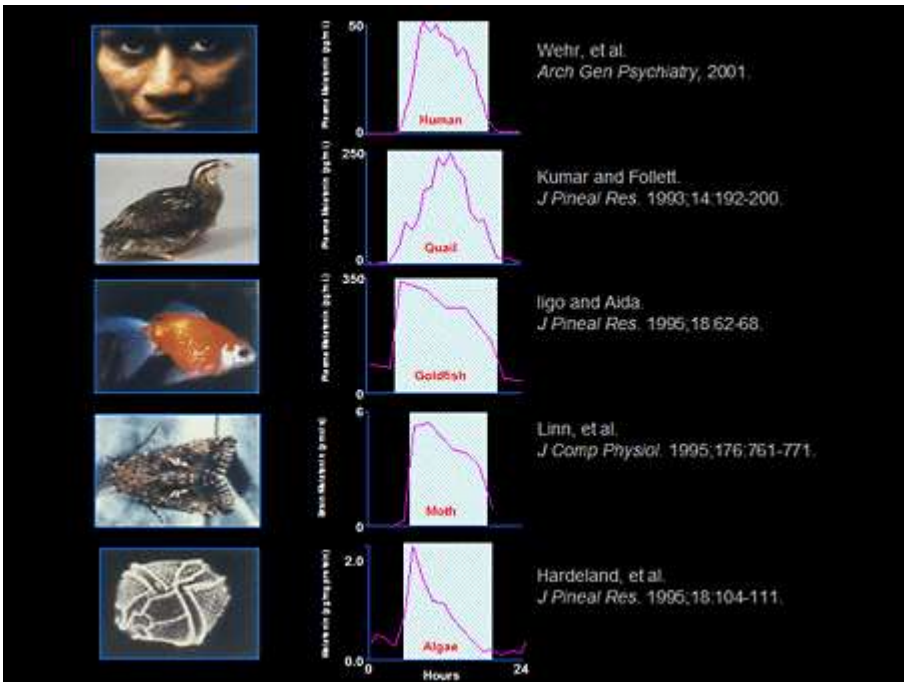
A lot of these findings that I've discussed are similar to, or resonate with, findings that have been described in depression in general, nonseasonal depression. They probably speak to the depressive part of the equation, but there also is the seasonal dimension of the equation: What is it that accounts for the seasonal pattern of recurrence in patients who have winter depression? And there, we have some guidance from animal research because there are many seasonal rhythms in animal behaviors and there's been extensive research on the physiological mechanisms that regulate these behaviors. We have attempted to apply this knowledge to the problem of SAD. In animals, the environmental signal that regulates seasonal behavior is the seasonal change that occurs in the length of the day -- the photoperiod. As days become shorter or longer, this causes changes to occur in reproduction, hibernation, migration, and many, many other animal behaviors.

The physiological mechanism that's employed by many animals involves changes in the duration of the secretion of melatonin, which is secreted principally at night. This signal chemically transduces the seasonal changes that occur in the length of the night around the animal and becomes a chemical signal of seasonal change. I'll come back to that in a moment with more specific information.



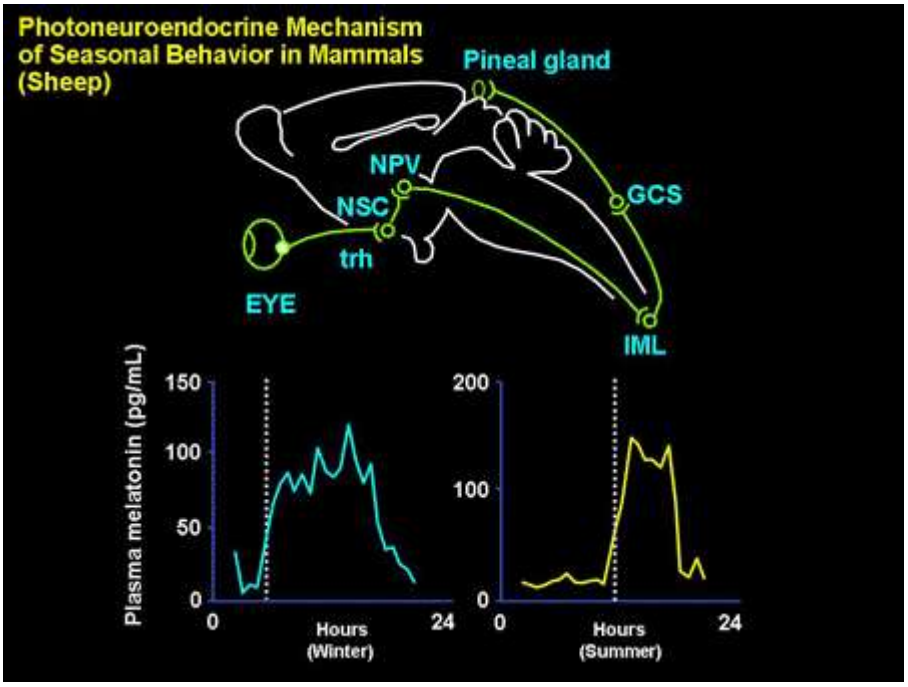
Slide 10.

So for example, in the case of sheep, as days become shorter in the winter, they enter the breeding season that's the beginning of pregnancy, and then as days become longer in the spring, lambs are born, and this timing ensures that the lambs are born at a fortuitous time of year. The sheep become anovulatory in the summer and the early fall, and then the cycle is repeated over again in the winter. The signal that the sheeps' brains are using is the change in the length of the interval between dawn and dusk.



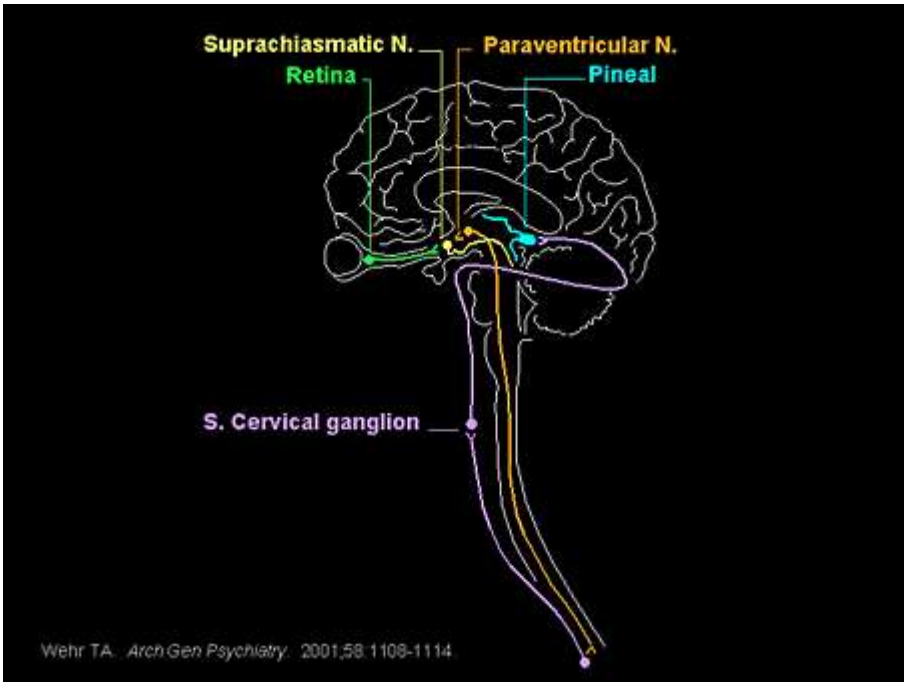
Slide 11.

Now the role of melatonin really crosses many different species. Melatonin is a very unusual hormone in that it's secreted only at night regardless of whether it's a day-active or night-active animal, and this occurs in many different species, ranging from algae to insects to fish to birds to mammals, including humans. The secretion begins in the evening at the beginning of the dark period, indicated in the slide by a light rectangle, and it ends at the end of the night and the beginning of the next day. As the seasons change and the nights become longer and shorter over the course of the year, the duration of the period when melatonin is secreted at night becomes correspondingly longer and shorter, and this changing duration of melatonin secretion is an indicator of the changing length of the nighttime outside. Cells in the hypothalamus and elsewhere that regulate seasonal behavior are able to detect melatonin's presence with melatonin receptors and are able to measure the duration of that presence and then use that information as a signal to induce or suppress various kinds of seasonal behavior. When the duration is long in the winter, those cells cause winter-type behaviors to occur, and when the duration of secretion is short in the summer, that is read as a summer signal and correspondingly causes summer-type behaviors to occur.



Slide 12.

The circuitry in the brain from the eye to the pineal gland that regulates this change has been extensively worked out in animals, shown here in a sheep brain.



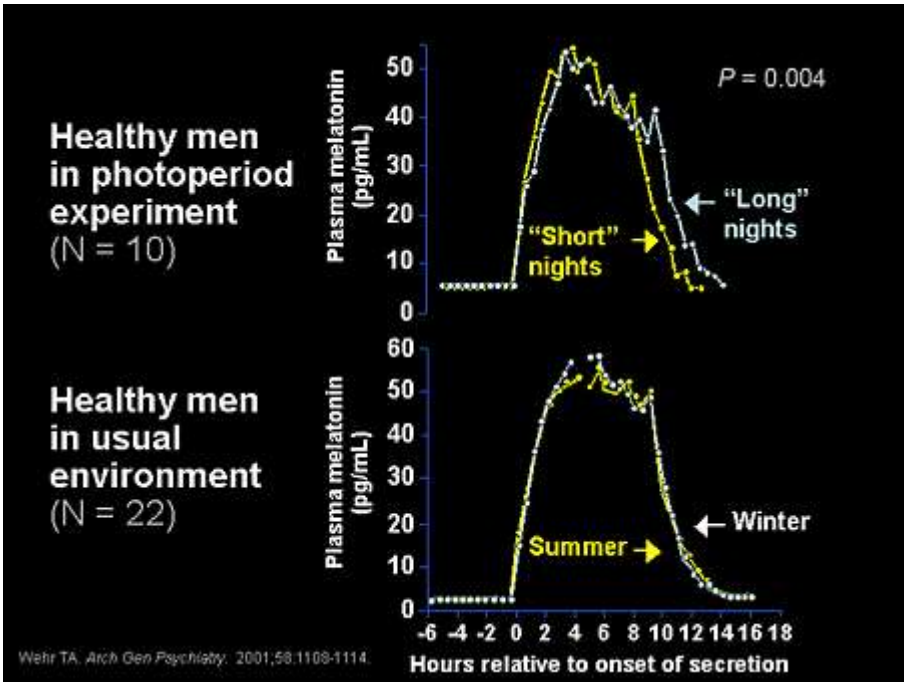
Slide 13.

Essentially, the same circuits have been identified in humans, as shown in this slide. The duration of nocturnal melatonin secretion is programmed by the biological clock, the circadian pacemaker which is in the suprachiasmatic nucleus of the hypothalamus. In the evening, it sends out a signal through a multisynaptic pathway; it goes down through the sympathetic outflow of the cervical spinal cord and back into the skull and into the pineal gland. In the evening, this signal switches on melatonin secretion; in the morning, it switches the secretion off. The suprachiasmatic nucleus, the body's clock, receives information about the length of the day through the retinohypothalamic tract, which goes from the eye to the hypothalamus, but it is important to note that the program originates in the suprachiasmatic nucleus, the program that specifies the length of melatonin secretion. So even if the animal is taken out of daylight and darkness and put into constant darkness, this clock mechanism will remember the length of the days to which the animal has most recently been exposed and program a melatonin duration that is longer in the winter and shorter in the summertime. This is a very important point to keep in mind in viewing the data that follow.

Pathophysiologic Evidence and Implications

Thomas A. Wehr, MD

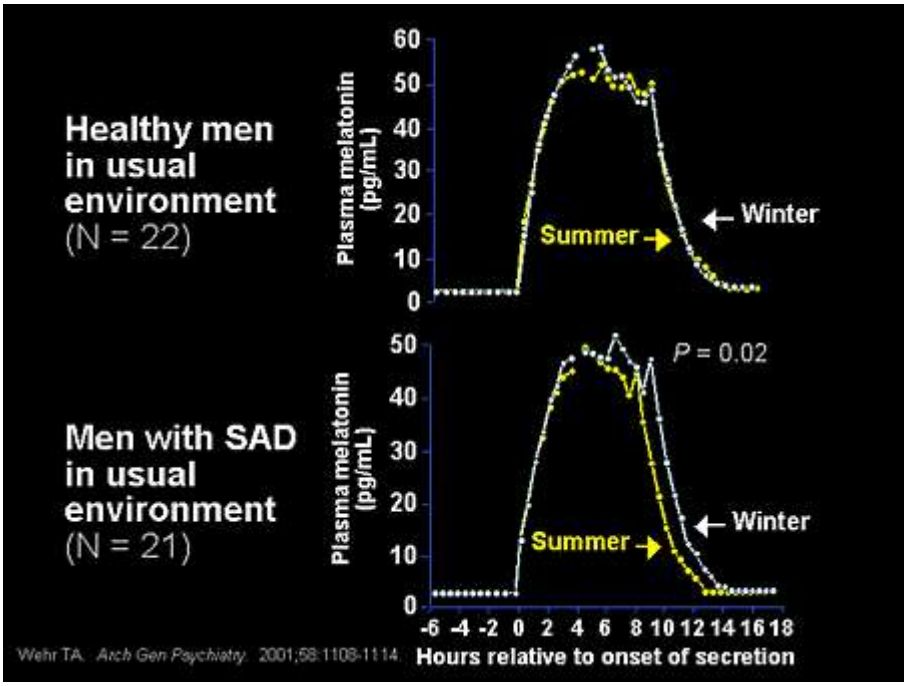
Studies of Melatonin in Humans



Slide 14.

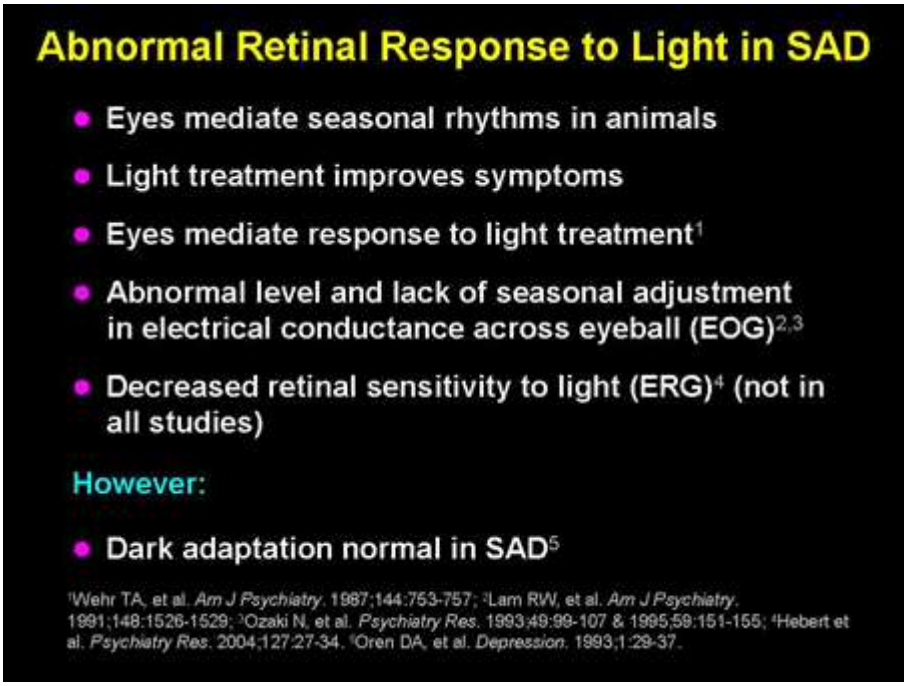
We had wondered whether humans in the course of their evolution had retained a similar mechanism; we know that they've retained all of these pathways that go from the retina to the pineal. And so we did an experiment in which we asked normal volunteers to spend 4 weeks in artificial long nights -- 14 hours long -- and then a similar period in simulated summer nights -- short nights that were 8 hours long -- and on different occasions. At the end of each of these periods, we placed them in continuous darkness for 24 hours and measured melatonin levels in their plasma. Remember, in that situation, we're measuring the length of the night, which their brain detected in the schedule by which they had most recently been living. And sure enough, we found that after they'd been exposed to long nights, they produced a longer pattern, a longer duration of melatonin secretion than they did after exposure to short nights. These data are shown in the upper half of the graph.

Now interestingly, if we looked at healthy volunteers living in their normal environment, going about their usual activities in the presence of artificial light that we all use, and measured their melatonin profiles in the wintertime and then again in the summertime in constant darkness, we found something very different. We found absolutely no change between winter and summer. And from this result, we infer that even though humans would be capable of perceiving and responding to changes in day length in the natural environment, that is not occurring in the modern world with artificial light, presumably because the artificial light to which we're exposed is misinterpreted by the human brain as being sunlight and so that we seem to be living on a constant unvariable long day year-round.



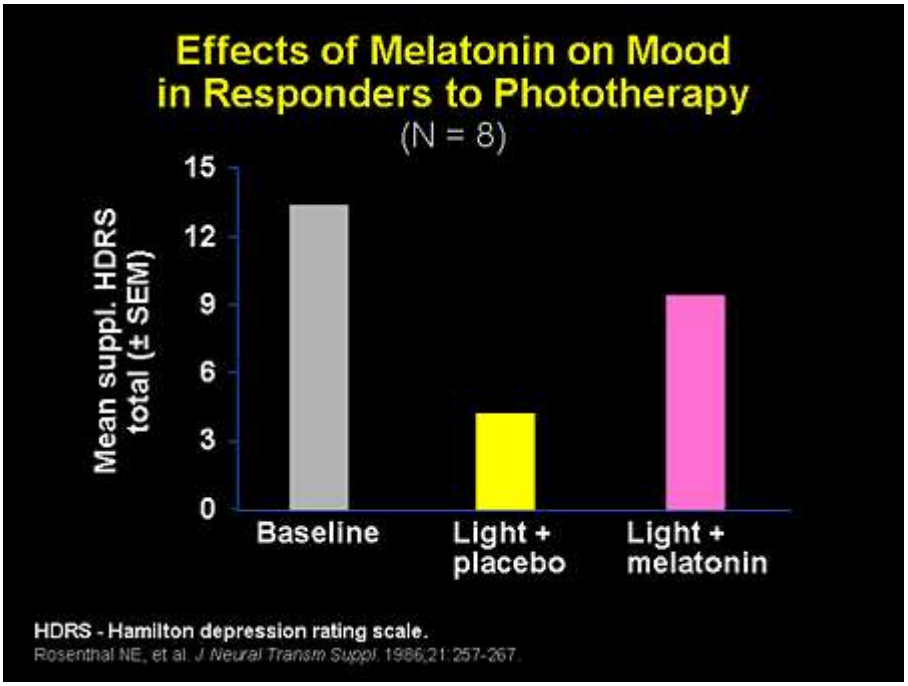
Slide 15.

We wondered if this would be the same in patients with winter depression, so we did an extensive study in which we studied healthy controls in the winter and the summer and patients with winter depression in the winter and the summer. Again, we found no change in the healthy controls between winter and summer in this important biological signal of seasonal change. However, in the patients, we found that in spite of the fact that they're exposed to artificial light in their normal environments, the duration of melatonin secretion was longer in the winter and shorter in the summer, so that they were producing the same chemical signal that many other mammals use to regulate seasonal rhythms.



Slide 16. Abnormal Retinal Response to Light in SAD

Now this raises a question of whether patients with winter depression are somehow less sensitive to light, because one way to understand this finding is that while patients are capable of responding to sunlight and detecting changes in the seasonal length of the day, they're not reacting to the relatively dimmer artificial light to which they're exposed after the sun sets. And there is some evidence to support this idea of decreased retinal sensitivity to light in patients with winter depression. Most notably, there have been findings of abnormal results with electro-ocular graphic measurement of electrical conductance across the eyeball. Most importantly, in a recent study that was relatively well conducted and relatively sensitive to these types of changes, a certain type of electroretinogram was measured in patients with winter depression and in healthy controls. The patients with depression were found to have decreased retinal sensitivity, a finding that might explain this difference between normal controls and individuals with winter depression; it might explain their particular vulnerability to seasonal change.



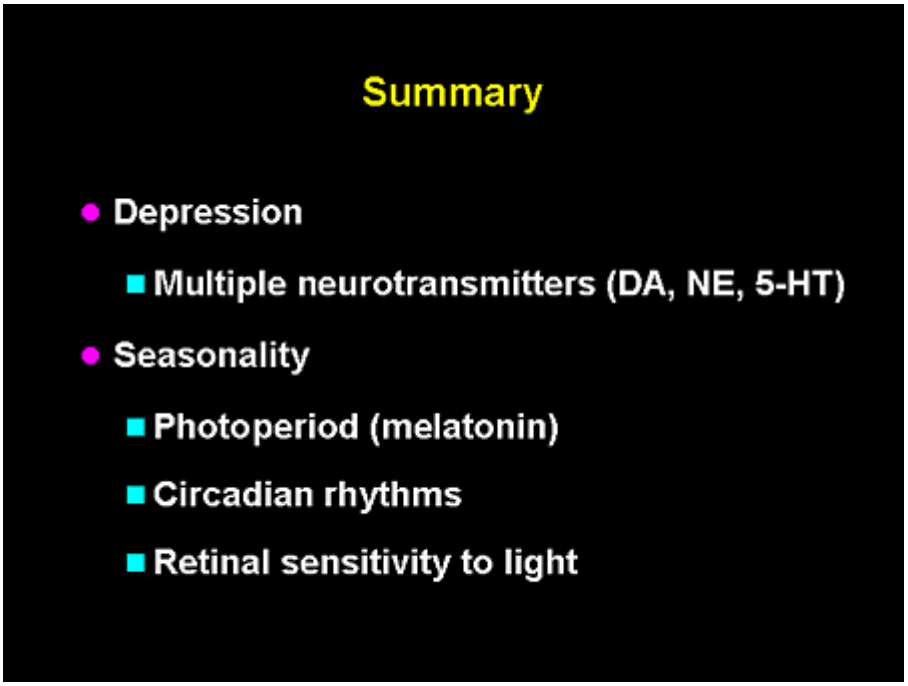
Slide 17. Effects of Melatonin on Mood in Responders to Phototherapy

Now in terms of whether melatonin might have a causal role to play in winter depression, a study was carried out by Rosenthal and associates a number of years ago in which patients' depression scores were measured at baseline, then they were treated with light, and then either placebo or melatonin was added to the light treatment in the patients who responded. It was predicted that if the increased duration of melatonin secretion in winter played a causal role in the pathophysiology and pathogenesis of winter depression, then adding back melatonin where light had suppressed it should re-introduce some of the symptoms of winter depression. And indeed, some of the most characteristic symptoms, namely those of oversleeping, overeating, carbohydrate craving, and weight gain, were reinduced by the addition of melatonin to the light treatment. So this one finding would tend to support the idea that these changes in melatonin duration, which regulates seasonal rhythms in animals, might be helping to trigger winter depression in patients with SAD.

Pathophysiologic Evidence and Implications

Thomas A. Wehr, MD

Summary



Slide 18. Summary

To summarize, there are a number of findings of abnormalities, particularly in neurotransmitter function in winter depression; some of these are very similar to those that have been described in nonseasonal depression and involve dopamine, norepinephrine, and serotonin. There's some evidence that humans have retained brain mechanisms that regulate seasonal rhythms in animals, that these mechanisms involve changes in the duration of melatonin secretion, and that the sensitivity of individuals to winter depression may partly depend on a reduced sensitivity to artificial light that has been introduced in modern life and that has suppressed seasonal rhythms in most individuals. And one could think of this as a kind of dual vulnerability, a vulnerability to depression and a vulnerability to change in season that's interacting to produce winter depression.

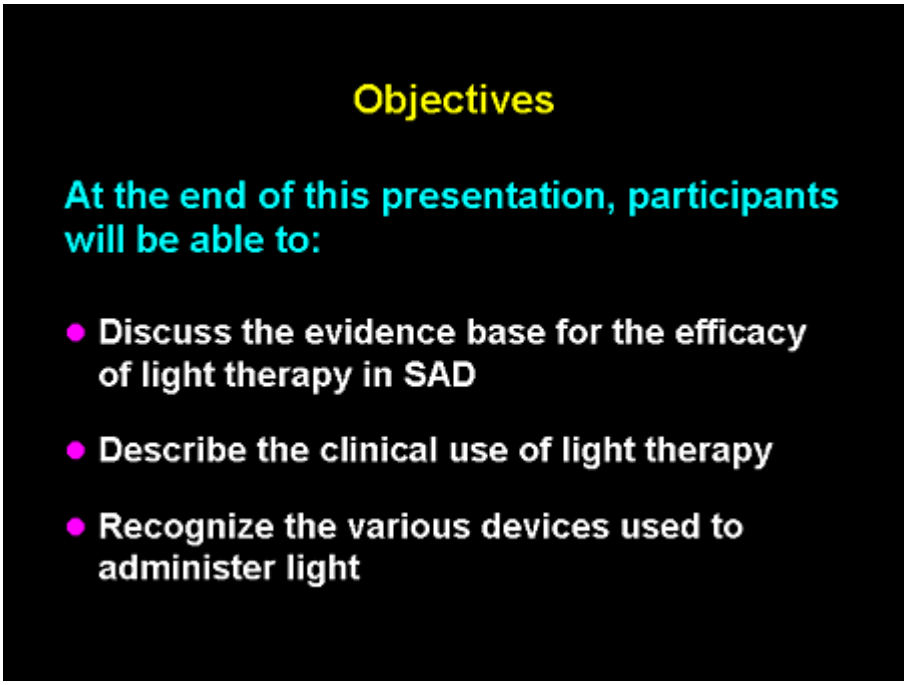
Light Treatment: State of the Art

Raymond W. Lam, MD

Introduction

Slide 1. Light Treatment: State of the Art

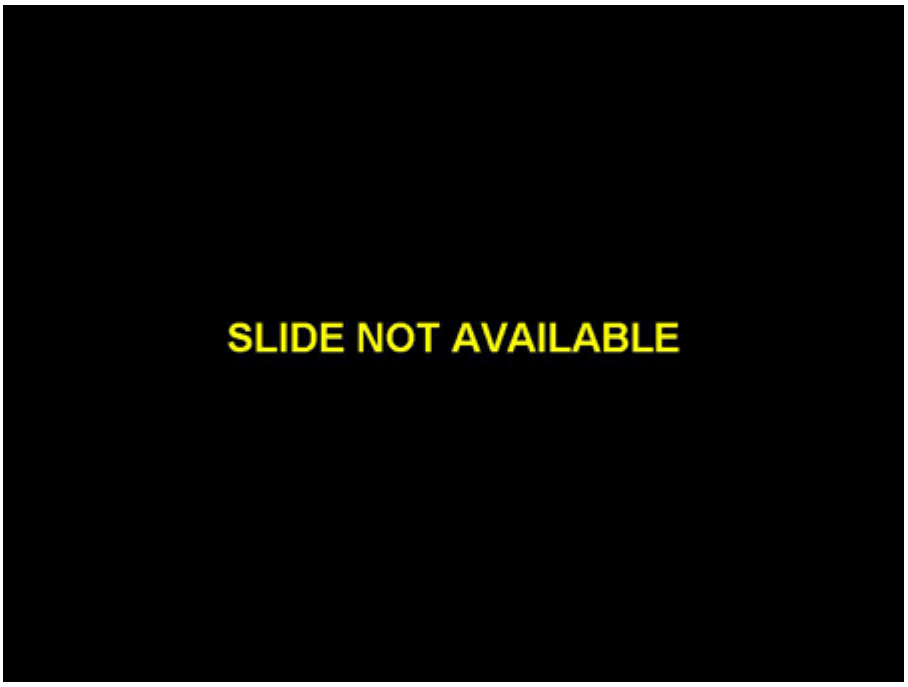
I'm Dr. Raymond Lam, and I'm director of the Mood Disorders Centre at the University of British Columbia Hospital in Vancouver, Canada. I'm going to talk about light treatment for winter depression, a status report.



