Seasonal Affective Disorder

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Many people may feel sad or down during the winter months, when the days are shorter and temperatures drop. For some people, this condition goes beyond the winter "blahs" and develops into a subtype of clinical depression that lasts throughout the late fall and winter months. This condition is known as seasonal affective disorder, or SAD. The term SAD was introduced in 1984 and has since been included in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders.

SAD is characterized by recurring, cyclic bouts of depression, increased appetite, and an increased need for sleep (Ford K 1992; Magnusson A et al 2003). It contrasts with most depressive disorders, which are characterized by sleep disturbances and diminished appetite (Magnusson A et al 2005). Besides mild depression, typical symptoms of SAD include anxiety, decreased activity, social withdrawal, increased sleep duration, increased appetite, weight gain, and carbohydrate craving (Rosenthal NE et al 1984; Sher L 2001).

SAD occurs in about 10 percent of the general population, although it is about twice as common among people who are treated for depression (Gross F et al 1996). It tends to be more common in the higher latitudes, where the winter days are comparatively shorter than at latitudes nearer the equator, and it occurs more often in women than in men (Rosen LN et al 1990; Gross F et al 1996; Magnusson A et al 2003). Studies have also shown that the tendency to develop SAD may run in families, which suggests a genetic component (Madden PA et al 1996). Family studies have shown that approximately 13 percent to 17 percent of people who have first-degree relatives with SAD will suffer from the condition themselves (Allen JM et al 1993;Thompson C et al 1988; White DM et al 1990; Wirz-Justice A et al 1986). The occurrence of SAD seems to lessen after the age of 55 (Gross F et al 1996).

What Causes SAD?

The 24-hour wake-sleep cycle, known as the circadian rhythm, is governed in part by the regular rise and fall of hormones, especially melatonin. Melatonin is the master sleep hormone; it is produced in the pineal gland. Researchers have identified a regular ebb and flow to human physiology and behavior throughout a normal 24-hour cycle (Hirota T et al 2004). Our overall pattern of wake-sleep depends on the proper functioning of an internal circadian clock, which lies deep in the brain. This circadian clock works with photosensors in the eyes to sense darkness. When darkness falls, the body begins to secrete melatonin, which is one of the factors that cause sleep. Melatonin continues to be secreted throughout the night, although the levels alter, and toward dawn, melatonin secretion gradually diminishes, allowing for wakefulness in the morning.

When there is a problem with this system, sleep disorders and other psychological problems can occur. Recent research has identified a number of possible abnormalities that may help explain SAD and offer therapeutic targets.

The melatonin theory. Early research focused on the shorter photoperiod in the winter, hypothesizing that shorter days led directly to SAD. Researchers initially attempted, with some success, to lengthen the photoperiod by exposing individuals to bright light both in the morning and in the evening (Rosenthal NE et al 1984; Winton F et al 1989). Researchers next focused on the secretion of melatonin, which controls the wake-sleep cycle. Although the 24-hour rhythm of melatonin secretion is generally the same in SAD patients and controls during winter months, researchers hypothesized that people with SAD had increased duration of melatonin secretion in the early morning hours (Checkley SA et al 1993; Partonen T et al 1996). This would explain why people with SAD have difficulty waking up and don't feel alert in the morning. Experiments with drugs to block melatonin secretion in the morning, thus decreasing the duration of its secretion, found the symptoms of SAD were relieved (Schlager DS 1994).

The phase-shift theory. According to this theory, developed in the late 1980s, people with SAD suffered from circadian rhythms that had fallen out of sync with the normal circadian cycle, which isn't quite 24 hours long. Some people may be "phase-advanced," meaning their bodies release melatonin too early in the evening, while others may be "phase-delayed," meaning they continue to release melatonin for too long into the day. According to the phase-shift theory, this abnormality occurs because the seasonal changes in light exposure somehow disrupt the normal functioning of the circadian clock.

Retinal hypersensitivity. One study found that the retinas of people with SAD are significantly less sensitive to light than those of controls, possibly because of neurotransmitter dysfunction (Hebert M et al 2004). However, other studies have found that people with SAD are hypersensitive to light (Terman JS et al 1999).

Neuroimmune dysfunction. Significant wintertime elevations of interleukin-6, a pro-inflammatory cytokine, have been noted in patients with SAD (Leu SJ et al 2001). Pro-inflammatory cytokines like interleukin-6 cause greater production of enzymes that deplete tryptophan from the blood. The result is serotonin deficiency in the brain (and the onset of depression).

Other studies have noted elevated neopterin (a marker of immune function) in response to reduced tryptophan in SAD patients (Stastny J et al 2003). These findings suggest that decreased tryptophan levels might lead to an overactive immune system (Hoekstra R et al 2003).

Low levels of neurotransmitters. Research suggests that people with SAD, like those with most other depressive disorders, may have low or abnormal levels of important neurotransmitters, including serotonin (a precursor to melatonin), acetylcholine, and dopamine (Jepson TL et al 1999; Schwartz PJ et al 1997; Depue RA et al 1989, 1990).