Slide 2. Objectives

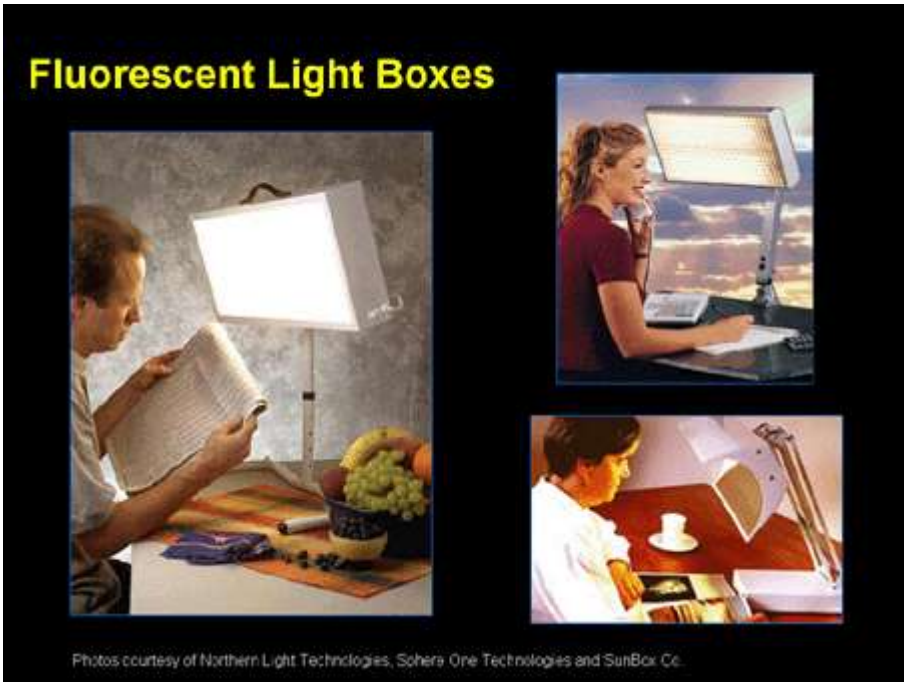
Here are the objectives for this presentation. We're going to talk about some of the evidence behind the efficacy of light therapy for seasonal affective disorder (SAD), and

describe the clinical use of light therapy based on clinical guidelines for SAD. We'll also briefly cover some of the various light devices used to treat people with SAD.



Slide 3.

Light treatment actually is used for a number of conditions including chronobiological sleep disorders, nonseasonal depression, and other depressive disorders, but I will focus on its use in SAD, which is, of course, a syndrome of recurrent winter depression in which people only are depressed during the wintertime and in summer they're in full remission feeling perfectly normal.



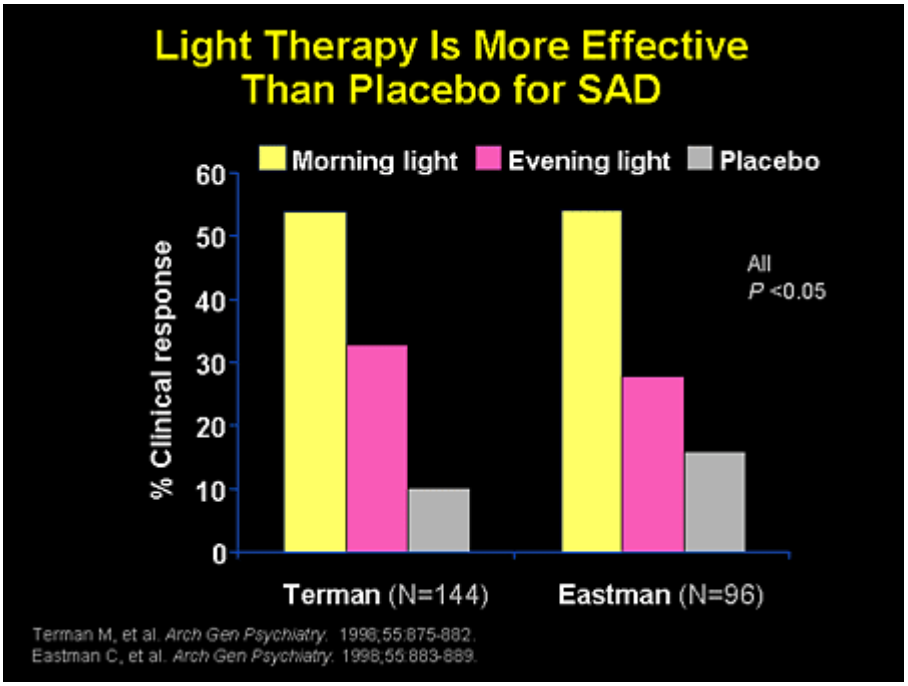
Slide 4. Fluorescent Light Boxes

Here are some of the gold standard light boxes that are recommended for use in light treatment. As you can see, they are various devices that sit on the desktop and are relatively portable. Patients sit in front of these lights for administration, and we regard fluorescent light boxes really as the gold standard for light therapy. However, there are a number of newer devices that are being investigated; for example, there are some much more portable light devices, which use new technology, light-emitting diodes, and a number of those devices look like they will be as good as light boxes for treatment of SAD.

Light Treatment: State of the Art

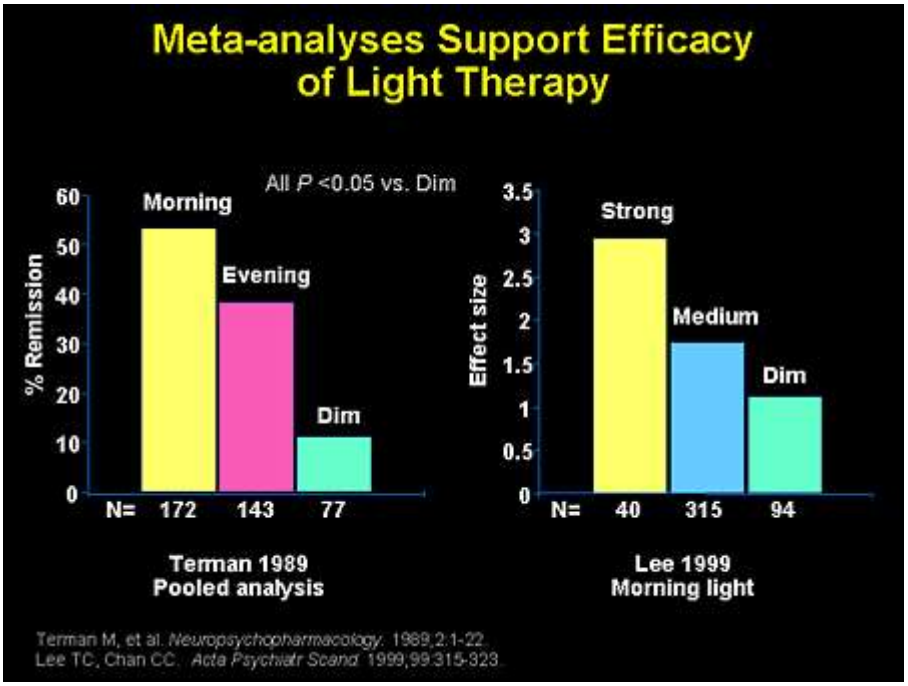
Raymond W. Lam, MD

Studies Supporting the Efficacy of Light Therapy



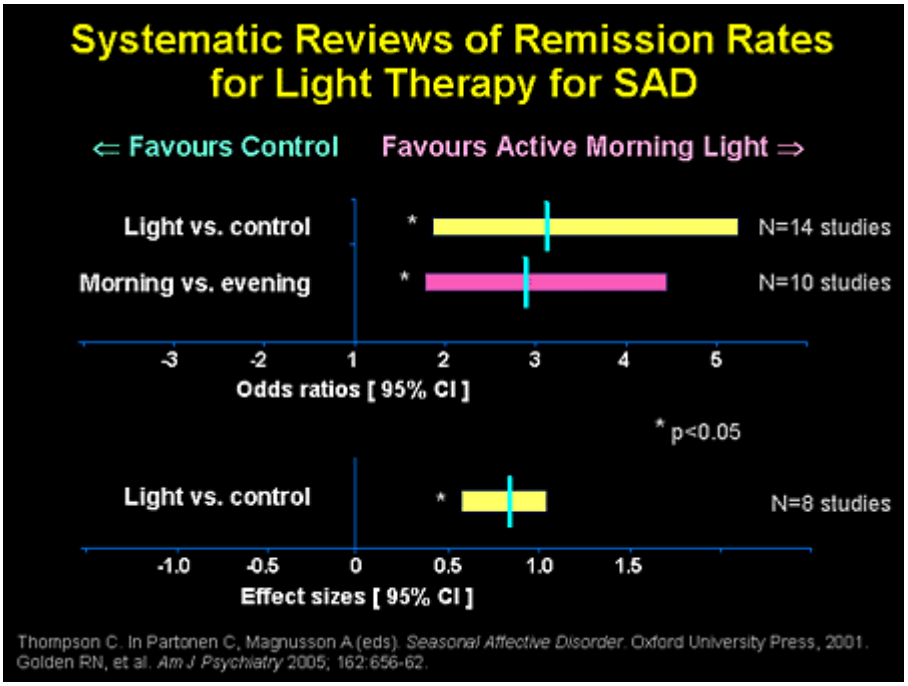
Slide 5. Light Therapy Is More Effective Than Placebo for SAD

Now many people have been skeptical about light treatment in the past in part because there have not been as many controlled studies as, for example, for antidepressant medications. However, in 1998, there were 2 larger-scale studies conducted, both of which showed clear evidence to support the efficacy of light therapy. In these studies reported in the *Archives of General Psychiatry*, both used plausible placebo-controlled conditions for the light treatment. One of the issues with light therapy is that it is a novel technology; people have to sit and use the light box, so you have to control for many of the behavioral factors that may lead to improvement in patients. And so it's important to design a plausible placebo control. Both of these studies actually used a very similar placebo control; they used negative ion generators, and the rationale for that is that people know about negative ions and the beneficial effects of negative ions. It's a technology as well; you have to sit in front of it, and so you can control for many of those behavioral factors that are in play when you're using light treatment. However, in Terman's study, they used a negative ion generator that emitted very low-density negative ions that are not thought to have any effect on human behavior. In Eastman's study, they used a negative ion generator that even though it had a nice light and made a nice buzzing noise, it actually did not emit any negative ions. And as you can see in the slide, it says percent clinical response, but it should be actually clinical remission. These are people who are perfectly well after 2-5 weeks of treatment with light. You can see that both studies show that the bright light treatment was significantly better than the placebo condition. In fact, both studies also showed evidence that light given in the early morning actually is superior to light given in the evening. So these are very consistent results using fairly large sample sizes, both of which support the efficacy of light treatment.



Slide 6. Meta-analyses Support Efficacy of Light Therapy

There are a number of meta-analyses that support the efficacy of light therapy. Meta-analysis is a statistical method used to pool a number of different studies together in order to come to a general conclusion. An early meta-analysis by Michael Terman in 1989 again showed that morning and evening bright light were significantly better than the dim-light placebo controls, and Lee's study in 1999 also showed a very similar effect where high-intensity light was significantly better than the dim-light placebo controls. The limitations of these 2 meta-analyses, however, were that they did not include only randomized controlled trials, so there were some open-label data that were incorporated in these meta-analyses as well as fairly small sample size studies that were included. More recent meta-analyses have been done using rigorous methodology to control for some of these design limitations in these previous meta-analyses.



Slide 7. Systematic Reviews of Remission Rates for Light Therapy for SAD

The first systematic review of light treatment was described by Thompson, and this was based on Cochrane collaboration methodology. As many of you are aware, the Cochrane collaboration is an international society focused on systematic reviews and meta-analyses, and they incorporate very rigorous methodology for pooling together these studies. This meta-analysis also showed that light was significantly better than control conditions and, in fact, that morning light exposure also was better than evening light exposure. This slide shows the odds ratios, which means that about 3 times as many people respond to bright light treatment compared with the control conditions, a clear case for efficacy. An even more rigorous meta-analysis was done by the American Psychiatric Association Task Force on psychiatric treatments, and there they only looked at the most rigorous randomized controlled trials. They identified 8 studies of light treatment vs plausible control conditions and also found that the light therapy was more efficacious compared with placebo-controlled conditions. Here, though, they describe the effect size, which is the measure of clinical effect over and beyond the control condition. And the effect size found in this study was about 0.8, which is a very large effect size for psychiatric treatments. Just in comparison, the usual effect size quoted for antidepressant studies in nonseasonal depression is between 0.4 and 0.5. So I think that there's now considerable evidence based not only on plausible randomized controlled trials, but also on systematic reviews and meta-analyses, that clearly show light treatment is an effective therapy for SAD.

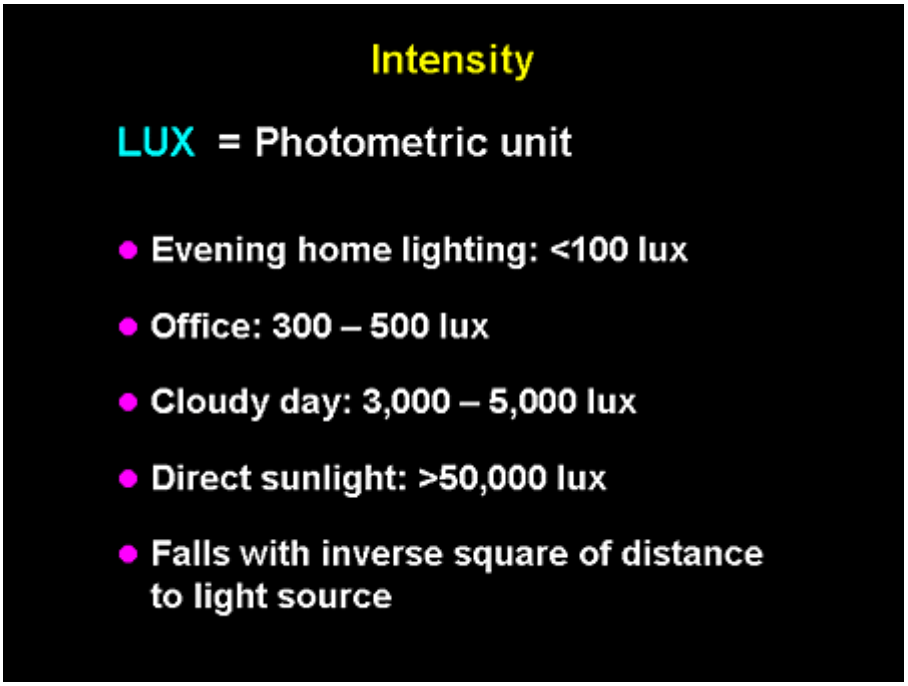
Light Treatment: State of the Art

Raymond W. Lam, MD

Clinical Considerations and Recommendations for Light Therapy

Slide 8. Effective Light Therapy

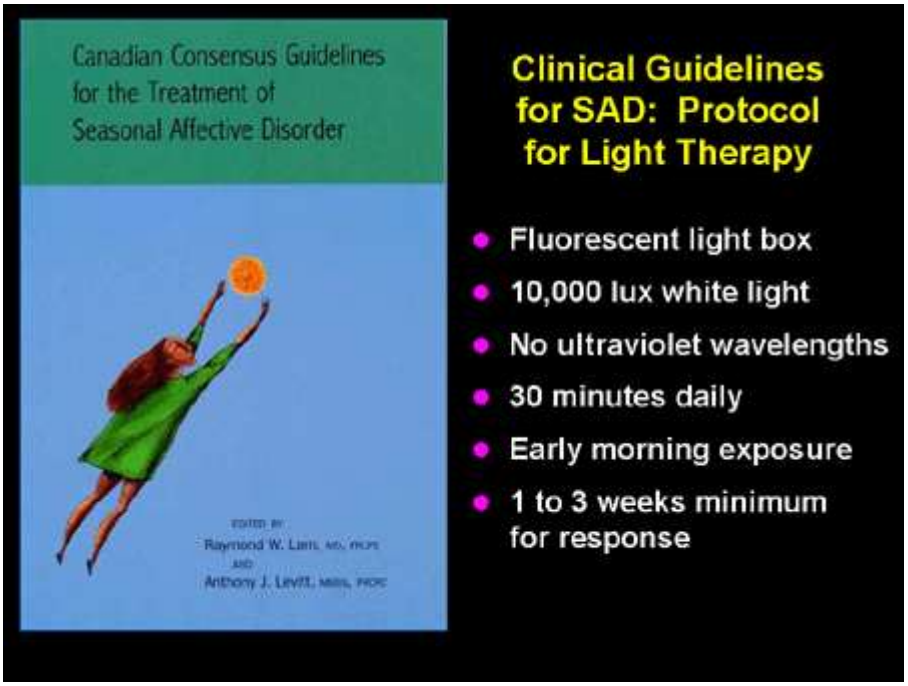
When we talk about the clinical use of light treatment, I always like to make sure that people understand what light therapy is not. And it's not just a matter of changing your kitchen lights; we know that it's really impossible to get indoor light up to the intensity that we think is important for these behavioral effects. There's certainly no evidence to suggest that tanning studios are effective light therapy; in fact, the effect we think is through the eyes, not through skin exposure and clearly not through the ultraviolet portions of the spectrum. So tanning by itself is not likely to be helpful for SAD, and you should definitely not open your eyes in those tanning beds because of the risk of ultraviolet exposure to the eyes. It's also not a special type of light, because our understanding currently is that it's the intensity of light that's more important than the particular spectrum, although there is some interesting new research suggesting that particular wavelengths of light may be a little bit better for some of the effects of bright light treatment. However, for SAD, those studies haven't yet been done to show that it's a special wavelength of light that may be more important.



Slide 9. Intensity

What is important in terms of parameters for light treatment? When we talk about parameters, intensity of light seems to be the most important one. Light is a very complex phenomenon and there are many different ways to measure light. The most commonly used method is called lux, which is a photometric unit. And just for a basis for comparison, when you're in a very brightly lit office, it is somewhere between 300 and 500 lux. When you're at home in your living room with social lighting, it's often less than 100 lux of exposure. The indoor light exposure actually is much less than outdoor light exposure. So, for example, the light outside on even a cloudy, gray, overcast day is often 3000-5000 lux. And when we're talking about being outside on a sunny day, you will get 50,000 lux of light exposure or higher. So we're talking about orders of magnitude difference in terms of the intensity of indoor light vs outdoor light.

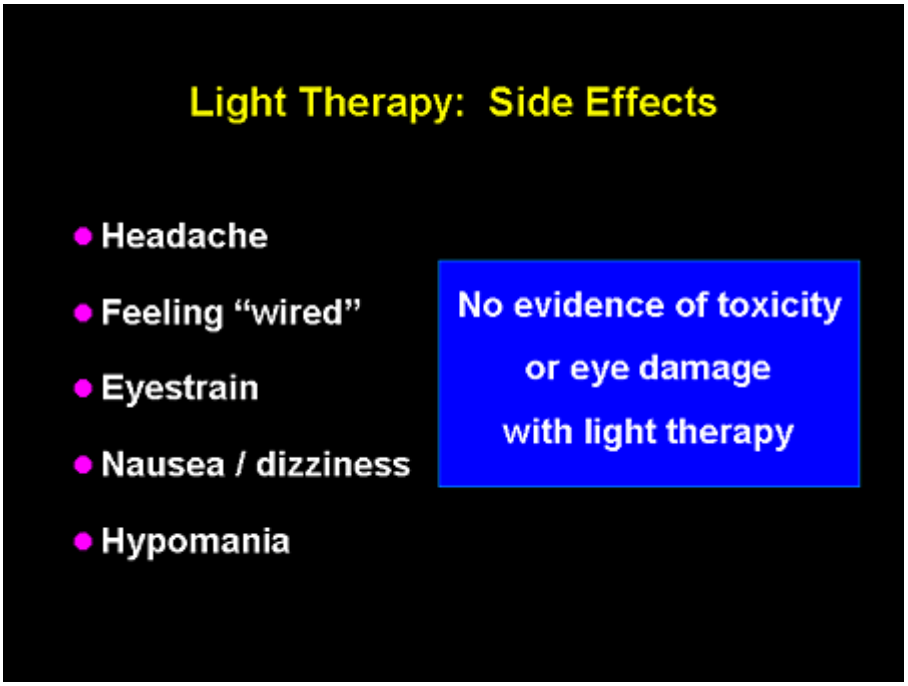
But the other important factor when we're talking about lux is that the lux rating falls with the inverse square of the distance to the light source. What that means simply is that the farther away you are from the light source, the more rapidly the lux intensity drops. It's very important when we're talking about light devices and their lux rating that you not only know what the intensity of light is, but at what distance that rating is because distance is fairly critical to ensure that you're getting the proper intensity of light.



Slide 10. Clinical Guidelines for SAD: Protocol for Light Therapy

We have completed clinical guidelines for SAD, put together by an expert panel in Canada, in which we reviewed all of the studies of light treatment using rigorous consensus methodology and came up with clinical recommendations for using light. The slide lists the clinical recommendations that came out of this consensus approach. Again, the gold standard for light treatment currently is a fluorescent light box using 10,000 lux of white light, given for 30 minutes a day. Most patients will respond to 30 minutes of exposure at that 10,000 lux rating. Lower intensity light devices generally require longer treatment durations. So, for example, when we started out in the field, we were using much larger 2000 lux light boxes, and there you need 2 hours of exposure for the same clinical benefit. And of course it's very hard to get 2 hours of exposure to a light box a day, so the newer 10,000 lux light boxes are beneficial in that you only need to have 30 minutes of exposure daily. Some patients need even less once they're feeling better. The ultraviolet wavelengths likely do not contribute to the antidepressant effect, and so almost all light boxes sold now have an ultraviolet filter so that you don't get some of the detrimental effects of ultraviolet light when you're getting your bright light exposure.

And again, from some of those data that I presented, it seems that early morning exposure is the most beneficial time for SAD patients in general. So for a particular person, it may not be as important in terms of the timing of light, but as a group, early morning seems to do better than evening light exposure. And generally speaking, the response to light is fairly rapid, so that many patients experience benefit within a week of using the lights; most patients will have a noticeable clinical benefit by 2-3 weeks and so we really feel that 3 weeks is the minimum trial to determine someone's response to light therapy.



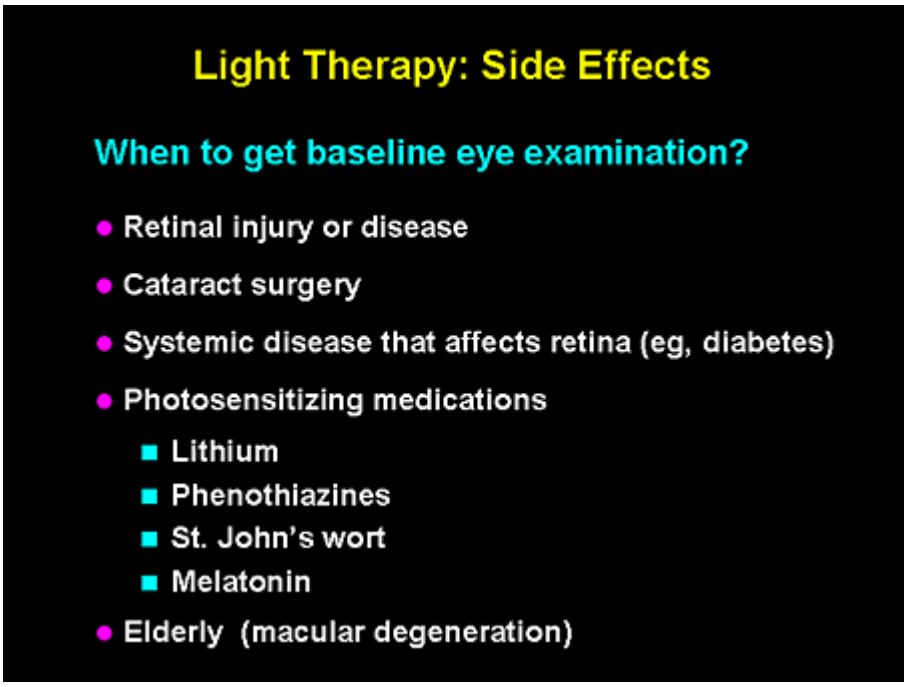
Slide 11. Light Therapy: Side Effects

There are some side effects of light therapy, despite it being a very natural treatment that many patients request because they've read about it in the papers or magazines. The common side effects of light actually are very similar to those of the newer antidepressant medications like selective serotonin reuptake inhibitors (SSRIs). Patients when they're using bright light treatment may complain of mild headaches. There's an alerting effect, an immediate alerting effect of bright light, which for some people makes them feel a bit wired or revved up or keyed up. Occasionally, patients will describe blurred vision or some eyestrain with using the bright light, maybe some mild nausea or dizziness associated with it. In patients at risk, there is a small risk of precipitating hypomania or mania with light therapy, so like any effective antidepressant treatment, there is that risk particularly in people who are at risk for bipolar disorder. I'll talk a little bit about what is needed when you're treating patients with bipolar disorder who have winter depressive episodes.

However, generally speaking, these side effects that are experienced with light are very mild, and I would say milder than those seen with antidepressant medications. They usually occur at the onset of treatment, and then once people are adjusted to the lights, they get better with time and they often respond just to reducing slightly either the intensity of light by sitting a little farther back from the light or by using it for a slightly shorter duration.

It is important to recognize that at the recommended intensity of light treatment there's no evidence of toxicity or eye damage with light therapy. There have been a couple of studies now in which there have been 5-year data; people have used light treatment every winter for 5 years or longer with detailed ophthalmologic examinations showing that there are no changes in eye function with chronic use of light treatment. So that's the

good news because, as I mentioned, it is the effect through the eyes that's important for the antidepressant effect. However, we still have to be a little bit cautious about using bright light because there are some theoretical changes that may occur in the retina with bright light exposure, and this may be exacerbated by medications that act on the retina. Even though there's no clinical evidence to suggest toxicity, I think there is some theoretical basis for concerns, particularly when people are taking adjunctive medications.



Slide 12. Light Therapy: Side Effects

We have some clinical recommendations for when to get, for example, a baseline ophthalmologic exam before starting light therapy. We don't feel that people need to have an eye examination routinely; however, if they have some risk factors for retinal disease, that would be the time to be careful and use a baseline eye examination and periodic monitoring, perhaps once a year to make sure that there aren't changes occurring in the eyes. And the slide lists the risk factors that we've identified: people who have pre-existing retinal disease; cataract surgery is not so much of a problem now as before when they used to remove the lens and not put in a replacement lens. The only problem with that is that the lens acts to block much of the ultraviolet exposure, but now most light devices have filters that filter out ultraviolet rays, and so it's not such a risk factor any longer for bright light effects. However, there are other systemic illnesses that affect the retina, and the most common of these is diabetes. There are some medications that do have effects on the retina, photosensitizing at the eye level, not necessarily through skin. And so for psychiatrists, some of the important medications to consider include lithium, phenothiazines and antipsychotics such as thioridazine. There are well-known effects on the retina with thioridazine. There is some evidence to suggest photosensitivity with St. John's Wort and with melatonin. In the elderly, there's a higher risk of macular degeneration, which is an eye disease associated with reduced vision and often is

asymptomatic. So it's helpful in the elderly to get a baseline eye exam, not necessarily because the light therapy will worsen macular degeneration -- there's no clinical evidence for that -- but because you want to be able to pick up a potential retinal problem before using bright light. In patients who have these risk factors, we would generally recommend a baseline eye examination prior to starting light treatment and periodic monitoring, perhaps once a year or so.

Slide 13. How Long Do You Continue Light Therapy?

Once someone is better with light treatment, and many of the larger naturalistic treatment studies suggest that about two thirds of patients get a very good response to light treatment alone, there are no great data to really show the optimal duration of treatment in terms of long-term maintenance. So the recommendations in the slide are based on clinical experience and consensus guidelines. Once people get better with light treatment, then, generally speaking, they should continue using lights for the duration of that winter season -- in other words, until the time that they would undergo their natural remission of depression, usually in the spring/summer months. There have been no withdrawal or discontinuation effects reported with light treatment, so it can be discontinued fairly abruptly; there's no worry about having to discontinue it slowly over the withdrawal period. If people stop the light therapy too soon, however, in the wintertime, they will generally relapse and the relapse follows the same timelines as response. So generally speaking, 2 or 3 weeks after stopping light treatment, most people's symptoms return and that's why we recommend that they continue the light treatment until the time of their natural spring or summer remission.

Now how about the next season? When should patients start using light treatment the following season if they've had a good response? That isn't something that's been well studied. Many times we recommend that patients start using their lights before the onset

of their symptoms; in other words, to really be sure that you prevent an episode of winter depression from happening, start the lights early, continue it through the winter so that patients really don't experience any symptoms at all. However, for some patients, they would prefer to use it at the first onset of symptoms, and the reason that is helpful sometimes is because the onset of effect is fairly rapid, many patients prefer to wait to make sure that they're actually going to have symptoms in the fall before starting to use their lights. And then once they start using their lights, particularly if their symptoms are mild, the onset effect occurs very rapidly and then they don't have problems for the rest of that season; so for many patients, that's a reasonable strategy. The only problem with that is that in our experience we've seen some patients who prefer to wait until the onset of symptoms. Because the onset is so insidious, they actually don't notice that they're starting to get depressed, and by the time they really realize it, they're in a full-blown major depressive episode and then it gets much harder to get the motivation to start using lights and they notice that they often lose a few months of productivity before they get treated again. So that's an argument for prophylactic therapy, or use of light before the onset of symptoms.

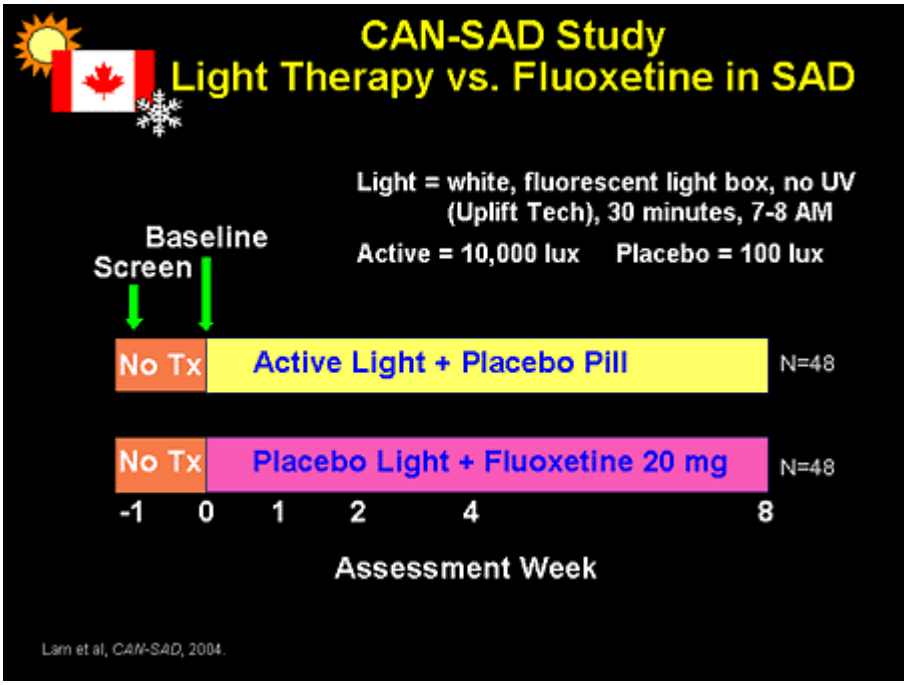
Light Treatment: State of the Art

Raymond W. Lam, MD

Canadian Study of Light Treatment vs Fluoxetine for Seasonal Affective Disorder: Methodology

Slide 14. CAN-SAD Study 2000 - 2003

One of the critical questions about light treatment is how does it compare with antidepressant medications? And in order to address that particular question, we conducted really the first large-scale comparison, a head-to-head trial of light treatment vs an antidepressant medication -- in this case, fluoxetine. This was a Canadian study, a multicenter, randomized, controlled trial investigating light therapy vs fluoxetine. It involved a reasonable number of patients, almost 100 SAD patients recruited over a period of 3 winters, and it's really the longest controlled light therapy study because we used 8 weeks of treatment in order to get a fair comparison between light and antidepressants. We looked at multiple outcomes, including symptomatology, quality of life, etc, and this was funded by the Canadian Institutes of Health Research in Canada.



Slide 15. CAN-SAD Study: Light Therapy vs Fluoxetine in SAD

The protocol actually was fairly straightforward. It was an 8-week study; there was a 1-week baseline in which patients were followed with no treatment just to establish baseline ratings, and then they were randomized to 8 weeks of treatment, either with active light or with fluoxetine. I mentioned, however, the importance of expectations and placebo response and that's because light is very different from antidepressants. So we wanted to control for some of the different expectation effects of people being treated with light vs medication. In our protocol, patients got both a light box and took a pill. However, half the group received active bright light, which was our standard treatment recommendation of a 10,000 lux fluorescent light box for 30 minutes a day in the early morning hours, and they got a placebo pill, whereas the other group got an active pill, fluoxetine 20 mg per day, but they got a placebo light box. For our placebo light box, we used a 100 lux light box; it was an identical light box except it emitted only 100 lux. And 100 lux is still a plausible control because it looks like a table lamp or something like that. We used some deception; we didn't tell them that some of the light boxes were dimmer than others, and so this was a plausible control condition to control for the

expectation effects of light. However, I should note that this is really an effectiveness trial, not an efficacy trial because, as you will notice, there's no double placebo condition. It's simply active light vs active drug, but we thought that would be a good design to answer this head-to-head clinical question.

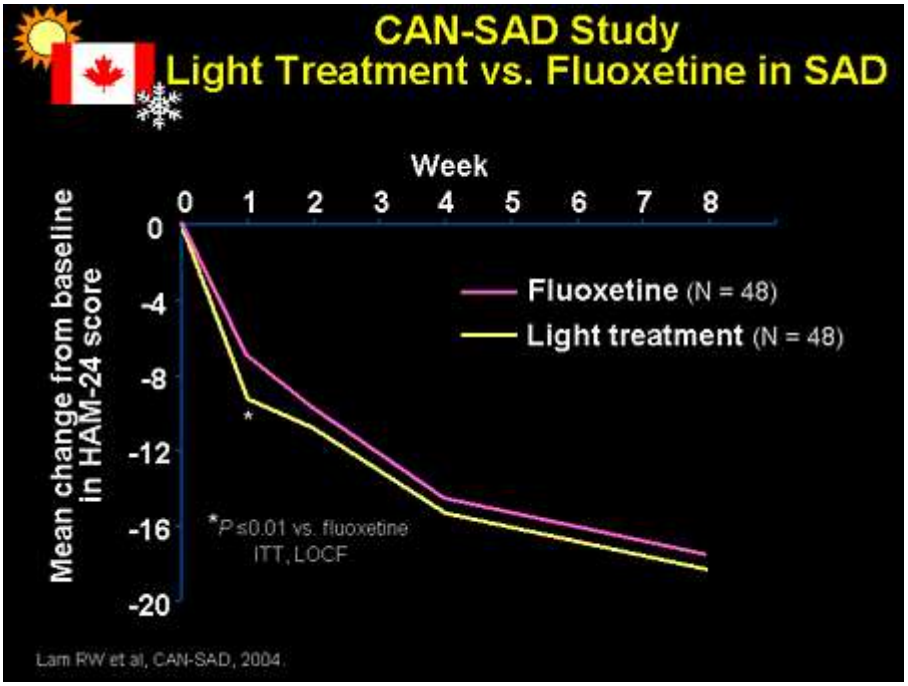
Slide 16. 10,000 Lux, Raised, Tilted Light Box

This slide shows the light box that we used; again, a standard light box. Patients were instructed on how to use it -- they had to sit at a certain distance. They used the light boxes at home because this was an outpatient study, and they came in weekly for ratings.

Light Treatment: State of the Art

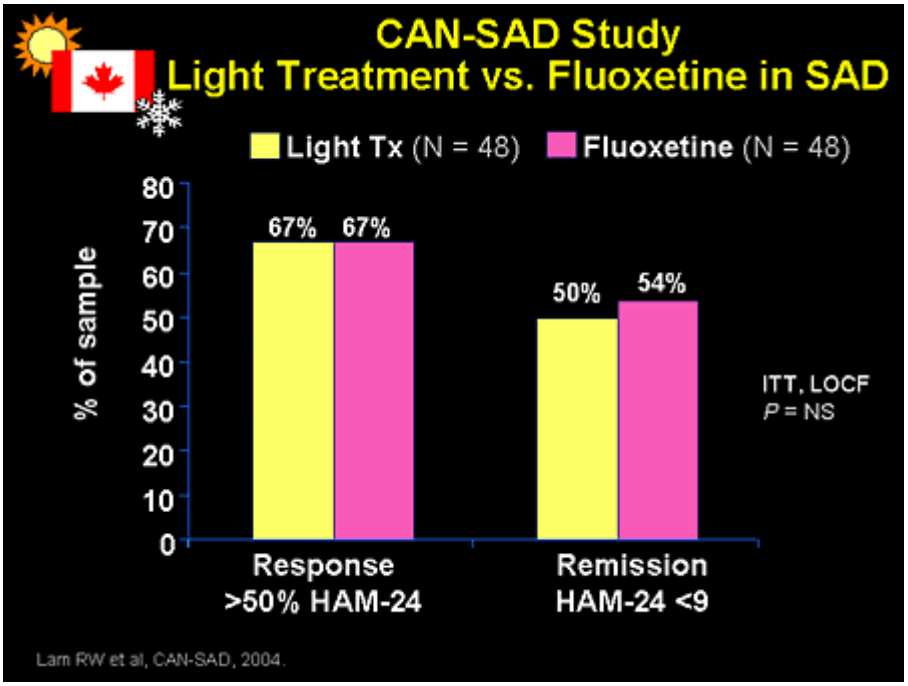
Raymond W. Lam, MD

Canadian Study of Light Treatment vs Fluoxetine for Seasonal Affective Disorder: Results



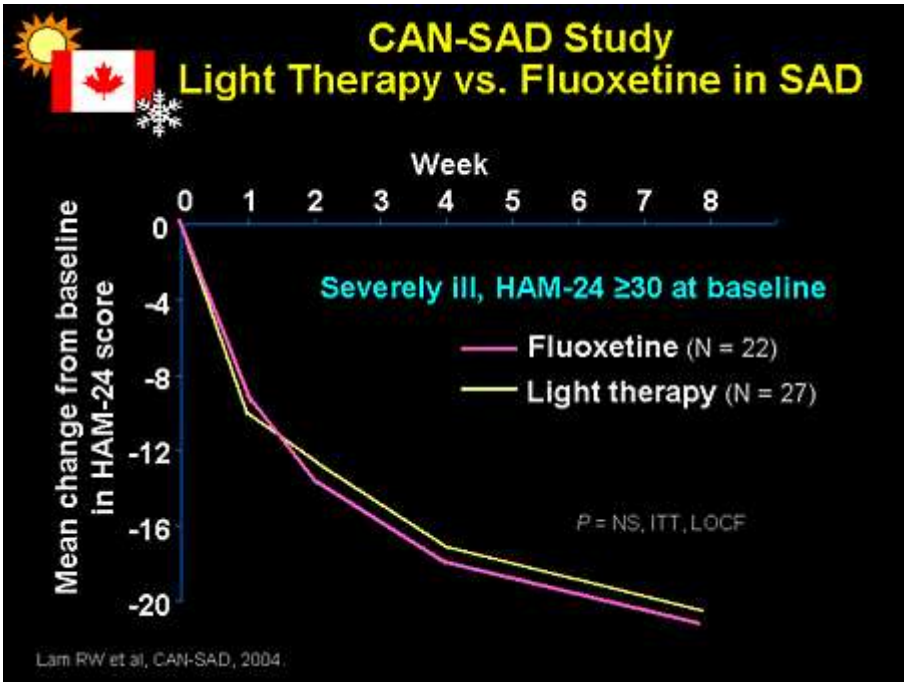
Slide 17. CAN-SAD Study: Light Treatment vs Fluoxetine in SAD

This slide shows the main results of the study, and you can see on the y-axis the change in the depression score; we used a 24-item version of the Hamilton Depression Rating Scale that includes both the typical and atypical symptoms of depression that are very important and more commonly experienced in people with SAD. Across the x-axis are the 8 weeks of the study. So the farther down the line goes, the greater improvement the patients are having at any given time point. As you can see, both light and fluoxetine work very well for these patients with SAD. At the end of 8 weeks, there was absolutely no statistical difference in the improvement in depression scores between the fluoxetine-treated patients and the light-treated patients. However, the light-treated patients did seem to have a slightly earlier onset of effect on a post-hoc analysis, so that by 1 week, there was a statistically significant superiority of light treatment compared with the fluoxetine. You can see that by week 2, the fluoxetine has caught up, and for the duration of the study, the improvement curves almost are superimposable. So both treatments were very effective for people with SAD; light treatment had a slightly faster onset of effect at 1 week compared with the fluoxetine.



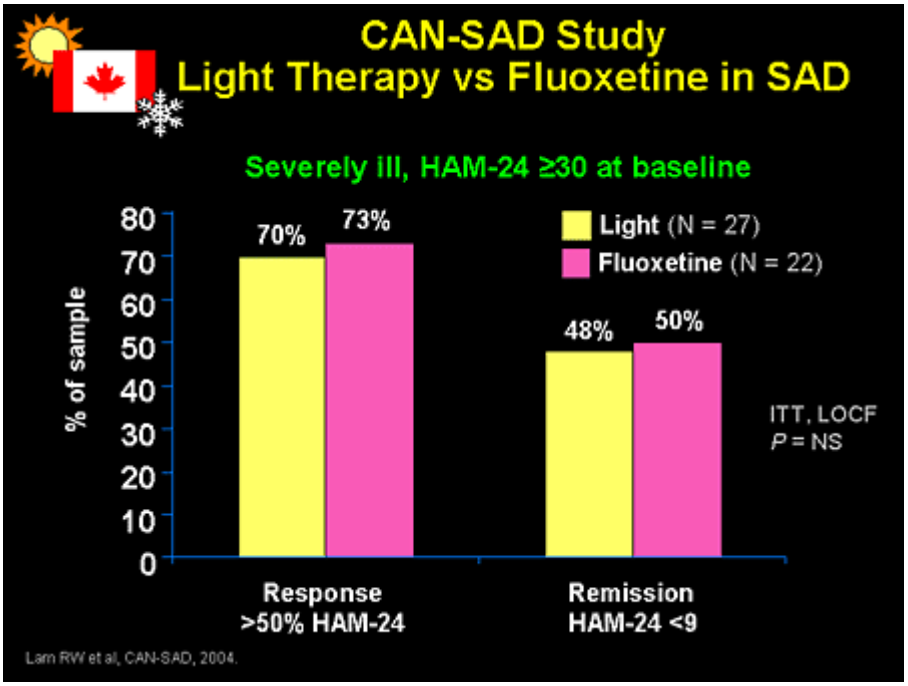
Slide 18. CAN-SAD Study: Light Treatment vs Fluoxetine in SAD

When looking at the response and remission rates, response we define as a 50% improvement in the Hamilton Depression Rating Scale; remission is a score on the Hamilton scale at the end of treatment that's within the normal range -- in this case, 8 or less. And this slide just shows the percentage of the sample that had both response and remission; you can see that about two thirds of the patients had a clear response to treatment after 8 weeks, whereas about 50, about half the patients, actually were in clinical remission, were back to baseline at the end of 8 weeks of treatment. And again, no significant differences between the light-treated or the fluoxetine-treated patients; both treatments were very effective.



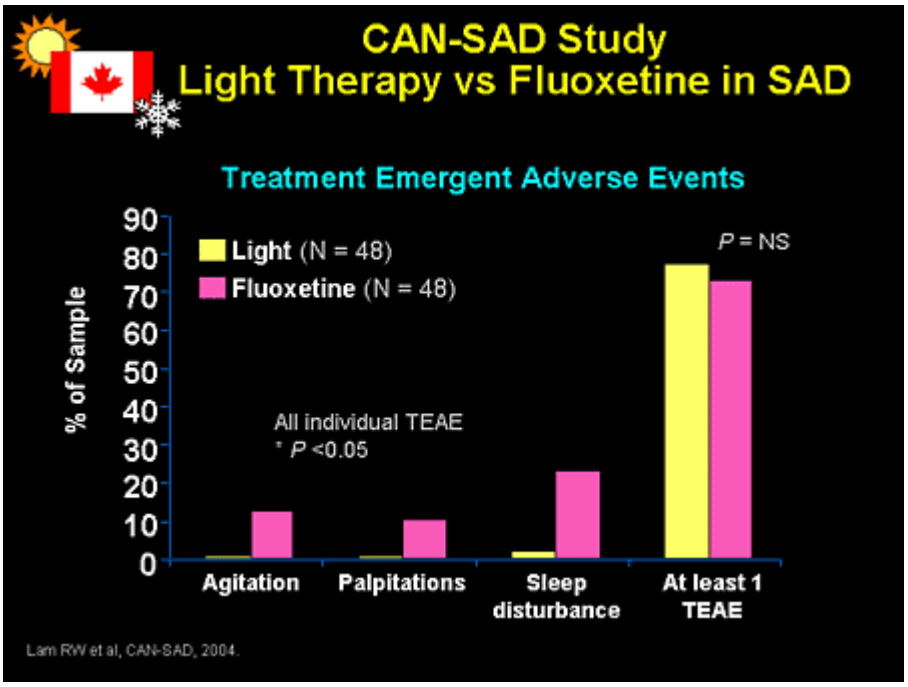
Slide 19. CAN-SAD Study: Light Therapy vs Fluoxetine in SAD

There's been some suggestion that light therapy works for people with milder cases of SAD, whereas we should maybe use medication treatment for the more severe cases. So we were interested in looking at those patients who at baseline were considered to be severely ill, and these we defined as people who had scores of 30 or higher on the Hamilton Rating Scale. And so again, these were severely ill outpatients because this was an entirely outpatient study; you can see that about half the patients seen in the study were rated as severely ill at baseline. When we look at the improvement over time, there was absolutely no difference in improvement between the light- and fluoxetine-treated patients. Both treatments seem to work well for these severely ill outpatients.



Slide 20. CAN-SAD Study: Light Therapy vs Fluoxetine in SAD

Similar results, again, for the response and remission rates. Interestingly, the people with the higher Hamilton ratings had an even better response to treatment, over 70% response rate with the 2 treatments. Again about half the patients got better -- got into remission at the end of 8 weeks. That's very good considering they all started at a score of 30 or higher; they had to get their scores within the normal range after 8 weeks, a very impressive remission rate for these patients. So it looks like even for severely ill patients, light therapy seems to be as effective as fluoxetine.



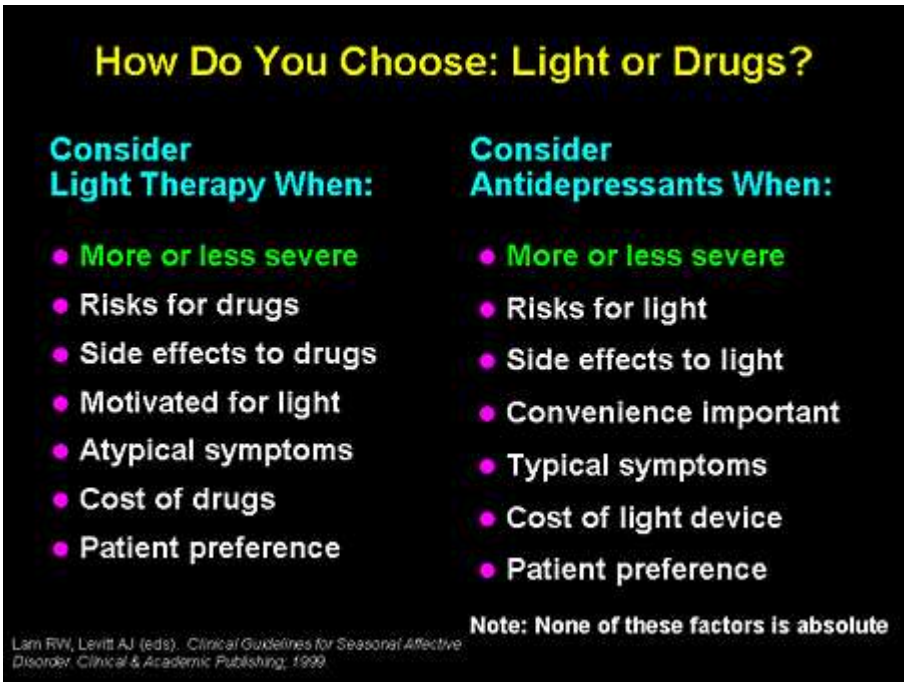
Slide 21. CAN-SAD Study: Light Therapy vs Fluoxetine in SAD

Finally, when we looked at the treatment-emergent adverse events or the side effects associated with the medications, not surprisingly, we found that some side effects were more common with the fluoxetine treatment, notably agitation, palpitations, and sleep disturbance. These were significantly higher in the fluoxetine-treated patients compared with the light-treated patients. But we did note that, in fact, if we looked at the number of people who experienced side effects, the number was almost the same for both light- and fluoxetine-treated patients. And if we looked at severity of the symptoms experienced, or the side effects experienced, there didn't seem to be much difference between the fluoxetine- and light-treated patients. So in this particular study, the adverse events probably are higher than in other clinical trials that you've looked at because we systematically asked for side effects. In most clinical trials, it's spontaneous report by the patient, and so we likely found more side effects than usual for a clinical trial. But the fact was not that light had few side effects because it was very well tolerated, but in this clinical trial, fluoxetine was very well tolerated so there were no differences between or very few differences between the 2 treatment groups.

Light Treatment: State of the Art

Raymond W. Lam, MD

Deciding Between Light Therapy and Antidepressants



Slide 22. How Do You Choose: Light or Drugs?

In the clinical guidelines, we had made some suggestions for when to consider light therapy as a first-line medication and when to consider antidepressants as a first-line medication. Severity now we feel is not an important consideration because both treatments appear to be effective for even more severely ill patients. However, there are some patients who may have additional risk factors for drug toxicity, for example, liver disease, etc. Others may have some small risks for light treatment, for example, retinal disease where you might want to consider using antidepressants first. Of course, you have to look at the side-effect profile, try to tailor the treatment to potential side effects that may be bothersome for patients. The one thing about light therapy, though, is that one does need to be motivated for treatment; you do need to use the light for 30 minutes or so a day on a daily basis. And so there is some motivation that's required, and we have patients who frankly tell us: "I would rather take a pill once a day than use the lights, even if the lights work really well for me." So that's a patient preference issue. There's been some suggestion that atypical symptoms are a predictor of response to light therapy, and so possibly people with more typical symptoms may want to consider antidepressants, although some emerging data suggest that, in fact, may not be true, that atypical symptoms also may predict response to antidepressants.

Cost of the treatment also is a consideration because light treatment actually is more cost-effective than medications when you consider that the upfront cost of a light box, which ranges between $150 to $300, is amortized over many years because you can use the light box on a year-to-year basis -- and so the cost of a light box is about one season's worth of the cost of an SSRI medication. However, many people do have drug reimbursement plans and so will have the cost of medications reimbursed, whereas the cost of a light device may not be reimbursed, although we have found many patients are able to get their light devices reimbursed by their health insurance company. And finally, patient preference clearly should play a role because our studies showed that the effects were very similar between light and antidepressants; so the patient preference of whether they would prefer to use light treatment or antidepressants should come into play when trying to decide on first-line treatment. Again, none of these factors is absolute; it's really considering all of these factors together that will help choose a treatment with your patient.

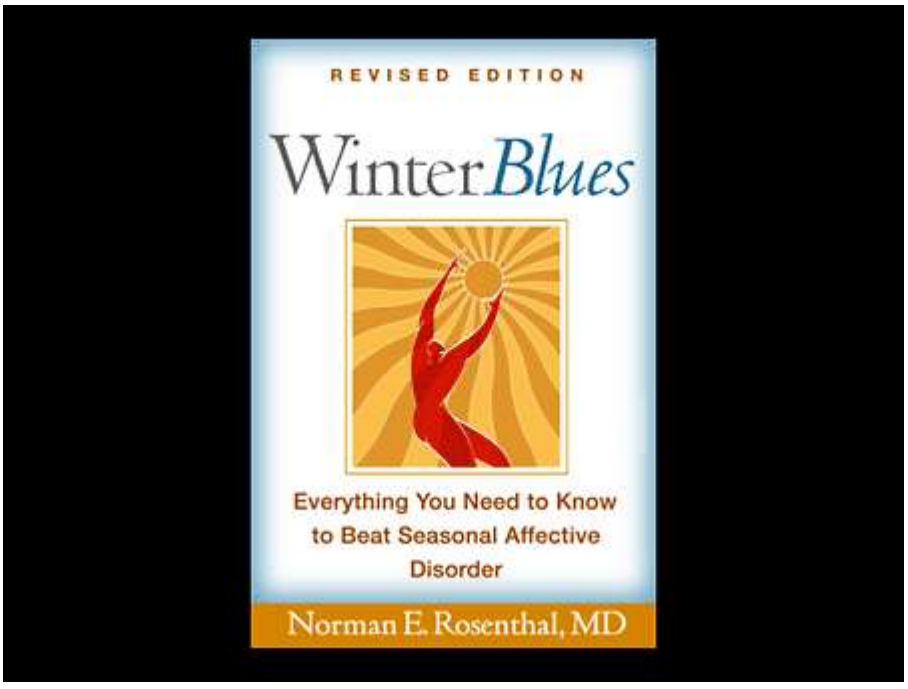
Light Treatment: State of the Art

Raymond W. Lam, MD

Resources for Light Therapy

Slide 23. SAD and Light Therapy Resources for Clinicians

So just to finish up, we've talked about light treatment, and if you would like to learn more about light treatment, we'll refer you to our clinical guidelines for the treatment of SAD as well as to a clinician resource package that we've put together for use in continuing medical education (CME) courses. This includes a lot of helpful information for clinicians including patient information sheets, review papers, rating scales, how to get a light -- that type of information, as well as our guidelines, actually is available for free download on our Web site.



Slide 24. SAD and Light Therapy Resources for Patients

The other very good resource for patients is a book by Norman Rosenthal on winter blues; it's a very readable book that describes a lot of important information about SAD and about treatment with light.

Slide 25. SAD and Light Therapy Web Sites

As I mentioned, in this slide are some important Web sites for further information. Our Web site has the clinician resource package available for free download as well as the clinical guidelines. The Society for Light Treatment and Biological Rhythms is the scientific organization that's interested in light and other circadian treatments, and the Center for Environmental Therapeutics is a very good resource as well for light treatment and other natural treatments for SAD and other conditions.

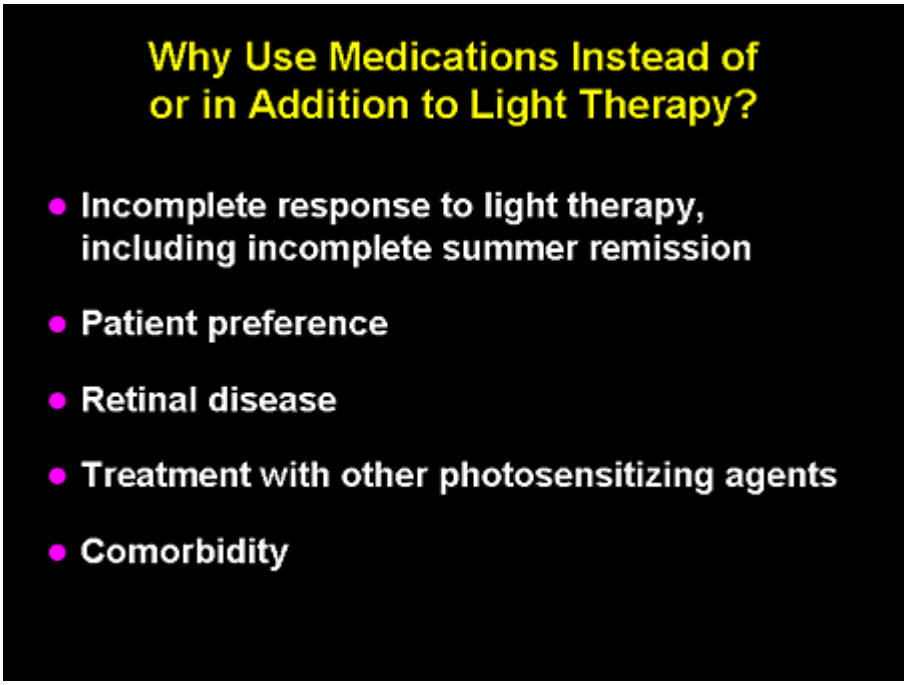
Medical Treatment Alternatives and Outcomes

Jennifer K. Pennell, MD

Rationale for Pharmacologic Treatment of Seasonal Affective Disorder

Slide 1. Medical Treatment Alternatives and Outcomes

My name is Dr. Jennifer Kern Pennell. I have a private practice in Cary, North Carolina. I'm a graduate of the Duke residency program, and I've been in private practice for 5 years, and surprisingly enough, there are quite a few cases of seasonal affective disorder (SAD) in North Carolina. We're becoming more and more aware of these cases as people are becoming more aware of SAD. So what I'd like to talk about is using medications to treat people who have SAD.



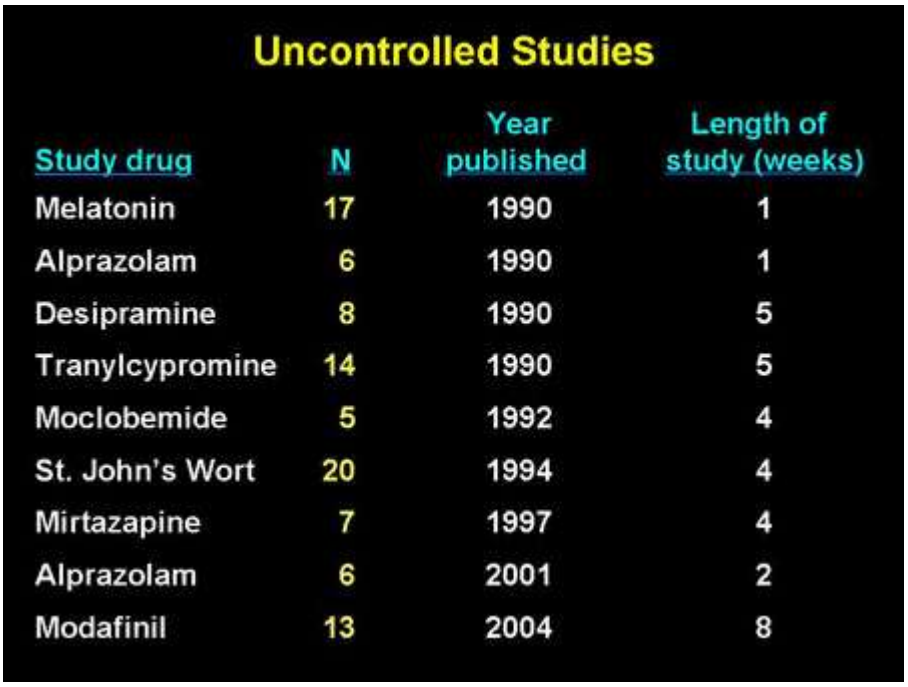
Slide 2. Why Use Medications Instead of or in Addition to Light Therapy?

First of all, why would someone use medications instead of light therapy or in addition to light therapy? Incomplete response is one of the biggest reasons. Remember that only about 65% of people respond to light therapy, so you're left with 35% of people who are having incomplete remissions and these are people in whom you might want to consider using medications. Secondly, patient preference; some patients just do not want to spend the time in front of a light box each day and will be upfront that they're not going to comply with that. Also, some patients may be interested in light-box therapy, but their insurance policies won't cover it, and they can't afford the upfront cost. Next, certain retinal diseases could be relative contraindications for light therapy; for example, if someone has a detached retina, or retinitis pigmentosa, you'd want to check with their ophthalmologist before prescribing light therapy. Some patients, if they're taking photosensitizing agents, may need to opt for medications due to retinal changes. And then there is comorbidity. For example, if you have a patient who has a personality disorder and already is taking an antidepressant, it would be reasonable just to increase their dosage in the winter if they have SAD.

Medical Treatment Alternatives and Outcomes

Jennifer K. Pennell, MD

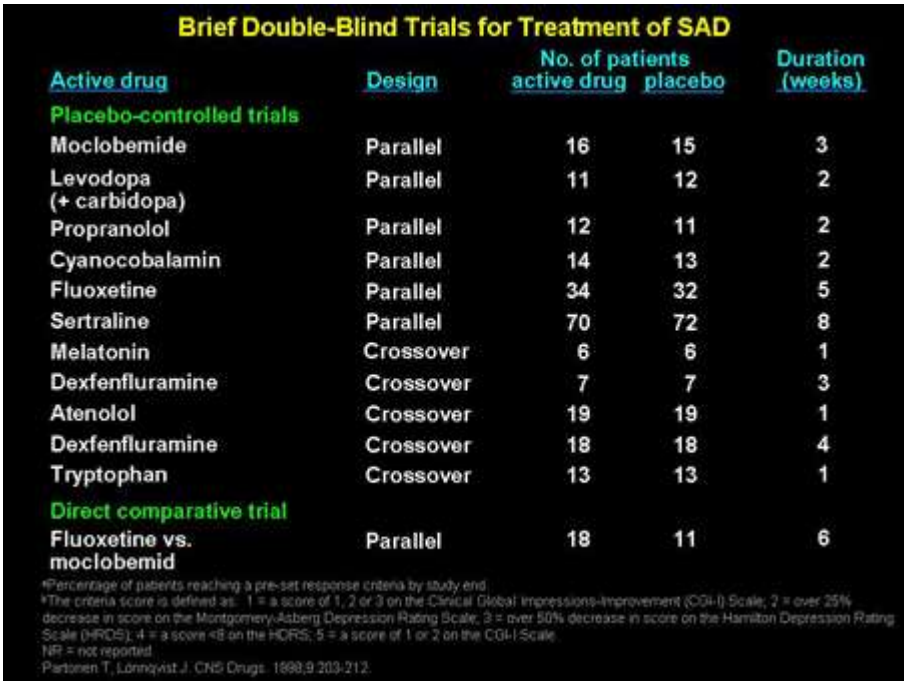
Limitations of Pharmacologic Treatment Studies of Seasonal Affective Disorder



Slide 3. Uncontrolled Studies

As this slide shows, there have been multiple uncontrolled studies looking at a wide variety of agents. However, these have obvious limitations; they're obviously

uncontrolled studies; but you'll note that they also have a small number of participants and relatively short length of study. Because of those limitations, it's hard to know how these agents actually would work in a real life setting.



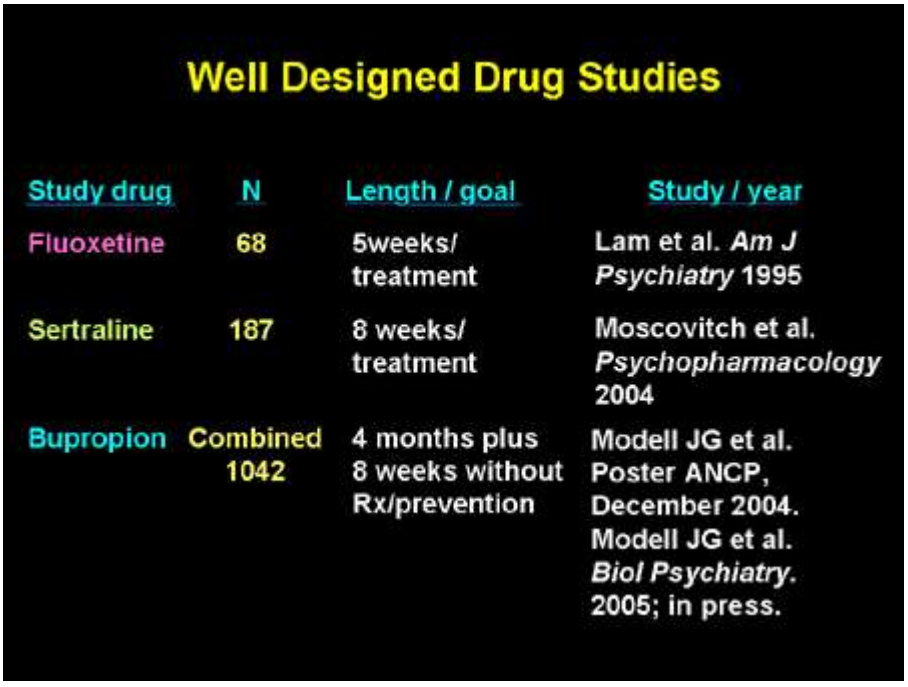
Brief Double-Blind Trials for Treatment of SAD

Active drug	Design	No. of patients active drug	No. of patients placebo	Duration (weeks)
Placebo-controlled trials				
Moclobemide	Parallel	16	15	3
Levodopa (+ carbidopa)	Parallel	11	12	2
Propranolol	Parallel	12	11	2
Cyanocobalamin	Parallel	14	13	2
Fluoxetine	Parallel	34	32	5
Sertraline	Parallel	70	72	8
Melatonin	Crossover	6	6	1
Dexfenfluramine	Crossover	7	7	3
Atenolol	Crossover	19	19	1
Dexfenfluramine	Crossover	18	18	4
Tryptophan	Crossover	13	13	1
Direct comparative trial				
Fluoxetine vs. moclobemid	Parallel	18	11	6

*Percentage of patients reaching a pre-set response criteria by study end.
†The criteria score is defined as: 1 = a score of 1, 2 or 3 on the Clinical Global Impressions-Improvement (CGI-I) Scale; 2 = over 25% decrease in score on the Montgomery-Asberg Depression Rating Scale; 3 = over 50% decrease in score on the Hamilton Depression Rating Scale (HRDS); 4 = a score <8 on the HDRS; 5 = a score of 1 or 2 on the CGI-I Scale.
NR = not reported.
Partonen T, Lonnqvist J. CNS Drugs. 1998;9:203-212.

Slide 4. Brief Double-Blind Trials for Treatment of SAD

There also have been numerous double-blind studies on the treatment of SAD, but many of these have had the same limitations as far as a small number of participants or very short duration of the study.



Well Designed Drug Studies

Study drug	N	Length / goal	Study / year
Fluoxetine	68	5weeks/ treatment	Lam et al. *Am J Psychiatry* 1995
Sertraline	187	8 weeks/ treatment	Moscovitch et al. *Psychopharmacology* 2004
Bupropion	Combined 1042	4 months plus 8 weeks without Rx/prevention	Modell JG et al. Poster ANCP, December 2004. Modell JG et al. *Biol Psychiatry*. 2005; in press.

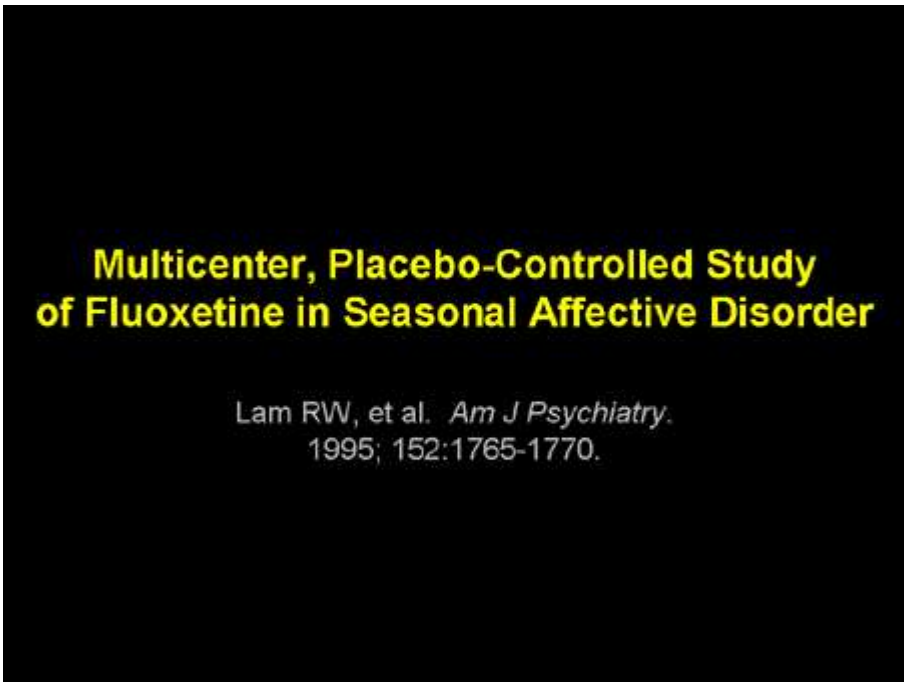
Slide 5. Well-Designed Drug Studies

What I'd like to do in this presentation is focus on 3 of the better-designed drug studies. The first two, the fluoxetine and the sertraline studies, actually are treatment studies, which means these drugs were used to treat people who were experiencing SAD. The third study, the bupropion study, actually was a prevention study, and it looked at preventing SAD in people who had a history of this illness.

Medical Treatment Alternatives and Outcomes

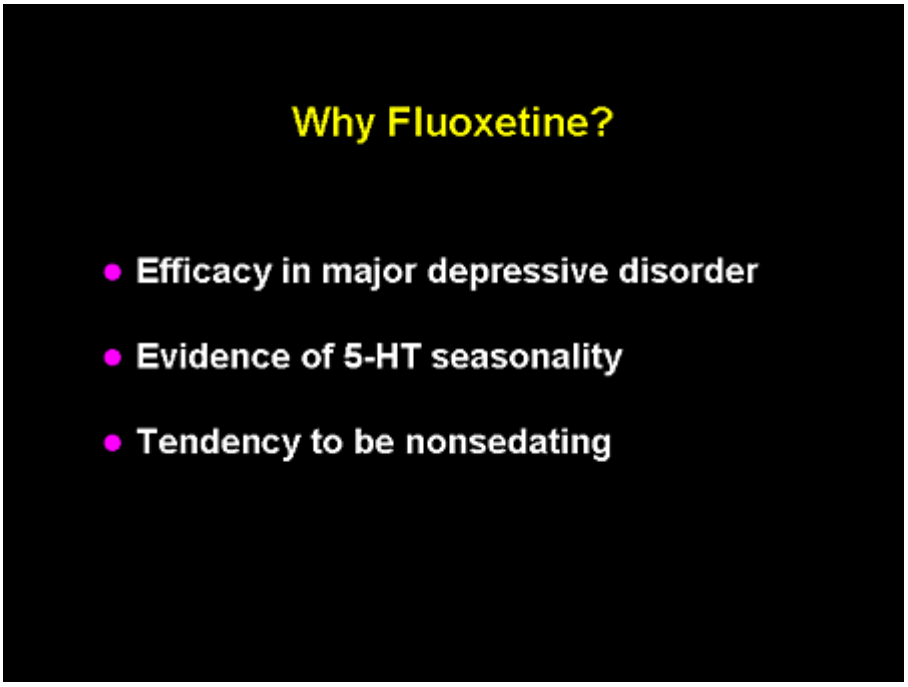
Jennifer K. Pennell, MD

Fluoxetine in Seasonal Affective Disorder: Methodology



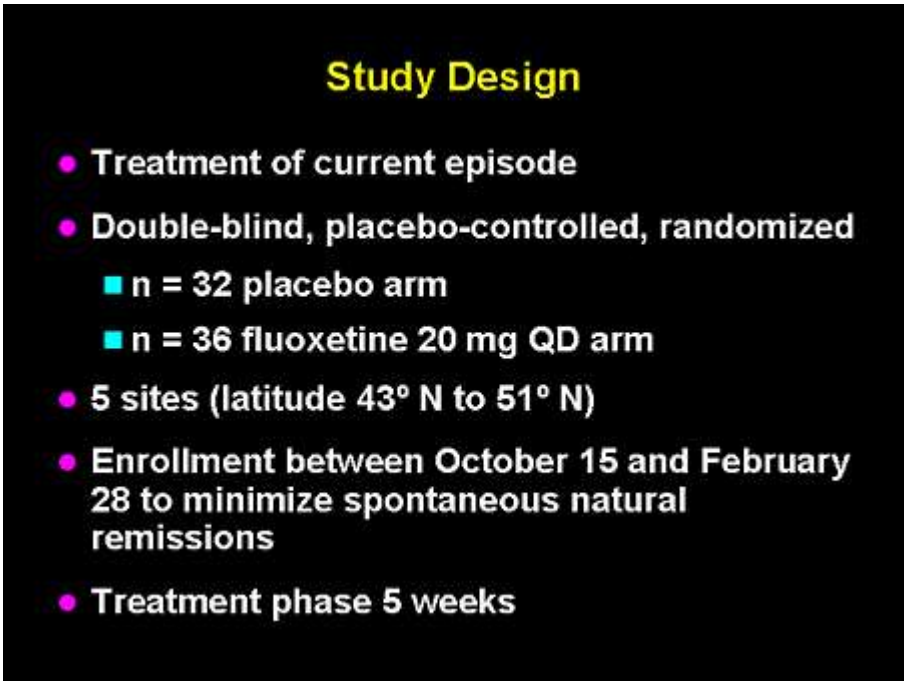
Slide 6. Multicenter, Placebo-Controlled Study of Fluoxetine in Seasonal Affective Disorder

First what we'll do is look at Dr. Lam's study on fluoxetine.



Slide 7. Why Fluoxetine?

First of all, why would researchers choose fluoxetine? It has efficacy in major depressive disorder; there is evidence of serotonin seasonality; and for many people, fluoxetine tends to be nonsedating, and that's a very important point in a population of patients who already are reporting poor energy and increased sleep.

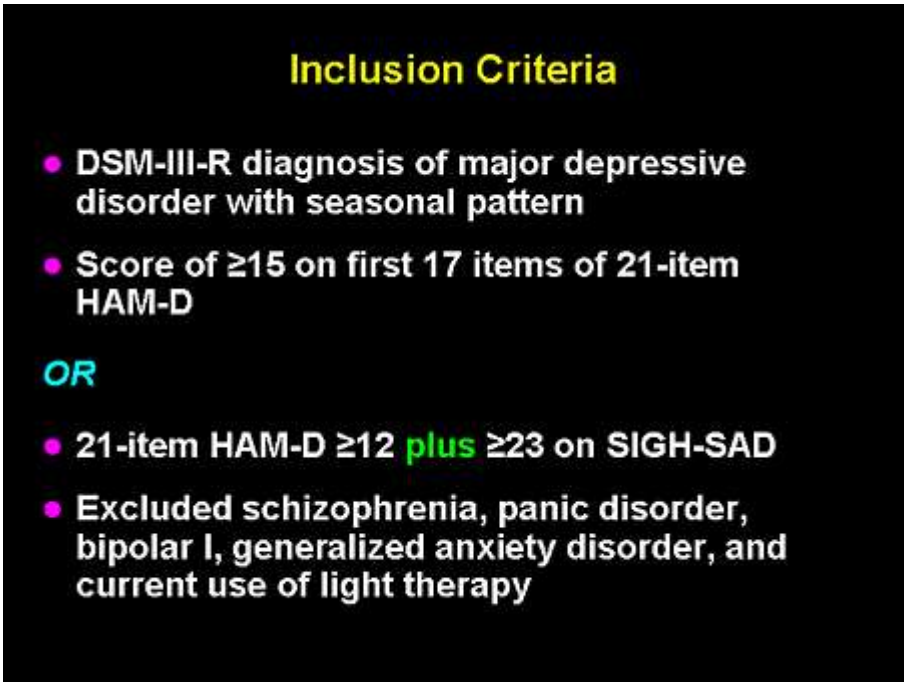


Slide 8. Study Design

The important things to note about this study design are that this was a treatment study, so people were currently depressed at their enrollment into the study. You'll note in the slide the numbers in the placebo arm and the fluoxetine arm; note that in the fluoxetine arm, people received a set dose of 20 mg a day. Treatment phase was 5 weeks. Importantly, enrollment into the study was limited to between October 15 and February 28, and this was in order to minimize the spontaneous natural remissions that are seen. This was a multicenter study, which increases its generalizability, and as you can see, all of the treatment sites were north of the 43-degree latitude line and south of 51 degrees.

Slide 9. Geographic Latitude Study Boundary

On this slide, note that the cities that are listed were not cities that participated in this study; those cities are just there for reference points.



Slide 10. Inclusion Criteria

As I said, this is a treatment study, so you'll note when you look at the score on the Hamilton Depression Rating Scale (HAM-D) or the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version (SIGH-SAD), these were people who already were depressed when the study was initiated. Of course, they had a diagnosis of SAD, and note that people who currently were using light therapy or who had bipolar disorder were excluded.

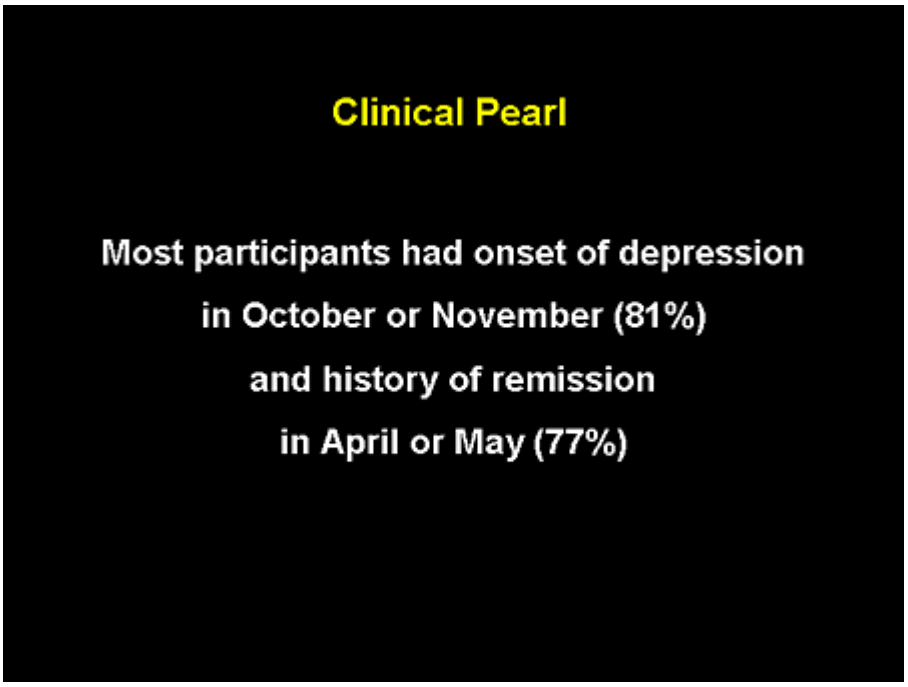
Slide 11. SIGH-SAD (Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder)

The SIGH-SAD was one of the scales used in the study, and this is a validated depression rating scale; it was validated by Terman and his group in 1998. Basically, it's a 21-item HAM-D with an 8-item addendum that looks at the atypical symptoms that frequently are seen in SAD.

Medical Treatment Alternatives and Outcomes

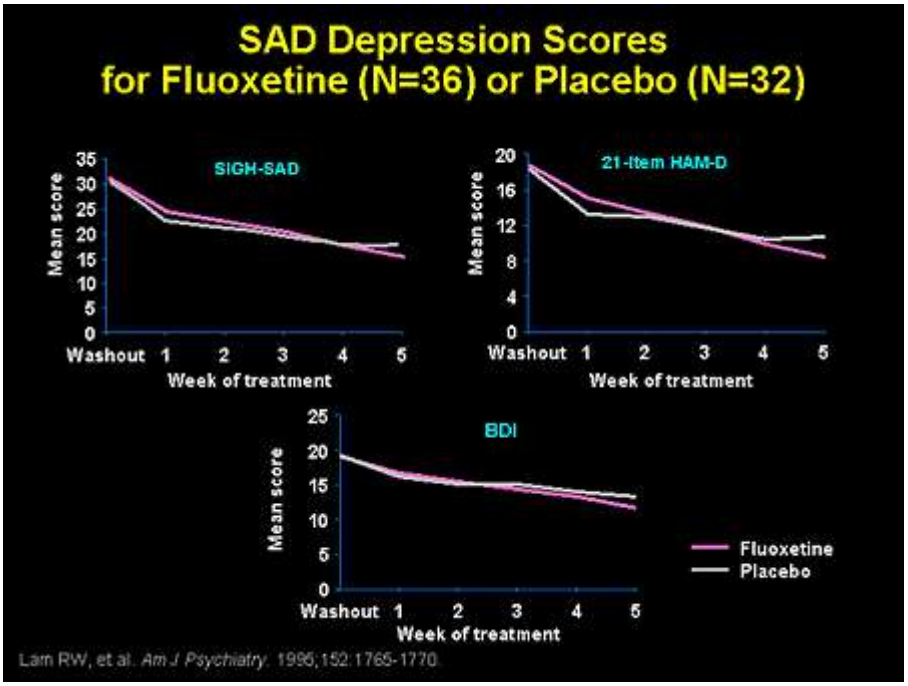
Jennifer K. Pennell, MD

Fluoxetine in Seasonal Affective Disorder: Efficacy



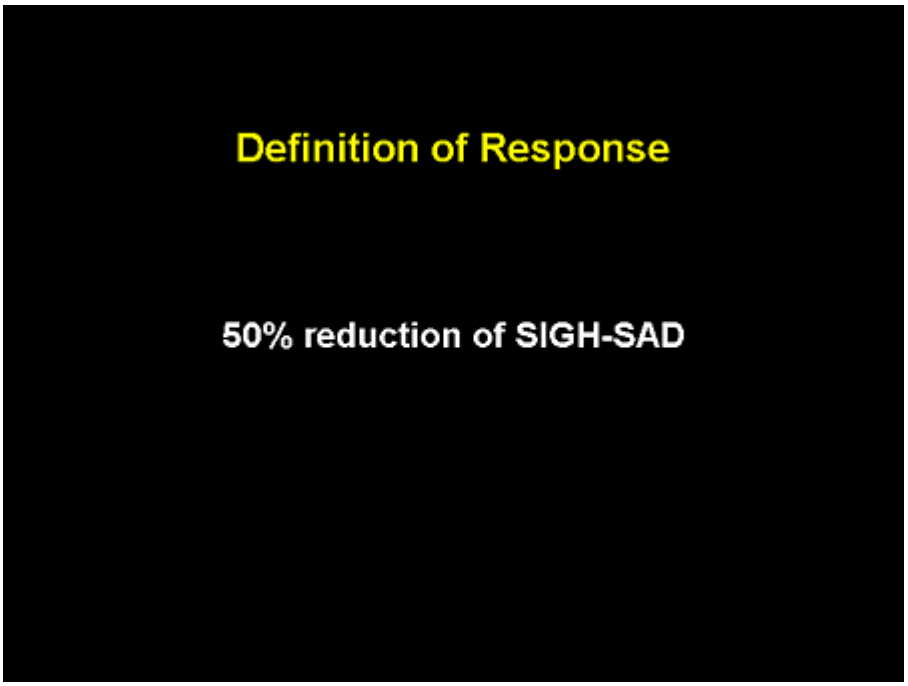
Slide 12. Clinical Pearl

One of the important things that came out of this study was that most of the participants actually had their onset of depression in October or November, and most had a history of spontaneous remissions in April or May, so it would be very important in your practices to start looking for the early symptoms of SAD starting in October.



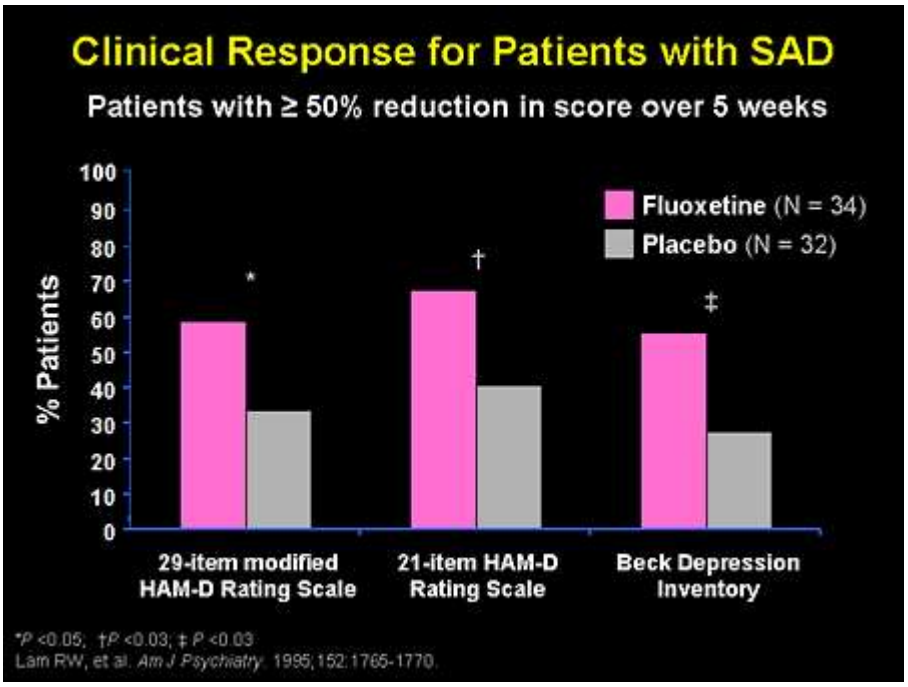
Slide 13. SAD Depression Scores for Fluoxetine (N=36) or Placebo (N=32)

As this slide shows, this study looked at the patient outcomes on the SIGH-SAD, the 21-item HAM-D, and the Beck Depression Inventory (BDI). And notice that both the fluoxetine and the placebo groups improved over time, but they did not have a statistical separation.



Slide 14. Definition of Response

The researchers looked at response, and they defined clinical response as a greater than 50% reduction in SIGH-SAD.



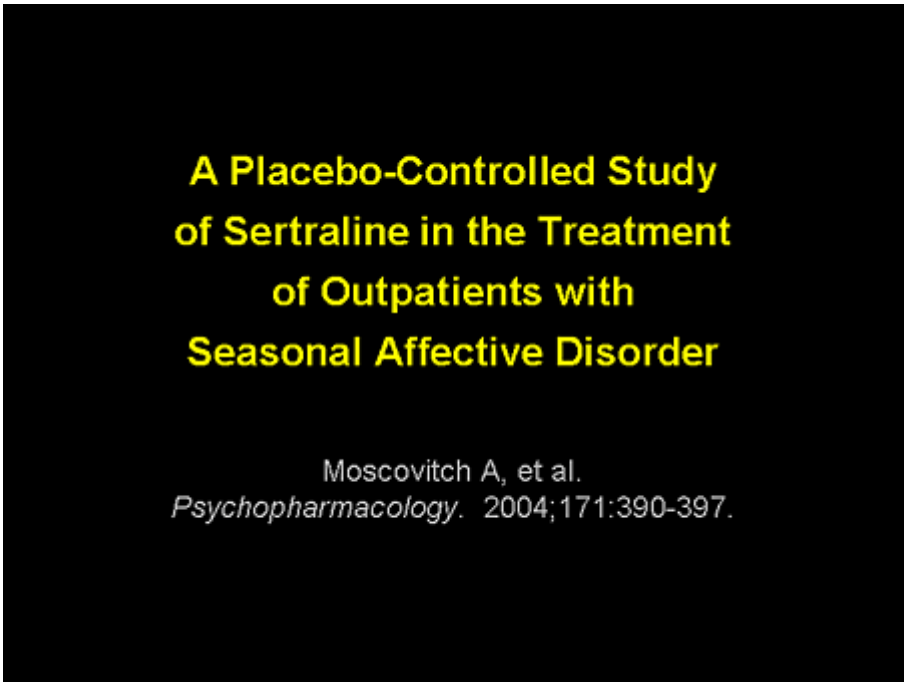
Slide 15. Clinical Response for Patients With SAD

They found that more people in the fluoxetine group met the definition for response than in the placebo group and that was a statistically significant finding. Because of the percentage of responders, it's reasonable to assume that fluoxetine can be useful in the treatment of SAD.

Medical Treatment Alternatives and Outcomes

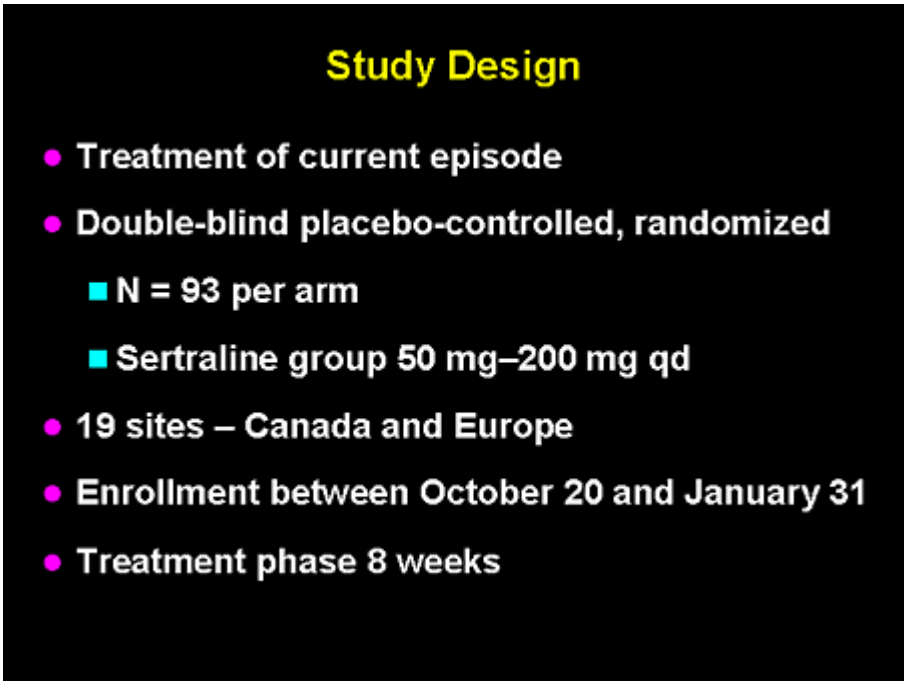
Jennifer K. Pennell, MD

Sertraline in Seasonal Affective Disorder



Slide 16. A Placebo-Controlled Study of Sertraline in the Treatment of Outpatients With Seasonal Affective Disorder

Next we'll look at the Moscovitch study, which looked at sertraline. This was once again a treatment study, so people were depressed at the time of enrollment into the study.



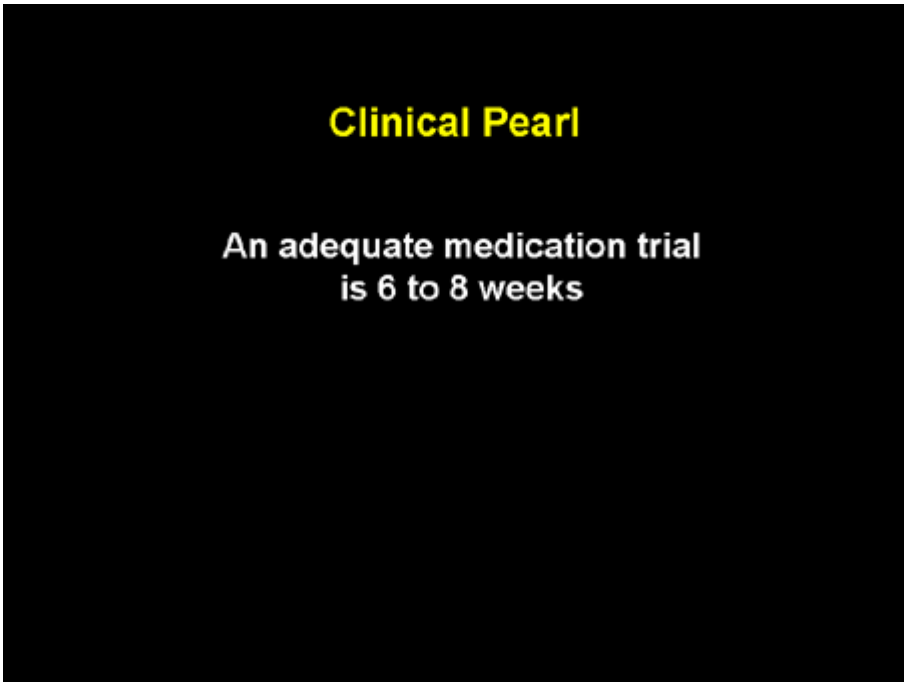
Slide 17. Study Design

Important things to note about the study design: there are a larger number of individuals, and this time, the sertraline group actually had variable dosing. People took anywhere

from 50 mg a day to 200 mg a day, depending on what dose they were able to tolerate. Once again, it was a multicenter study, which increases its generalizability, and enrollment once again had to be limited in order to minimize the effect of the spontaneous natural remissions. Also note that the treatment phase is 8 weeks, which is a little bit longer than the Lam study. Really the important thing to note is once again, because this was a treatment study, people actually were already depressed at the beginning of the study.

Slide 18. Results

The primary outcome, which was looking at the SIGH-SAD score over time, showed that sertraline was greater than placebo, and this was statistically significant. However, when they looked at actual response, and once again that was a 50% decrease in the SIGH-SAD score, 55.9% of the sertraline participants met criteria for response, whereas 50% of the placebo group did, too.



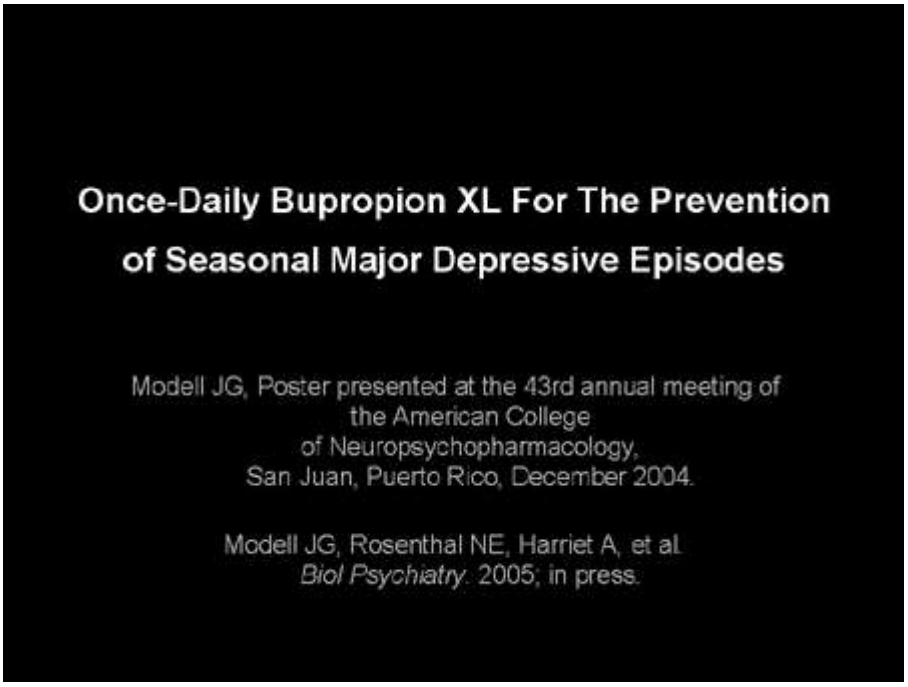
Slide 19. Clinical Pearl

So what can you make of these findings? This was a positive study, as shown by the primary outcome measure, but the effect size was relatively small. Also, when looking at clinical response, the sertraline rate actually is similar to what is seen in other studies for major depressive disorder, but the placebo rate is a little bit high, which is not unusual in a study. These studies were done primarily because we knew both fluoxetine and sertraline worked in the treatment of major depressive disorder, and it always was assumed they also would work in SAD, and these studies indicate that they would be reasonable treatments for SAD. Another very important clinical pearl to come out of these 2 studies would be how long to keep a person on a medication. An adequate medication trial for any patient should be 6-8 weeks; after 8 weeks, if the patient has not adequately responded to one of whatever medication you've tried, it would then be reasonable to try a different treatment method.

Medical Treatment Alternatives and Outcomes

Jennifer K. Pennell, MD

Bupropion in Seasonal Affective Disorder: Methodology



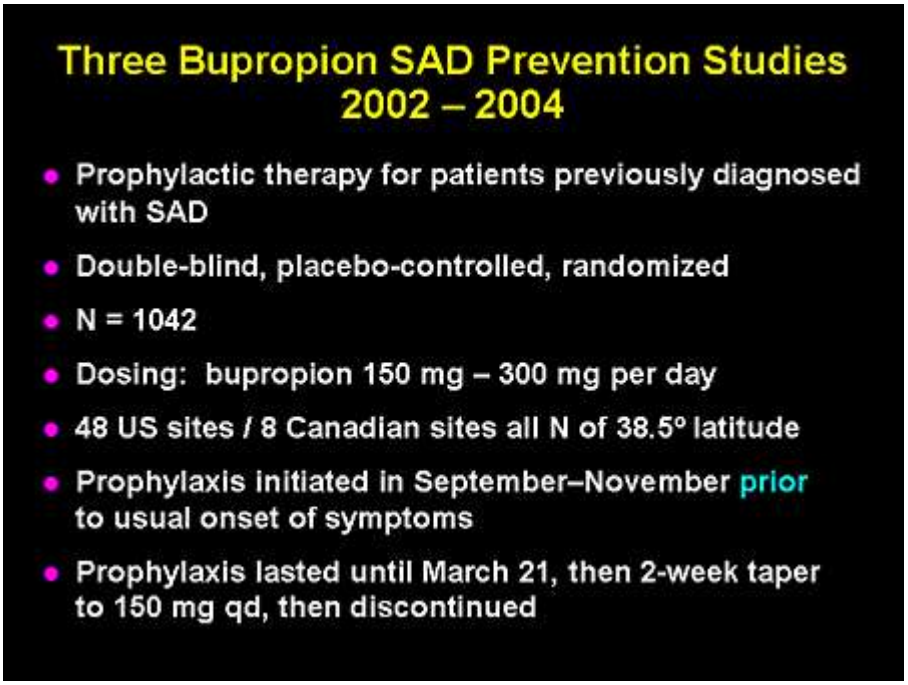
Slide 20. Once-Daily Bupropion XL for the Prevention of Seasonal Major Depressive Episodes

Next I'd like to look at the bupropion data, and this actually is a very different study because it looked at actually preventing SAD for people who had a history of SAD.

Slide 21. Why Bupropion?

Bupropion was chosen for the study for several reasons: of course, it has efficacy in major depressive disorder, and there's evidence that the noradrenergic and the

dopaminergic systems are involved in SAD. But also, too, this was a preventative study, so this study actually looked at putting non-ill people on a medication, and because of that, this medicine has to have excellent tolerability. And indeed, bupropion does tend to be nonsedating; some people actually experience weight loss, and it does have lower sexual dysfunction and actually makes an excellent choice for this study.



Slide 22. Three Bupropion SAD Prevention Studies 2002 - 2004

There actually are 3 different bupropion studies; all of them were prevention studies, which mean that these were people who had a history of SAD, but at the time they were enrolled in the study, they were not depressed. You'll notice that there are a very large number of participants -- 1042 -- and in the active treatment group, there was variable dosing and dosing was dependent on how much an individual patient could tolerate. In this study, because it was a prevention study, people actually started the medicine in September to November, and this was prior to their usual onset of symptoms, and then a participant stayed on either active drug or placebo until March 21. Then there was a 2-week taper for anyone who was on 300 mg, and then medications were discontinued.

Slide 23. Geographic Latitude Study Boundary

Once again, this was a multicenter study, and all the sites actually were north of the latitude line that's indicated in the slide. Once again, the cities on the map are just there for your reference and are not actually the cities involved in the study.

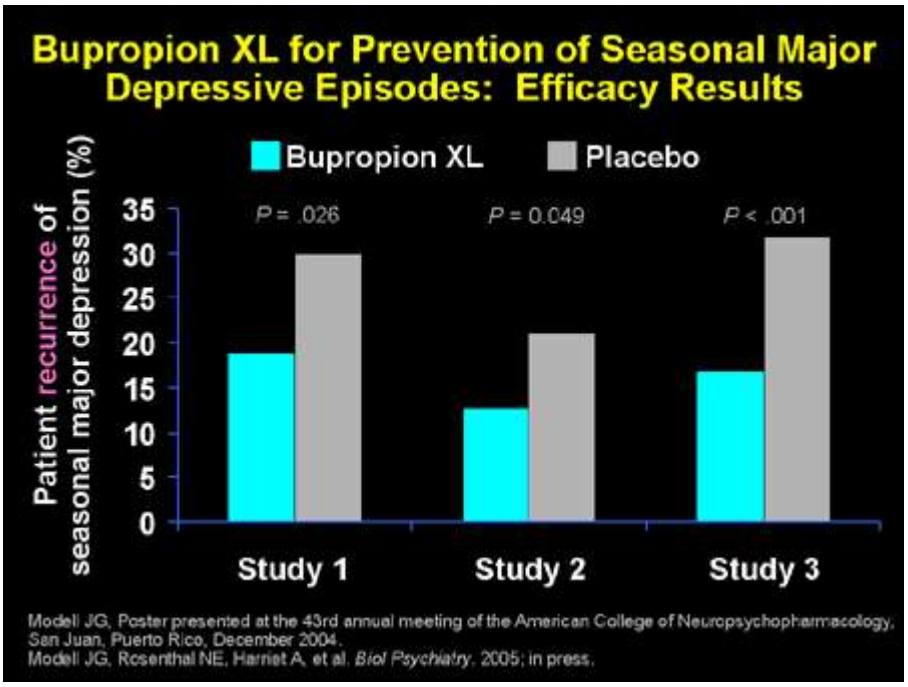
Slide 24. Inclusion Criteria for All 3 Studies

The inclusion criteria for all 3 of the studies were the same. Because this was a prevention study, people were nondepressed, as you can see by their HAM-D and SIGH-SAD scores in the slide. And like the fluoxetine study, bipolar I disorder was excluded.

Medical Treatment Alternatives and Outcomes

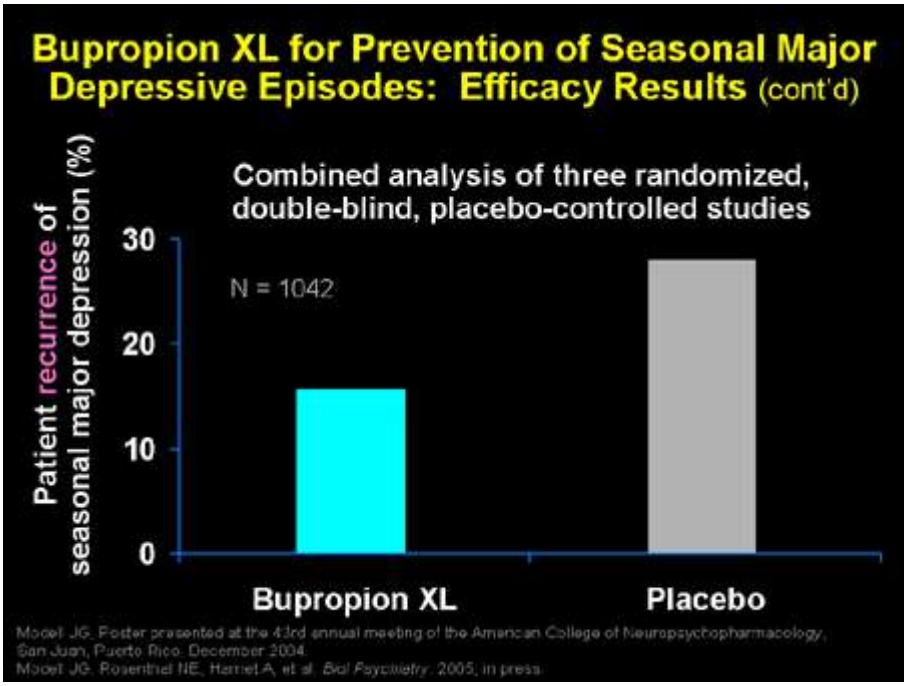
Jennifer K. Pennell, MD

Bupropion in Seasonal Affective Disorder: Efficacy



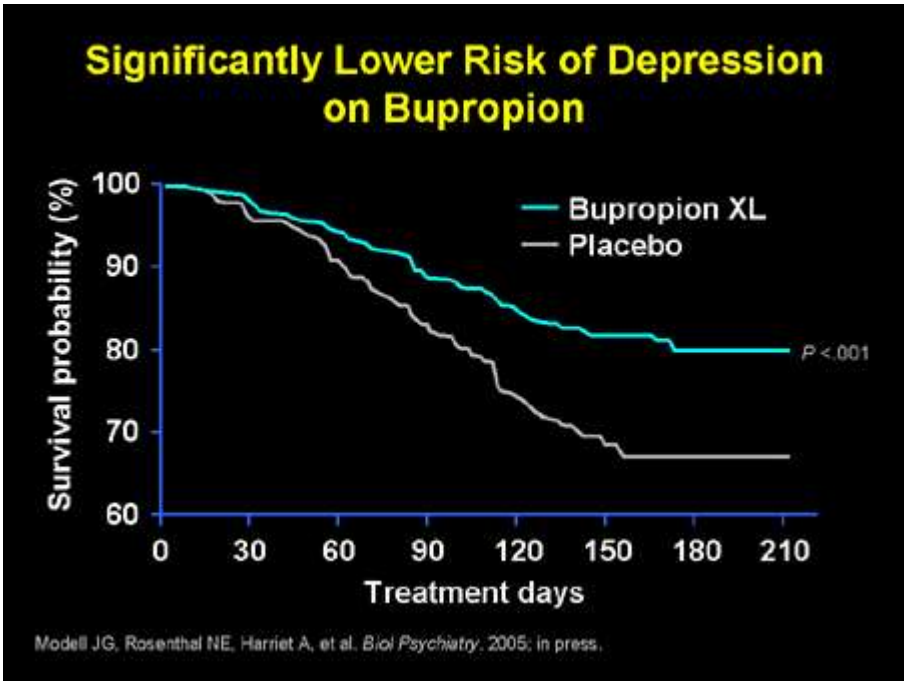
Slide 25. Bupropion XL for Prevention of Seasonal Major Depressive Episodes: Efficacy Results

This shows that for all 3 of the studies, patients who received bupropion XL had fewer recurrences of their SAD than the placebo group, and these findings were statistically significant in each of the 3 studies.



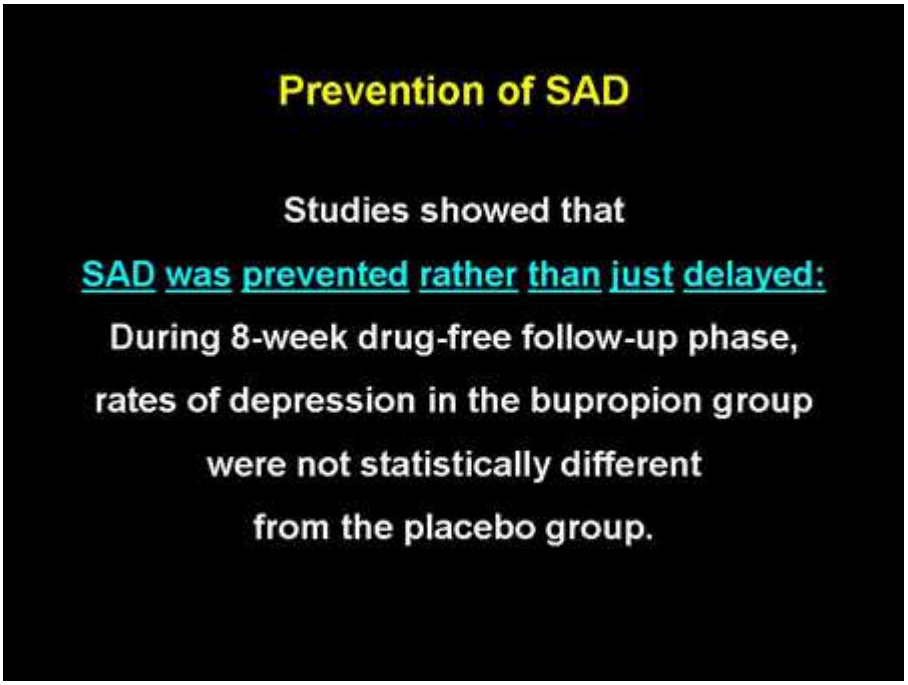
Slide 26. Bupropion XL for Prevention of Seasonal Major Depressive Episodes: Efficacy Results (cont'd)

When the data are combined, they found that out of the 1042 participants, only 16% of the bupropion XL patients had a recurrence of their SAD vs 28% of the placebo patients, and this too is statistically significant.



Slide 27. Significantly Lower Risk of Depression on Bupropion

In this slide, the survival probability curve once again shows that there were fewer placebo patients at the end of the study who were nondepressed and there are more bupropion XL patients who did not have depression.



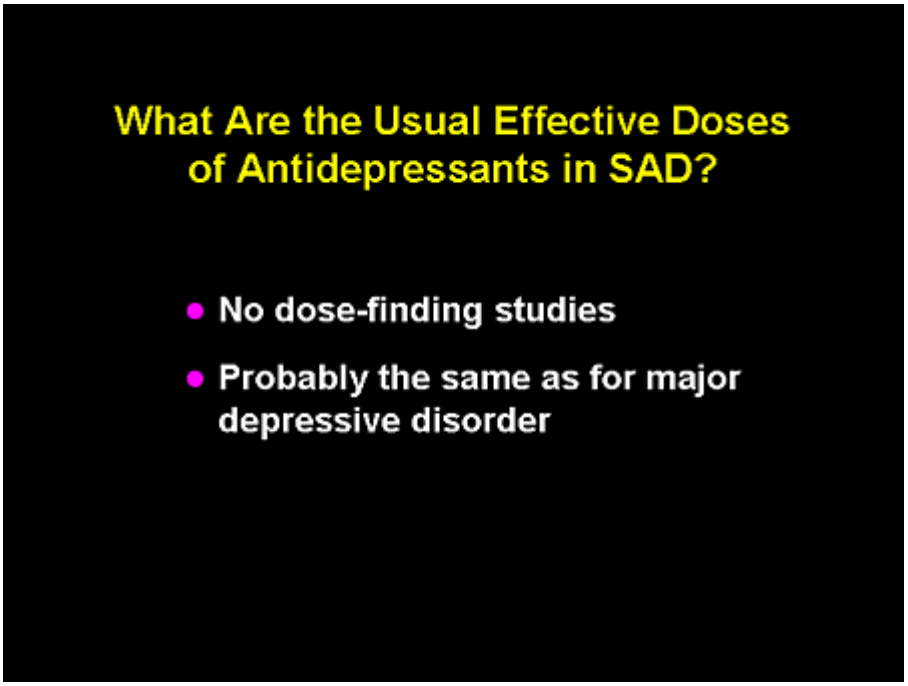
Slide 28. Prevention of SAD

Because this was a prevention study, the study needed to show that SAD actually had been prevented rather than having its onset delayed by medications. So 2 weeks after spring, both placebo and bupropion XL were discontinued; then all of the nondepressed participants were followed for an 8-week drug-free period, and then during that time, their depression rates were compared. And what they found was that the people who had received bupropion XL did not differ in their relapse rate when compared with the people who received placebo, showing that the SAD had been prevented and that the people no longer needed medication now that winter had passed.

Medical Treatment Alternatives and Outcomes

Jennifer K. Pennell, MD

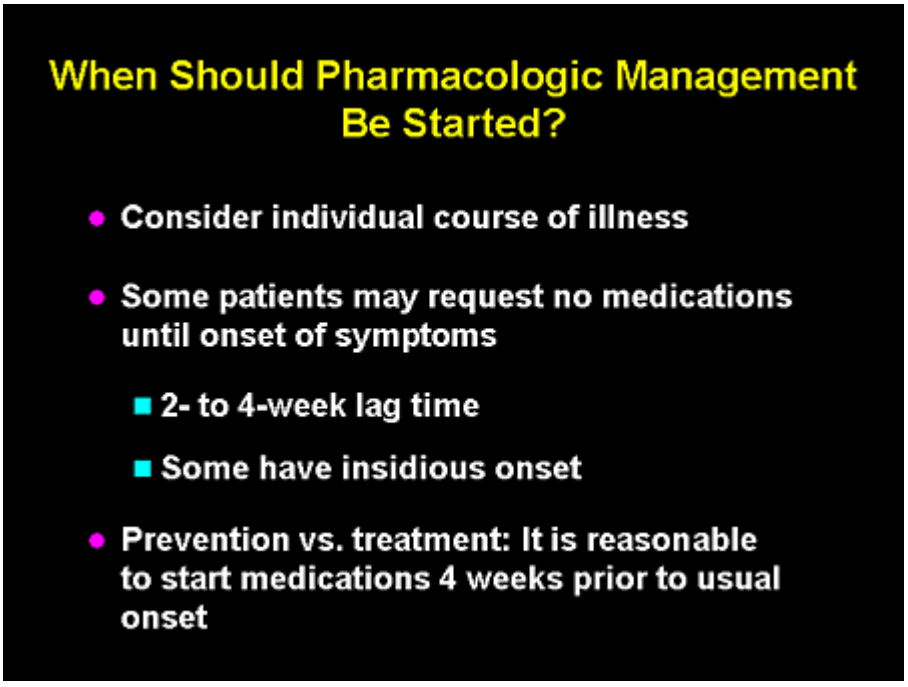
Pharmacotherapy Treatment Recommendations



Slide 29. What Are the Usual Effective Doses of Antidepressants in SAD?

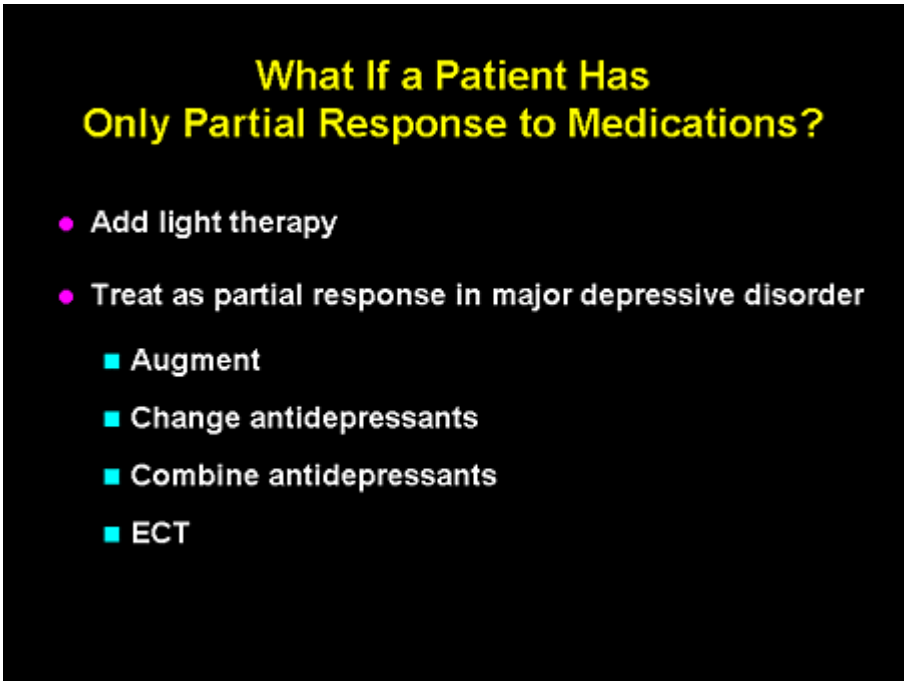
So what I'm going to do next is tell how you can apply this data in your own clinical practice, looking both at expert opinion as well as clinical data.

First of all, what's the usual effective dose of antidepressants in SAD? No study to date has been a dose-finding study, but experts agree it's probably the same as for major depressive disorder. For example, in the sertraline study, the average dose of sertraline was 111 mg per day, and the most common dosage was 100 mg per day.



Slide 30. When Should Pharmacologic Management Be Started?

Then when should medications be started? The first thing you need to do is consider the individual's own history. When does this individual have his or her usual onset of symptoms? Once that's determined, you then need to decide whether the patient will be treated only if symptoms occur or if the patient will receive prevention treatment. Remember that some patients do not have a depression that recurs every winter season and some patients tend to have milder depressions. Patients who fit in that category may opt to hold medications until the onset of symptoms; if that's the case, you need to remind the patients that once they have onset of symptoms and start medications, there will still be a 2-4 week lag time. Some patients have such an insidious onset of symptoms that they often don't notice the symptoms until they're very depressed, and that group might need to consider prevention, which would be taking the medications every winter, even before symptoms occur. And if a patient opts to do that, the patient should start medications about 4 weeks prior to usual onset of symptoms.



Slide 31. What If a Patient Has Only Partial Response to Medications?

What if a patient has only partially responded to medications? If the patient has never tried light therapy, doesn't have any relative contraindications for light therapy, and would like to try light therapy, it is very reasonable to add that to the medications, and there's really no reason at that point to stop the medications. Otherwise, you would treat it as you would a partial response in major depressive disorder; you could use various augmentation strategies. You could change their antidepressant, you could combine antidepressants, or for severely ill patients, you might want to consider electroconvulsive therapy. Remember, because each of those treatments has a lag time and because an adequate treatment trial should really be 8 weeks, it might take several winter seasons before you find the right combination that will benefit your patient.

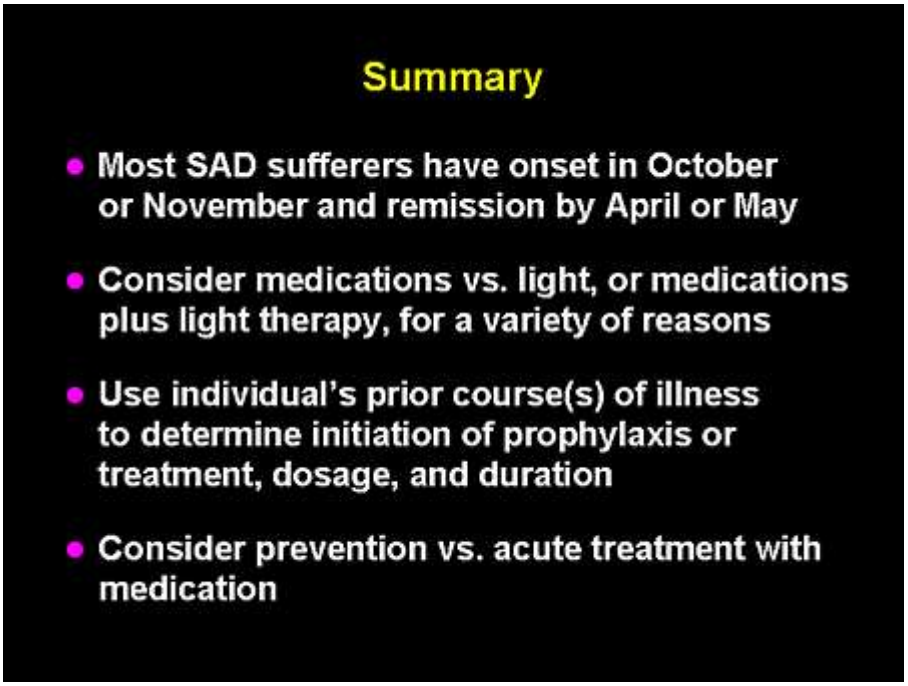
Slide 32. When Should Medications Be Tapered and Discontinued?

When should medications be tapered and discontinued? Once again, look at the individual's disease course. If a patient has very clear SAD, you would discontinue their medications at the time of their usual spring remission. Also note that some patients will have a history of developing hypomania in the spring or summer, and these would be patients in whom you also would want to discontinue their medications in the spring. For some patients, it may be reasonable to continue their medications year round; some patients have such a short depression-free period that they just opt to stay on medications. If a patient has incomplete remission, or if a patient has transient summer symptoms, it would be reasonable to continue their medications. You'll sometimes see people who have very clear SAD, but who have a recurrence of their depressive symptoms if there's an extended cloud cover in the summer. If you have patients who are very prone to that or if their depressions are very severe, they might want to continue medications year round.

Medical Treatment Alternatives and Outcomes

Jennifer K. Pennell, MD

Summary



Slide 33. Summary

So in summary, remember that most people who develop SAD will have their onset of symptoms in October and November, and they'll have spontaneous remissions in April or May. There's a variety of circumstances you need to look at in order to determine if someone will take medications plus light therapy or medications instead of light therapy. Also, you'll use an individual's prior course of illness in order to determine whether the patient will receive prophylaxis or treatment, what that treatment should be, what type of dose they'll need, and their duration of treatment. And as previously stated, always consider whether a patient wants to prevent the onset of SAD or would prefer treating an active case.

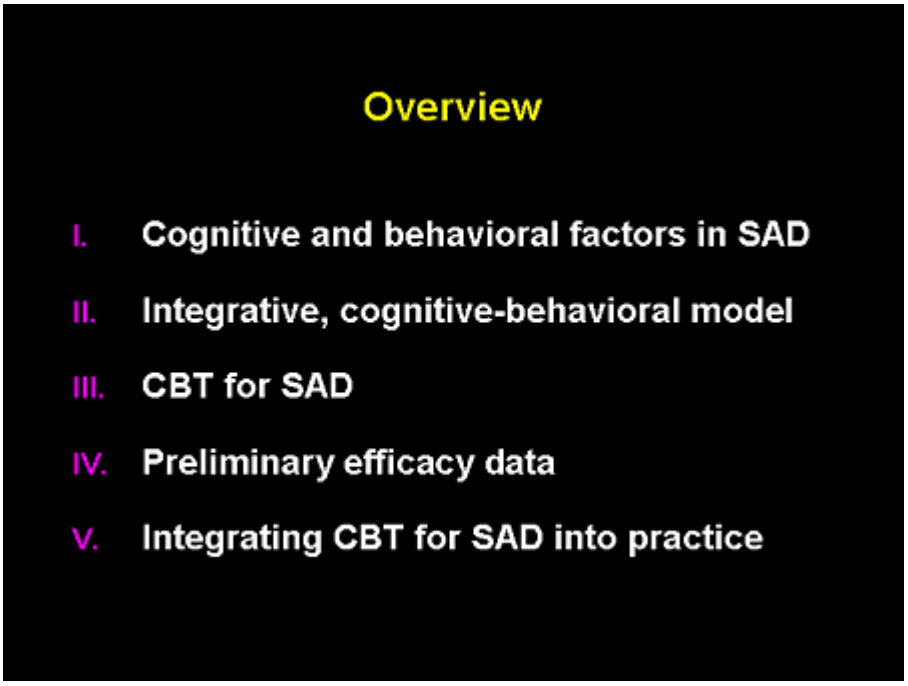
Supplementary Cognitive-Behavioral Therapy for Improved Results

Kelly J. Rohan, PhD

Cognitive and Behavioral Factors in Seasonal Affective Disorder

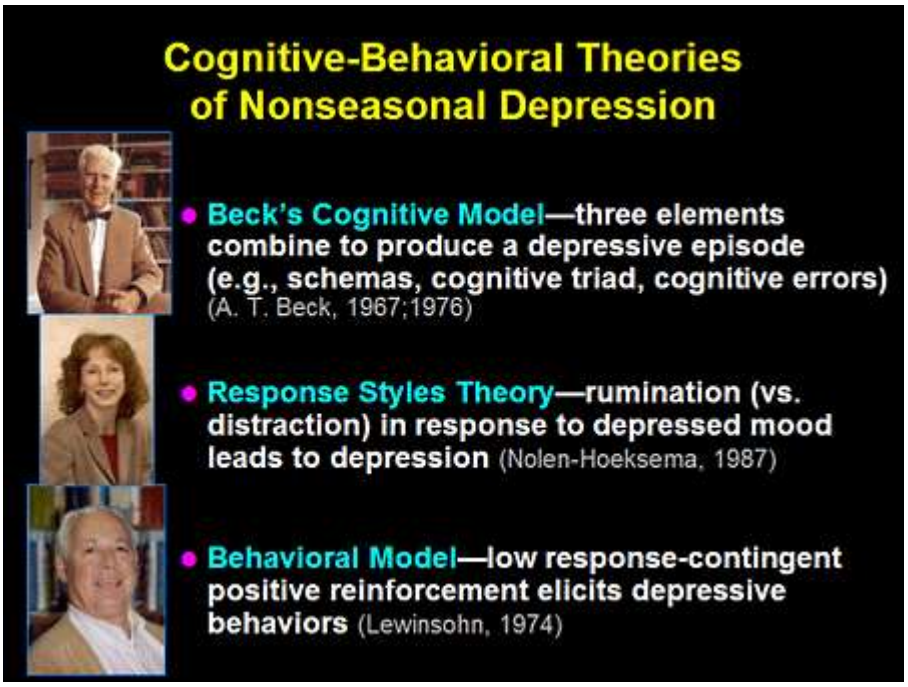
Slide 1. Supplementary Cognitive-Behavioral Therapy for Improved Results

Hello, my name is Kelly Rohan, I'm a clinical trials researcher, and I specialize in seasonal affective disorder, or SAD. And today I'm going to talk about how to integrate cognitive-behavioral therapy (CBT) into comprehensive treatment of Seasonal Affective Disorder.



Slide 2. Overview

First of all, I want to go over some evidence that cognitive and behavioral factors are involved in SAD; then I'd like to walk you through a working conceptual model that we use for SAD in my lab, called the integrative cognitive-behavioral model, which explains how cognitive and behavioral factors could be integrated into an overall understanding of SAD. Next, I'd like to tell you about CBT for SAD, the protocol that we use and the components that it involves, as well as describe some of the preliminary efficacy data that we have generated in our clinical trials. Finally, I will leave you with some news that you can use about how to integrate cognitive and behavioral treatment strategies into your clinical practice with SAD patients.



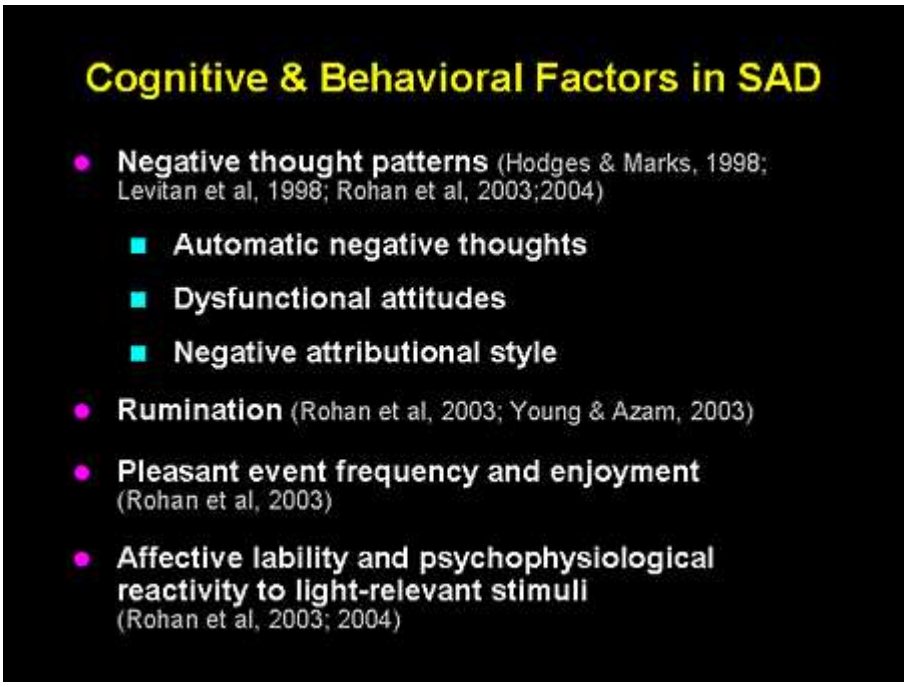
Slide 3. Cognitive-Behavioral Theories of Nonseasonal Depression

Before I can go over how cognitive and behavioral factors may be involved in SAD, I need to describe the cognitive and behavioral theories of nonseasonal depression that underlie these constructs. Perhaps the most popular model in this category is Beck's cognitive model. According to this model, when a negative life event occurs, it activates maladaptive schemas containing negative core beliefs, especially the negative cognitive triad, which are negative beliefs surrounding the self, the world, and the future. Once activated, the schemas in the negative cognitive triad generate negative automatic thoughts, negative stream of consciousness thoughts, which contribute to cognitive errors, also sometimes called cognitive distortions - systematic errors in thinking that maintain the triad despite evidence to the contrary. All of these factors, according to Beck's cognitive model, come together to produce a depressive episode.

Response styles theory is also a cognitive model of depression. According to response styles theory, when individuals become depressed, they do 1 of 2 things: they either ruminate or distract. Rumination behaviors are any thoughts or behaviors that direct attention inward toward the depressed mood and their causes and consequences. In

contrast, distraction is doing something active to divert attention away from depressed mood. In several research studies, it's been shown that rumination leads to more severe and longer-lasting depressive symptoms, as well as to major depression onset, more so than in distraction.

From a more behavioral and a less cognitive perspective, Lewinsohn's model proposes that depression is related to a low rate of response-contingent positive reinforcement, and this is thought to explain the low activity level that's common in depression.



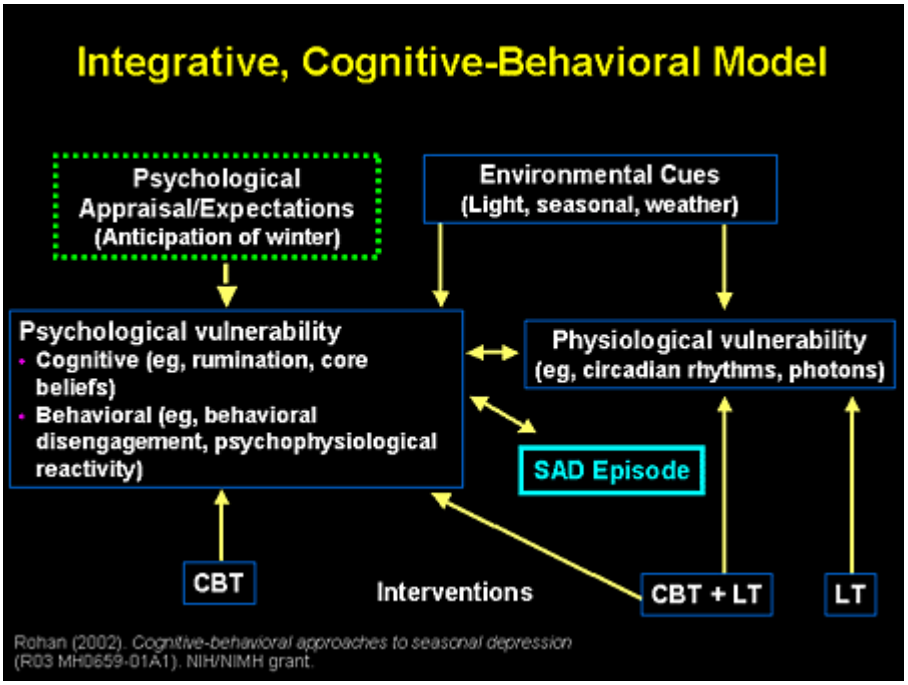
Slide 4. Cognitive and Behavioral Factors in SAD

So how well did these cognitive and behavioral theories of nonseasonal depression apply to SAD? Several studies in my lab as well as others suggest that these models apply relatively well. Many of the negative thought patterns that are common in Beck's cognitive model appear to be operative in SAD as well. Several cross-sectional and prospective longitudinal studies have found these factors to be common in SAD: automatic negative thoughts or stream-of-consciousness and cognitive ruminations associated with depressed mood. For example: "I'm no good," and "Why can't I ever succeed?" Also common are dysfunctional attitudes, which are underlying assumptions that may predispose an individual to depression; for example, believing it is difficult to be happy unless one is good-looking, intelligent, rich, and creative. A negative attributional style is the tendency to explain negative life events in terms of internal, stable, and global reasons or explanations.

It's been shown that individuals with SAD have a higher propensity towards rumination than individuals without SAD, and 2 studies have shown that the more individuals with SAD ruminate in the early fall, the more severe their symptoms are during the following winter season. In terms of those behavioral factors, it seems that there's a pattern in

pleasant events whereby the capacity to enjoy activities seems to decline in the fall, and then the frequency of engaging in these pleasant events that are positively reinforcing behaviors declines in the winter, perhaps to match that enjoyment level.

Finally, in my lab, we've been testing a conditioning model of SAD. If we show an individual with a history of SAD a digital photograph of a dark, dreary, cloudy sky, we find a transient increase in depressed mood, as well as several psychophysiological changes; for example, increased skin conductance response magnitude as well as increased surface facial electromyogram activity in the corrugator muscle, which is a brow-pursing muscle associated with a frowning response.



Slide 5. Integrative Cognitive-Behavioral Model

This slide shows our integrative cognitive-behavioral model, which attempts to explain how cognitive and behavioral factors can be integrated into an understanding of SAD. According to this model, there are 2 pathways to SAD episode onset. One is the traditional route, where somehow the environment changes, particularly the photoperiod declines, which activates a physiological vulnerability, perhaps one involving a circadian rhythm disturbance or insufficient photons to the retina. The new component to our model is this idea of a psychological vulnerability as well as a physiological vulnerability. And this, according to our model, consists of some of the same negative cognitive factors that are associated with nonseasonal depression -- rumination and maladaptive core beliefs -- and behavioral factors, including behavioral disengagement as well as possibly a classically conditioned psychophysiologic reactivity to low-light stimuli in the environment. We see the psychological and the physiological vulnerability components as interactive and reverberating, serving to maintain a SAD episode once it begins.

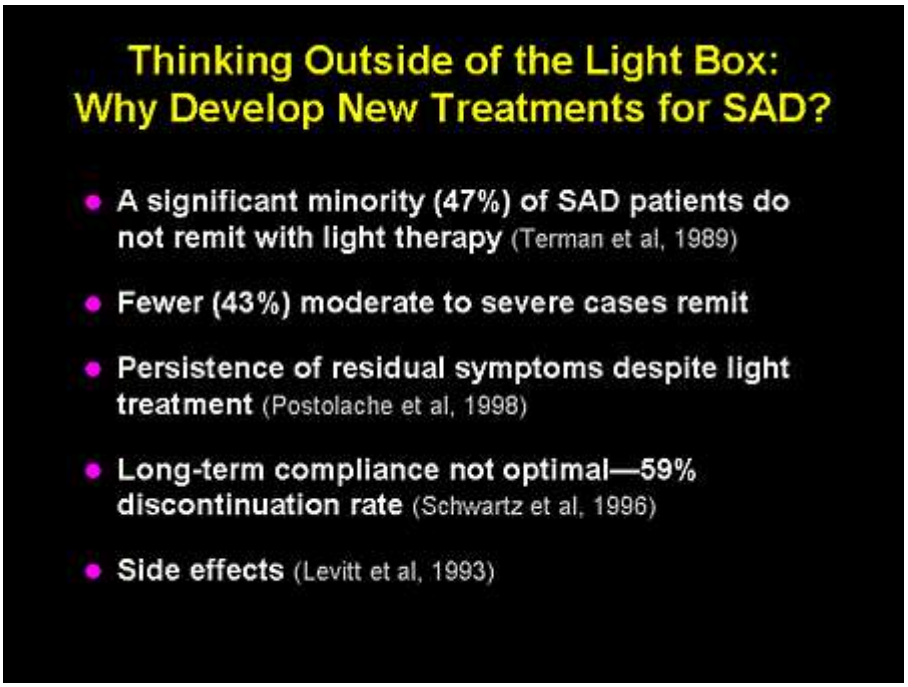
Another inroad to SAD episode onset, according to this model, is a more psychological route whereby individuals with SAD, due to their repeated history of major depression in the winter, actually can come to anticipate their symptoms over time with thoughts such as: "Oh no, it won't be long now; I'll be feeling depressed with signs that winter is approaching such as leaves changing color, the days getting shorter, and so on." This kind of a psychological process may activate that psychological vulnerability, which then trips the physiological vulnerability, and the end result is the same, contributing to SAD episode onset and maintenance.

Interventions are listed across the bottom of the slide. Light therapy, it's believed, is a direct inroad to that physiological vulnerability component. A CBT modified for SAD may be a way to access the psychological vulnerability component. Therefore, a combination of CBT and light therapy together may simultaneously target both the psychological and the physiological vulnerability in a kind of one-two punch for the best overall treatment.

Supplementary Cognitive-Behavioral Therapy for Improved Results

Kelly J. Rohan, PhD

Cognitive-Behavioral Therapy for Seasonal Affective Disorder

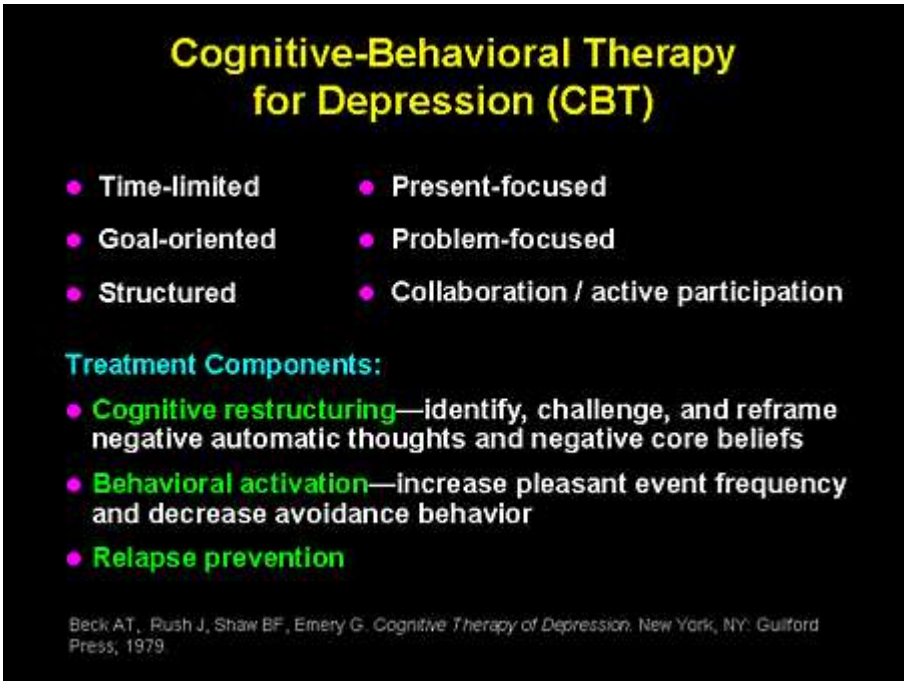


Slide 6. Thinking Outside of the Light Box: Why Develop New Treatments for SAD?

Light therapy is established, effective, and the best available treatment for SAD, so why should we bother thinking outside of the light box to develop supplementary or

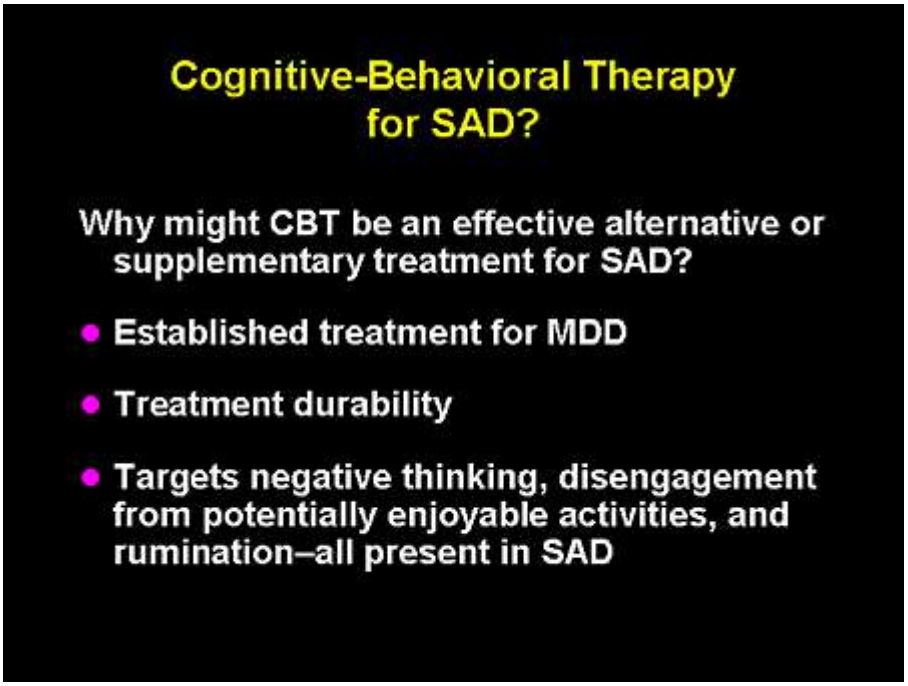
alternative treatments? There are several reasons. First of all, a significant minority, meaning 47% of SAD patients, do not meet remission criteria at the end of a light therapy trial. We need new treatments to address that 47%. Even fewer cases meet remission criteria if we focus exclusively on the moderate to severe cases; only about 43% of these patients will meet remission criteria at the end of a light therapy trial. Another reason is that if we follow SAD patients over time, we find that they're more depressed following a trial of light therapy in the winter than during a subsequent summer season spontaneous remission state. What this means is that light therapy is not a complete treatment; it does leave some residual symptoms.

Probably the most compelling reason on the list in the slide is the fourth one: compliance. Unfortunately, it appears that long-term compliance with light therapy is not optimal. A study conducted in National Institute of Mental Health (NIMH) patients treated with light therapy found that about 59% discontinued light therapy following the trial. When asked why, they cited reasons such as perceived inconvenience and perceived ineffectiveness. Lastly, side effects tend to be mild and manageable but can be serious and sometimes lead to removal from a protocol in light therapy.



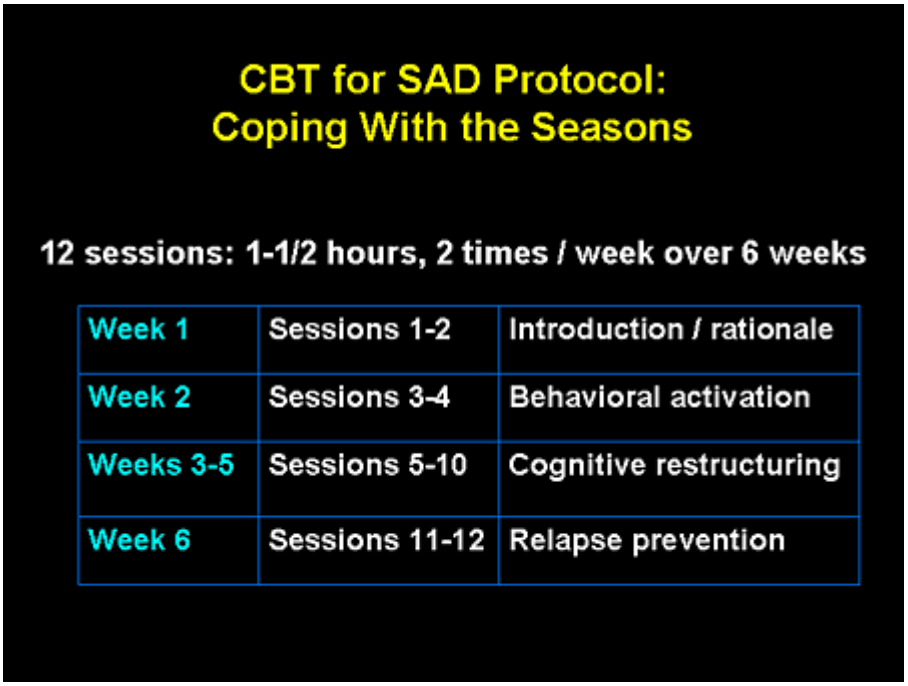
Slide 7. Cognitive-Behavioral Therapy for Depression (CBT)

Cognitive-behavioral therapy developed for nonseasonal depression is a time-limited, directive, structured treatment focused on here-and-now problems. The therapist and the patient collaborate together to actively work on goals. Cognitive-behavioral therapy has several components; we try to teach these patients skills. Cognitive restructuring seeks to identify, challenge, and change any automatic negative thoughts associated with depression as well as maladaptive core beliefs. Behavioral activation is trying to increase positive reinforcement by scheduling in pleasant activities. Relapse prevention is actively using the skills learned in CBT to try to prevent recurrence of depression.



Slide 8. Cognitive-Behavioral Therapy for SAD?

Why might CBT be a candidate treatment as an alternative or supplementary treatment for SAD? Well, first of all, it's an established treatment for nonseasonal major depressive disorder. Over the past 40 years, the efficacy of CBT has been demonstrated for major depression. Importantly, the benefits of CBT for depression appear to extend beyond the point of termination. Studies now have been carried out up to 6 years following treatment termination and have found that CBT is associated with a reduced risk for major depression recurrence relative to clinical management over time. Lastly, as I mentioned, research suggests that the viable targets are there -- negative thinking, behavioral disengagement, and rumination are all present in SAD. These are the constructs that CBT for depression targets; there is something to work with here.



Slide 9. CBT for SAD Protocol: Coping With the Seasons

The CBT for SAD protocol that we have manualized and developed in my lab is structured in the following way. I call it a kind of boot camp version of CBT because we don't have the luxury of doing weekly sessions for 20 weeks. We would run into spring, the patients would spontaneously remit, the treatment would look great, but the data would be meaningless, so we have to compact it. We have 12 sessions that are compacted into a 6-week time frame, 2 sessions per week, 1.5-hour sessions each. We start out with a basic introduction to the treatment and a treatment rationale, the integrative cognitive behavioral model in lay terms. Then we quickly move into behavioral activation, scheduling pleasant activities back into the person's daily life. Most of the treatment focuses on cognitive therapy using cognitive restructuring -- identifying, challenging, and changing any negative automatic thoughts and negative core beliefs that we identify. And lastly, we specifically target relapse prevention. Seasonal affective depression more easily lends itself to specific relapse prevention strategies than nonseasonal depression because we know just when the vulnerable time is going to arrive. So we focus on how to use the skills learned to cope with subsequent winter seasons.

Slide 10. CBT for SAD Protocol: Coping With the Seasons

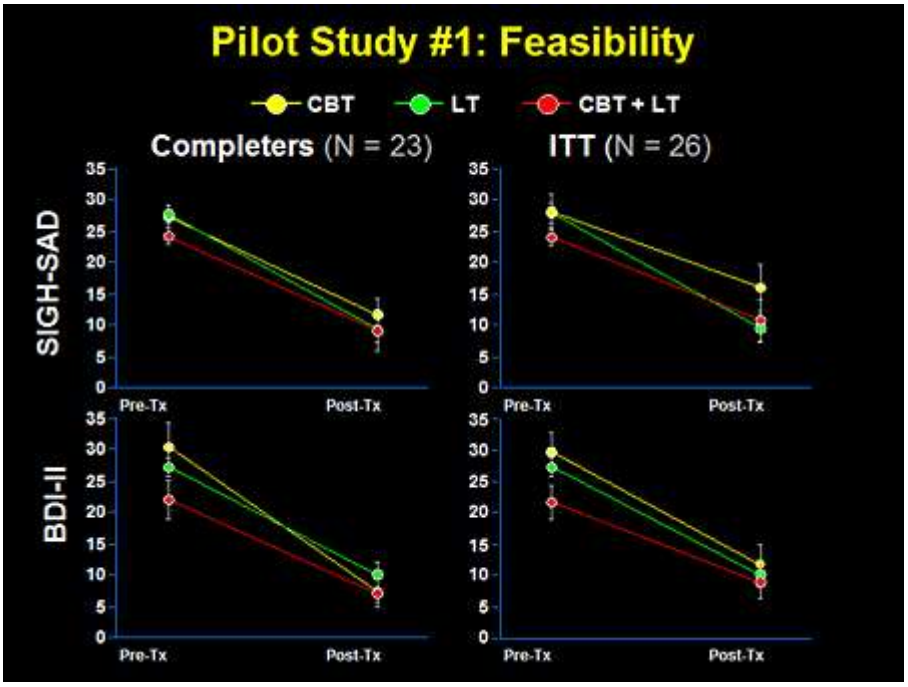
There are many ways that the CBT for SAD protocol has been tailored to be more appropriate for the SAD population. We didn't just take CBT for depression and slap it on SAD; we tried to tailor it in several ways. First of all, we openly acknowledge a role of the physical environment as well as cognitions and behaviors and SAD episode onset and maintenance. All of the various CBT strategies that we use are framed around ways to promote improved coping with the winter season. Behavioral activation is introduced as a way to get patients out of "hibernation mode" and to develop new wintertime interests, something to look forward to during the wintertime. A lot of our cognitive restructuring focuses specifically on negative thoughts about low-light availability, the winter season, and weather.

In doing the clinical trials on this new treatment, we began with a small feasibility study conducted in a single winter season. We randomized 26 adults in the Washington, DC, metro area who had history of major depression recurrent with seasonal pattern, no comorbid axis I disorder, and no ongoing treatment to 1 of 3 protocol conditions: our CBT protocol, as described, conducted in a small group format, about 4-8 participants per group; a standard light therapy protocol involving 10,000 lux of cool white fluorescent light emitted by a standard light therapy box in 2 45-minute doses, 1 dose first thing in the morning and 1 dose in the evening; and combination therapy, which involved the full CBT protocol and light therapy protocol together.

Supplementary Cognitive-Behavioral Therapy for Improved Results

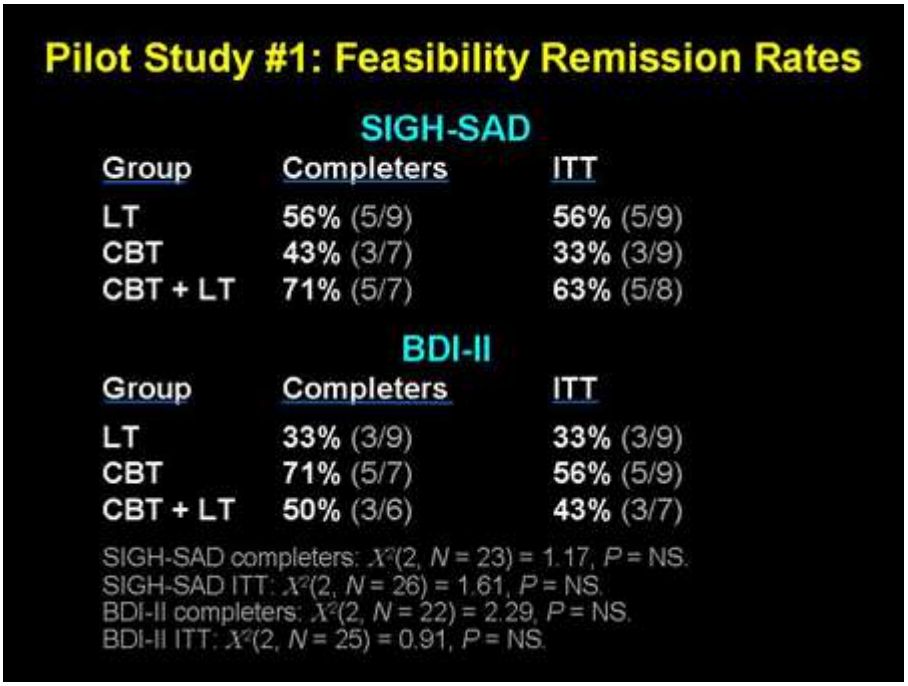
Kelly J. Rohan, PhD

Short-term Benefits of Cognitive-Behavioral Therapy in Seasonal Affective Disorder



Slide 11. Pilot Study #1: Feasibility

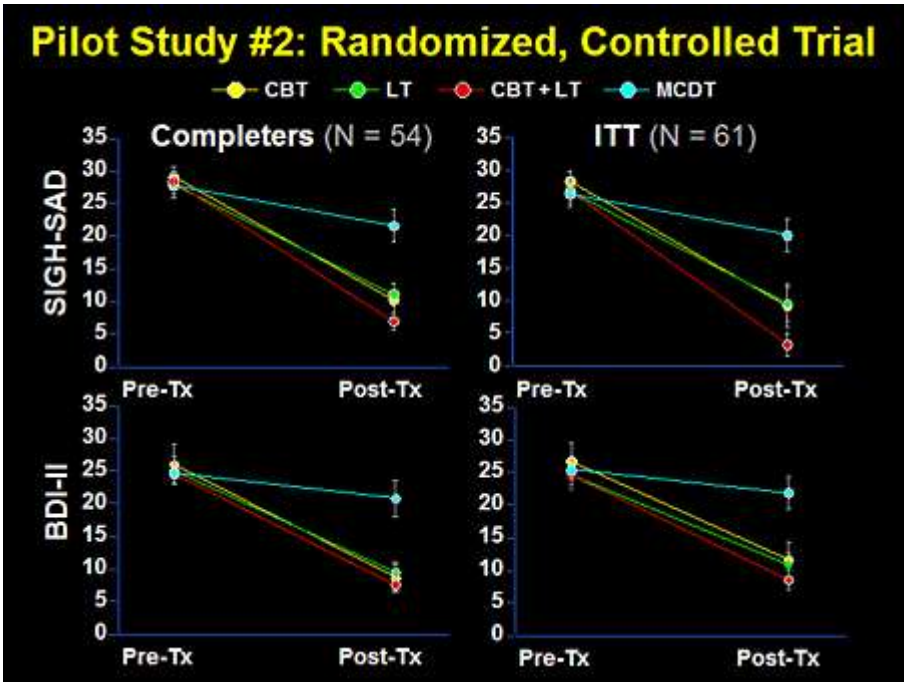
This slide presents results from this feasibility trial. The Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder (SIGH-SAD) is an interview administered by a blind rater to assess depression severity. The Beck Depression Inventory-II (BDI-II) is a questionnaire measure of depression severity. The completer sample included the 23 individuals out of the 26 individuals randomized who actually completed the 6-week treatment phase. The intent-to-treat, or ITT sample, consists of all randomized participants. For any participant who dropped out, their pretreatment score was used as a conservative projection of their posttreatment score. Across both measures and in both types of analyses, there are significant occasion main effects, meaning that depression severity significantly reduced over the 6-week treatment phase comparably across all 3 treatment conditions. There were no treatment group differences here. Depression improved, regardless of measure in the completer and the ITT sample.



Slide 12. Pilot Study #1: Feasibility Remission Rates

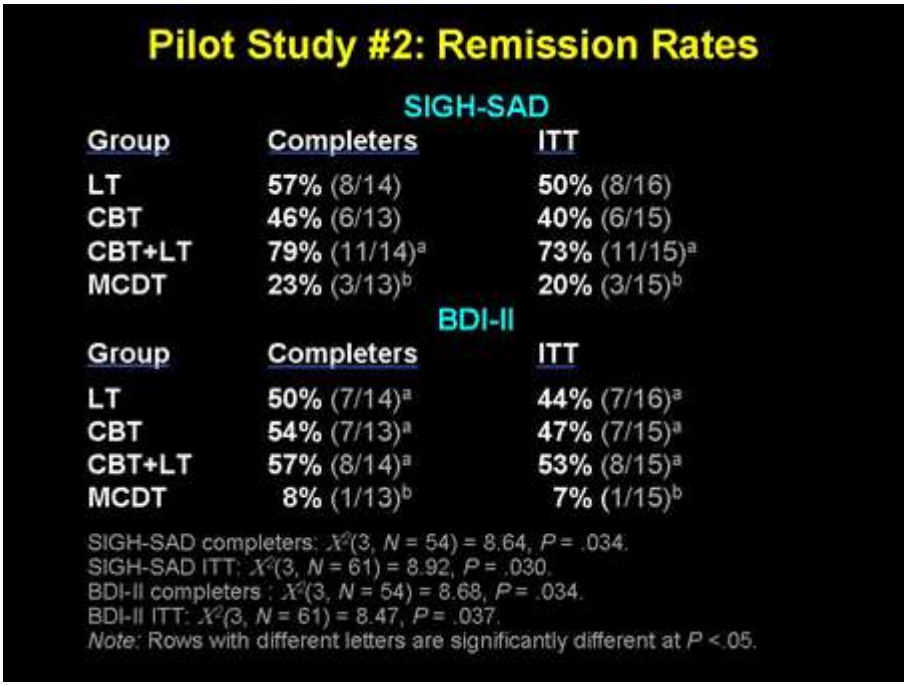
In terms of remission rates, remission sets the bar relatively high. What I'm presenting now is just descriptive information about patterns; there were no statistically significant treatment group differences here. All of our chi squares were nonsignificant. If we use SIGH-SAD remission criteria, descriptively we saw the best remission rate in our combination sample in both the completers and ITT analyses. The combination of CBT and light therapy descriptively had the best remission rate. And using BDI criteria, defined as a BDI score of 8 or less, a very nondepressed threshold, we actually saw the best remission rate in our CBT-alone group here. Again, this is just descriptive, there were no statistically significant differences.

Encouraged by our promising data from the feasibility study, we next initiated a randomized, controlled clinical trial. This was a 3-year study where we used the same inclusion and exclusion criteria in a similar design; the 3 active treatment conditions were the same, but we added a control group, a sort of wait-list control group. This was denoted by minimal contact delay treatment in this slide. We randomized 61 adults with major depression recurrent with seasonal pattern in this study to 1 of 4 treatments, and 54 of them actually completed the 6-week treatment phase. Another new aspect of this trial above and beyond the feasibility study was that we hired an expert light-therapy consultant to individually adjust the light therapy dose based on each patient's side effects, phase shifts, and sleep profile.



Slide 13. Pilot Study #2: Randomized, Controlled Trial

Essentially what we found in both the completer and ITT sample across 2 different measures, the SIGH-SAD and the BDI-II, is that depression significantly and comparably improved from pre- to posttreatment in all 3 active treatment conditions. However, the control group did not show significant change across the 6-week interval. All 3 active treatment groups are significantly different than the control group at posttreatment; in other words, active treatment groups had lower depression scores at posttreatment compared with our wait-list control group, and it's the same pattern across both measures and both samples.



Slide 14. Pilot Study #2: Remission Rates

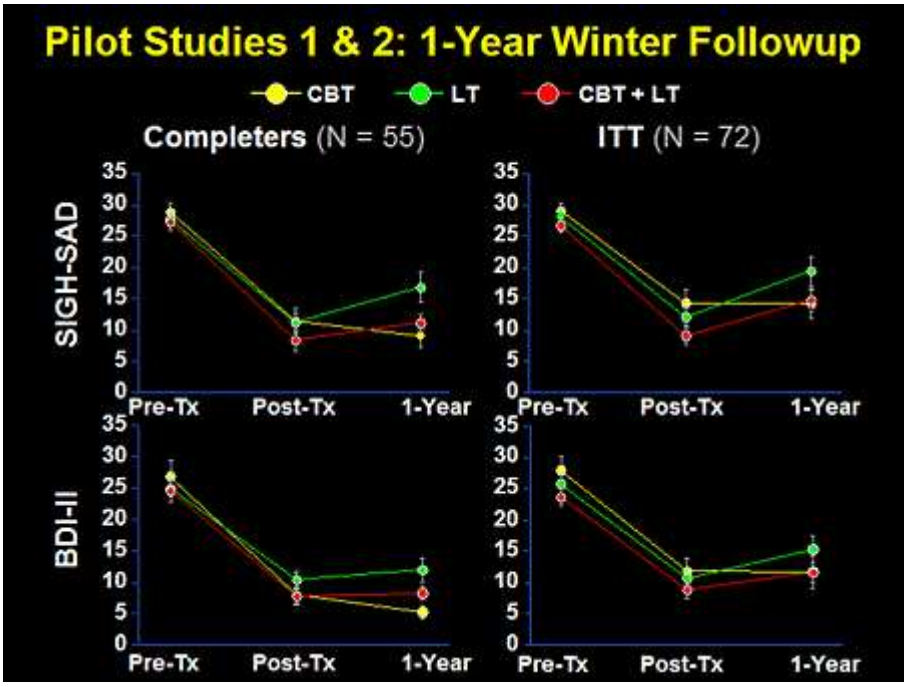
In terms of remission rates, because we had a slightly larger sample now, we did find some statistically significant differences. Using SIGH-SAD remission criteria, the combination group had a greater percentage of remissions than the control group, and this was in both the completer and the ITT sample, about a 79% to 73% remission rate, respectively, in combination therapy, which is exceptionally good and to my knowledge, the highest that's been reported in any study to date. Using BDI-II remission criteria, we found that all 3 active treatments had a statistically superior remission rate compared with our control group with no other significant differences between the groups, and this pattern of results applied across the completer and the ITT sample.

Another interesting feature of this work is that we brought our patients back for a 1-year follow-up visit, which occurred in January or February, 1 year after treatment completion. Luckily, we used the same inclusion and exclusion criteria in pilot studies 1 and 2, so we've combined these samples to get the largest sample possible to present these data. So basically if we pool studies 1 and 2 together, we had randomized 72 individuals to CBT, light therapy, or combination treatment across these 2 studies. Of those, 55 returned at the 1-year follow-up visit. We have run both ITT and completer analyses; for any dropout, we used the pretreatment score as a conservative projection of 1-year score.

Supplementary Cognitive-Behavioral Therapy for Improved Results

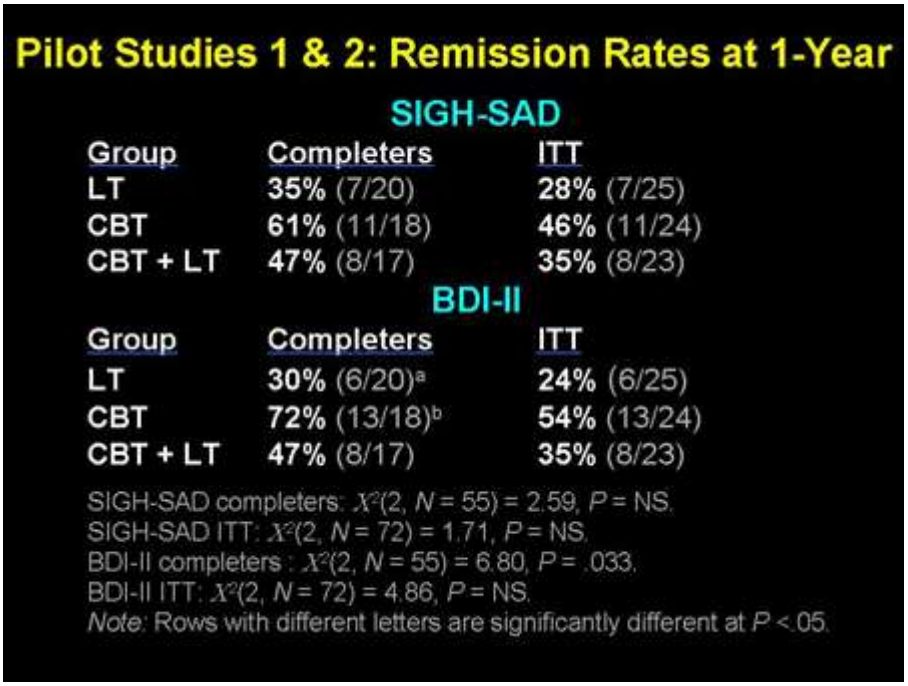
Kelly J. Rohan, PhD

Long-term Benefits of Cognitive-Behavioral Therapy in Seasonal Affective Disorder



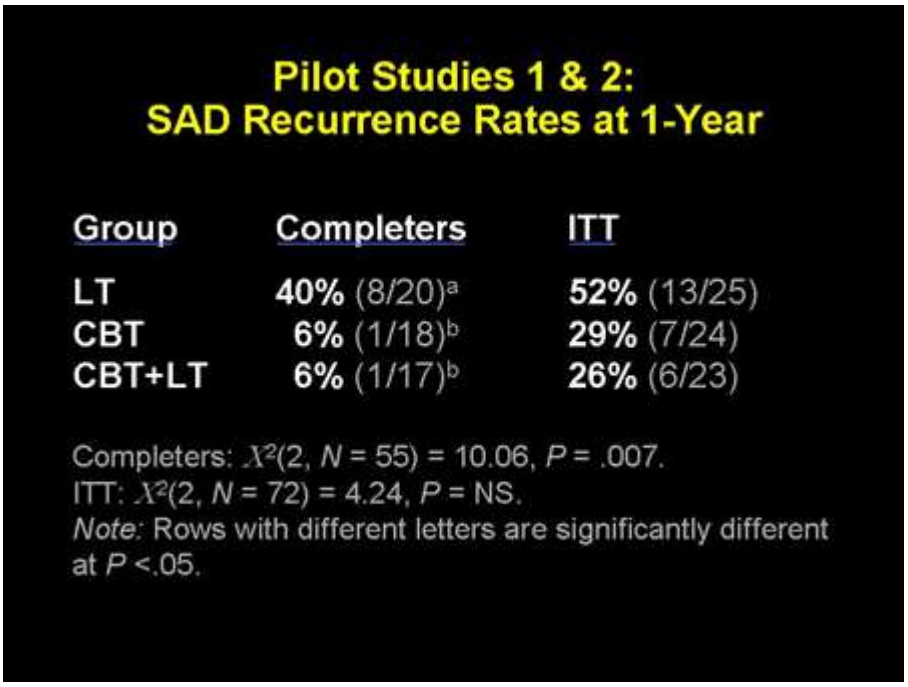
Slide 15. Pilot Studies 1 and 2: 1-Year Winter Follow-up

What we find is that in the SIGH-SAD, in the completer sample, the CBT-alone group had a lower SIGH-SAD score than the light-therapy group at 1 year. The mean of the CBT group and the completer sample in the SIGH-SAD is about a 9 compared with a mean of about a 17 in the light-therapy group at 1 year, and this is a statistically significant difference. On the BDI-II, the pattern was the same; in the completer sample, the CBT-alone group scored about a 5, and this was statistically superior to the light therapy group, which scored about a 12, on average, at that 1-year follow-up visit. The pattern actually was the same in the ITT sample; however, it did not reach statistical significance.



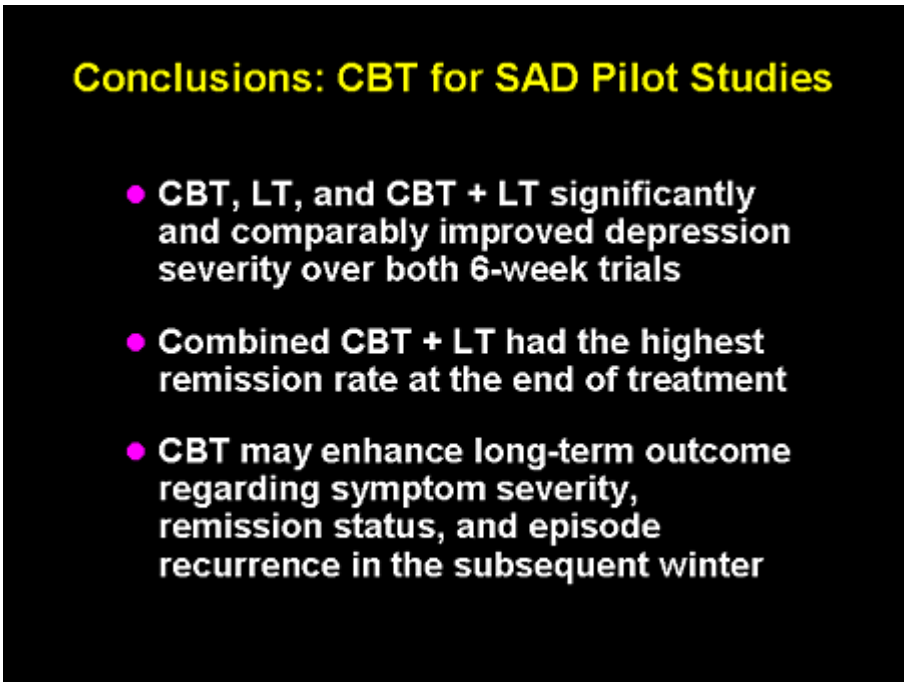
Slide 16. Pilot Studies 1 and 2: Remission Rates at 1 Year

This slide shows the remission rates that we observed at that 1-year follow-up visit. Many of these remission rates are just descriptively reported; we didn't find a lot of statistical significance here, but descriptively as you can see, the CBT-alone group actually had the highest remission rate in all analyses across both measures in both the completer and ITT sample. There is one statistically significant difference here; in the completer sample, the CBT group had a superior remission rate, about 72%, relative to the light therapy-alone group, about 30%.



Slide 17. Pilot Studies 1 and 2: SAD Recurrence Rates at 1 Year

The recurrence rate was another outcome at this 1-year follow-up. This set the bar relatively high at a SIGH-SAD score of 20 or higher to qualify for a full-blown episode recurrence. And here we found in the completer sample that the CBT and the combination group had about a 6% recurrence rate, and that this was statistically superior to that observed in the light-therapy-alone group, which was about 40%. The same pattern holds in the ITT sample but did not reach statistical significance.



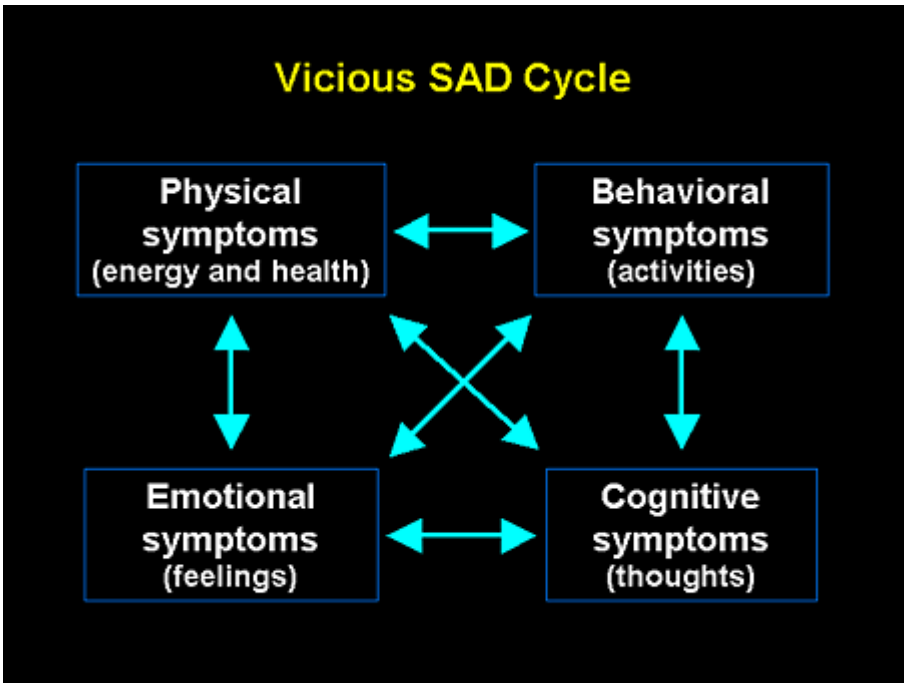
Slide 18. Conclusions: CBT for SAD Pilot Studies

So what can we conclude from these 2 pilot trials? I think it's safe to say that CBT, light therapy, and their combination all appear to significantly and comparably improve depression severity over a 6-week trial. When it comes to remission, the combination of CBT and light therapy together seems to have the highest remission rate acutely at the end of treatment, about a 73% to79% remission. However, we have to weigh this against what we're beginning to observe at that 1-year follow-up. If you initially treat with CBT alone, this appears to enhance long-term outcome regarding symptom severity, remission status, and episode recurrence in the subsequent winter season 1 year later. And I should add that our 1-year follow-up was a naturalistic follow-up -- just bringing people back and determining what their status was like at that time, how people were doing, at that 1-year follow-up visit. We didn't prescribe any particular kind of treatment over that 1-year interval; everyone was given a standard referral list, and they knew what their choices were, including light therapy.

Supplementary Cognitive-Behavioral Therapy for Improved Results

Kelly J. Rohan, PhD

Integrating Cognitive-Behavioral Therapy Into Treatment of Seasonal Affective Disorder



Slide 19. Vicious SAD Cycle

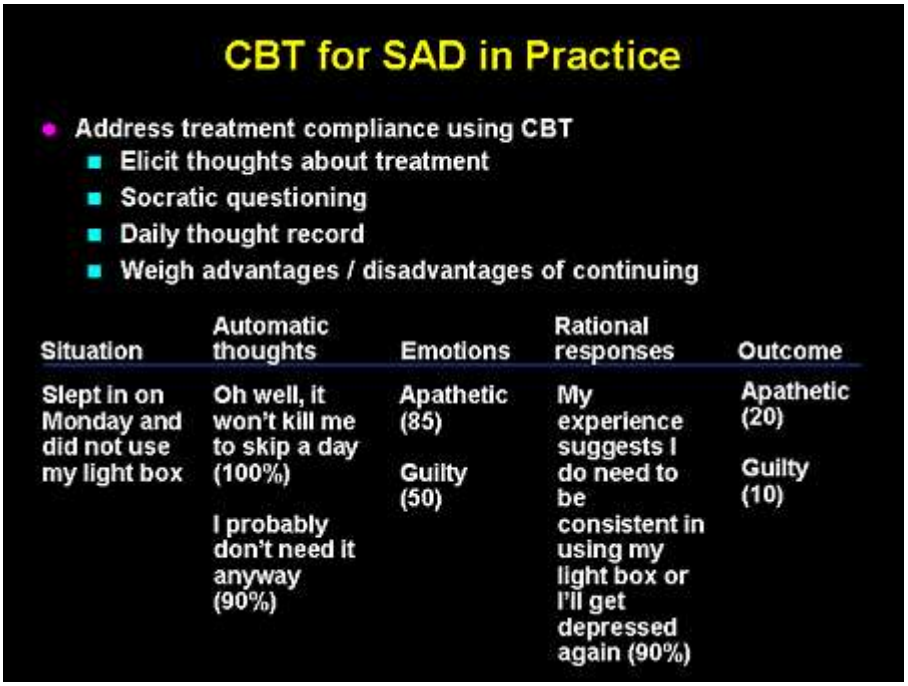
Now, on to the news that you can use. This slide illustrates the vicious SAD cycle, which is an early psychoeducational component in our CBT for SAD intervention. This is meant to provide the framework for the interventions that follow. We believe that SAD consists of a physical, behavioral, cognitive, and emotional component and that these components all interact with one another to contribute to SAD episode onset and maintenance. Evidence does suggest that a SAD episode begins with just 1 or 2 symptoms and then the other symptoms gradually develop on top of those in a kind of snowball effect. The progression of symptoms seems to be individual-specific, not general to all cases. Understanding a given patient's vicious SAD cycle can elucidate points of intervention. So for example, let's say that a patient initially experiences fatigue and low energy level in the fall. This might lead to sleeping too much, or hypersomnia, which could lead to doing less enjoyable activities because he or she does not have the energy to do them, or lost time due to sleeping too much. This could then lead to withdrawing from other people, which could lead to feeling blue, emotional, which contributes to thoughts such as, "I can't get started," "I'm no good," and "Winter is unbearable," which could then serve to intensify depressed mood, which could then make the individual want to sleep even more, and so on. Mapping out a given patient's vicious SAD cycle could clarify this progression as well as highlight possible points for intervention.

As noted in my model, it's possible that the vicious SAD cycle begins with the cognitive thoughts such as: "I hate winter and it won't be long now before I'm experiencing SAD

again." I treated a patient a couple of years ago who, upon that first workday after switching from Daylight Savings Time, would get out of work in the dark and go home directly to bed instead of going to the gym with friends. This would obviously suggest a possible intervention point of continuing with the gym behavior as opposed to going home and going to bed.

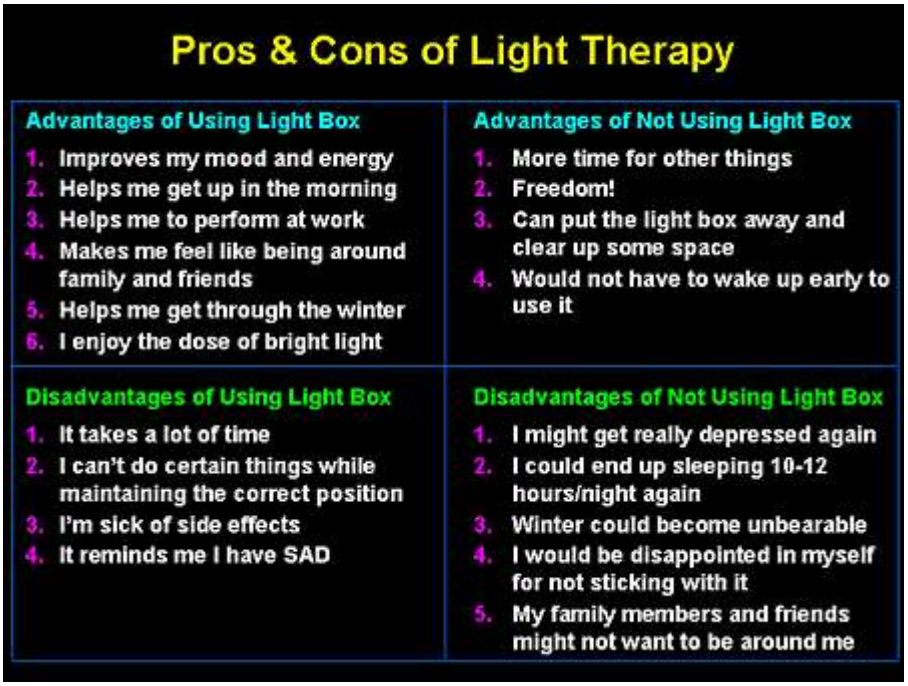
Slide 20. CBT for SAD in Practice

So as just described, one way that you can integrate CBT into your practice is to outline the vicious SAD cycle for these cases, which will help to identify early warning signs and points of intervention. Other things that you may do with the behavioral component include scheduling pleasant activities. This can sometimes be difficult with patients, but you always can problem-solve new wintertime interests. If you have patients who are particularly outdoors-oriented or like gardening and things that are sort of season-specific, you may have to be creative in generating new wintertime interests or identifying ways to modify those season-specific activities such that they can be done on a smaller scale during the wintertime. Another thing that you may do is refer to a provider who has expertise in CBT. The Academy of Cognitive Therapy and the Association for Advancement of Behavior Therapy both maintain Web sites that provide referrals to providers across the United States.



Slide 21. CBT for SAD in Practice

I also think that CBT has a role in treatment compliance; whether you're treating with medications, light therapy or combination treatment, I think that cognitive therapy could be used as a tool for motivating compliance. One thing that you may do is use a daily thought diary or thought record to identify thoughts that are interfering with treatment compliance. A classic situation that may arise is when a patient says: "I slept in on Monday and didn't use my light box." The negative automatic thoughts and reaction to this situation were: "Oh, well, it won't kill me to skip a day," which was believed at 100%. And, "I probably don't need it anyway," also highly believed at 90%. This led to emotions such as apathy and guilt. The rational response that this patient generated was: "My experience suggests that I do need to be consistent in using my light box or I'll get depressed again," a highly believable rational response at a rating of 90%. The outcome in this case was good; the rational response was effective and apathy and guilt were reduced.



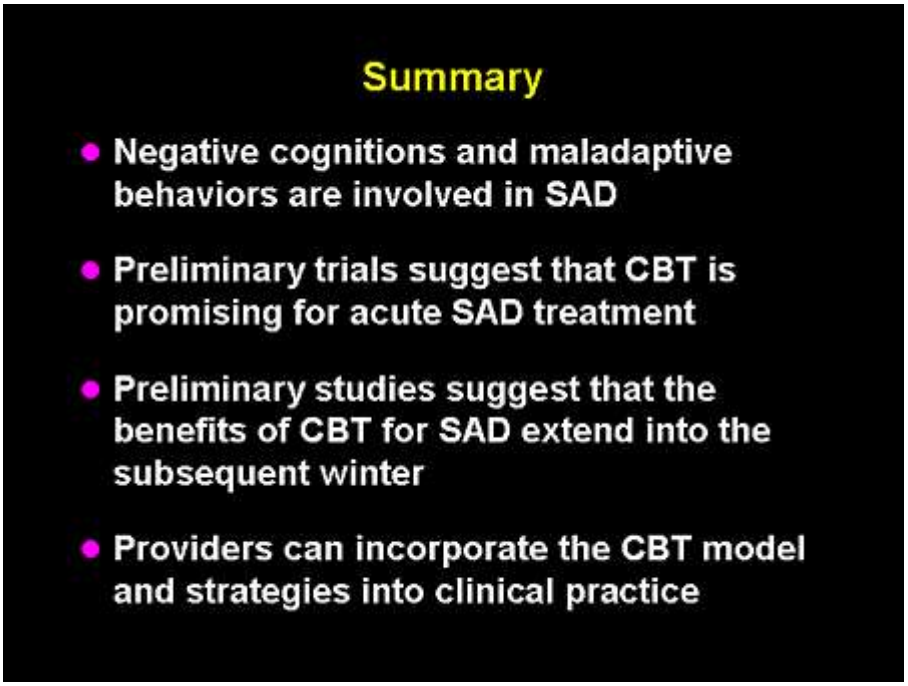
Slide 22. Pros and Cons of Light Therapy

Another way to use a cognitive technique in promoting treatment compliance is a decisional balance sheet. The point of this exercise is to compare the advantages and disadvantages of complying with treatment vs the advantages and disadvantages of not complying with treatment. In the case of light therapy specifically, where treatment guidelines recommend daily use of a light box from onset of first symptom through spontaneous remission in spring every year, this can be a particularly helpful exercise. Ideally, you want the advantages of complying and the disadvantages of not complying to outweigh the disadvantages of complying and the advantages of not complying in order to motivate treatment compliance. What you can do in this case is pull out a blank sheet of paper, break it up into 4 quadrants, and have a discussion with your patient around these issues and try to achieve the balance that's desirable.

Supplementary Cognitive-Behavioral Therapy for Improved Results

Kelly J. Rohan, PhD

Summary



Slide 23. Summary

In summary then, it appears that negative thoughts as well as maladaptive behaviors are involved in SAD onset and maintenance. Preliminary trials suggest that CBT is promising for acute SAD treatment. Preliminary studies also suggest that the benefits of CBT for SAD may extend into the subsequent winter season treatment durability, and lastly, providers can incorporate some cognitive and behavioral strategies into their everyday clinical practice for better results.

Authors and Disclosures

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