Among people with SAD, serotonin levels vary from season to season, with some of the lowest levels observed during December and January (Carlsson A et al 1980). This may explain why patients with SAD crave carbohydrates during the winter season: serotonin is involved in regulating feeding and satiety (Lam RW et al 2000a). Studies have also shown that the rate of production of serotonin in the brain is dependent on the length of exposure to bright sunlight and that turnover of serotonin in the brain is much lower during the winter season (Lambert GW et al 2002). Administration of a serotonin-like drug, m-chlorophenylpiperazine, produced increased activation and euphoria in depressed patients with SAD but not in controls or in SAD patients during summer (Schwartz PJ et al 1997). Some research suggests that the change in serotonin levels may result from reduced levels of vitamin D3, which are often observed in cases of SAD. Administration of 400 IU or 800 IU of vitamin D3 to people with SAD during late winter appeared to improve mood (Lansdowne AT et al 1998).

Untreated patients with SAD also have lower concentrations of norepinephrine compared to their normal counterparts (Schwartz PJ et al 1997). Research suggests that the reduced norepinephrine activity is linked to the hypersomnia, or increased need for sleep, that is common among people with SAD (Lam RW et al 2000b). Finally, low dopamine activity has been observed in SAD patients (Depue RA et al 1989, 1990).

Conventional Treatment of SAD

The first-line treatment for SAD is light therapy. During light therapy, patients are exposed to bright light early in the morning in an attempt to reduce the secretion of melatonin and stimulate a more natural waking cycle. Studies of patients with SAD indicate that bright light therapy in the morning produces greater therapeutic effect than evening light (Eastman CI et al 1998; Lewy AJ et al 1998b).

Although bright light therapy is an effective method for treating SAD, some people do not respond, because of either side effects or lack of adherence to its use (Pjrek E et al 2004). This

lack of adherence may result from the inconveniences associated with bright light therapy. First, bright light therapy is most effective if used early in the morning for 30 to 45 minutes, but patients with SAD may have difficulty awakening (Lewy AJ et al 1987a,b; Terman JS et al 2001; Pjrek E et al 2004). Second, the devices used can be expensive and may not be covered by insurance (Pjrek E et al 2004). Finally, light therapy is time consuming, with most studies recommending 30 to 45 minutes of direct exposure to the light source.

In addition to light therapy, a number of drugs may be prescribed, including the following:

Selective serotonin reuptake inhibitors. The selective serotonin reuptake inhibitors (SSRIs) fluoxetine and sertraline are the two antidepressants most commonly studied in the treatment of SAD (Lam RW et al 1995; Moscovitch A et al 2004). SSRIs inhibit serotonin reuptake within synapses (Potter W et al 2001), thus making more serotonin available to interact with serotonin receptors. Studies have also been conducted to determine the effects of SSRIs on melatonin levels in patients with SAD. Results have shown that the SSRI fluoxetine significantly reduces melatonin levels in these patients, while other antidepressant agents (e.g. tricyclics) actually elevate melatonin levels (Childs PA et al 1995). Because of the natural fluctuation in melatonin levels throughout the day, the timing of SSRI administration may be an important consideration to ensure that levels of melatonin are reduced at the appropriate time (e.g., in the morning).

Selective noradrenaline reuptake inhibitor. Reboxetine is a novel selective noradrenaline reuptake inhibitor available in European countries, although its application for approval in the United States has been denied by the Food and Drug Administration. It has been shown to be effective in treating depression (Kasper S et al 2000). A dose of 8 mg reboxetine daily has been shown to relieve both the depressive and the atypical symptoms associated with SAD within two weeks. Side effects include dry mouth and constipation, but they were generally transient and mild in intensity (Hilger E et al 2001). For more information, go to www.reboxetine.com.

Modafinil. Hypersomnia, or the increased need for sleep, is a common problem associated with SAD. Modafinil is a drug known to promote wakefulness and has been studied in the treatment of SAD (Lundt L 2004). Modafinil is thought to selectively promote wakefulness by influencing the sleep-wake centers of the brain (Scammell TE et al 2000). Studies using modafinil in treatment of narcolepsy and major depressive disorder have indicated that modafinil can improve wakefulness and reduce fatigue (DeBattista C et al 2003; Menza MA et al 2000). In a study of treatment with 100 mg modafinil during week 1, followed by 100 mg or 200 mg for weeks 2 to 8, modafinil significantly improved SAD symptoms, reduced fatigue, and was well tolerated (Lundt L 2004).

Melatonin's Role in SAD

Melatonin, a hormone produced in the pineal gland, is responsible for regulating sleep and core body temperature at night (Arendt J et al 2005). The role of melatonin in SAD is complicated and the subject of some controversy. Under normal circumstances, levels of melatonin increase in the evening, prior to bedtime, peak in the middle of the night, and decrease gradually as morning approaches (Macchi MM et al 2004). Among people with SAD, excessive duration of melatonin secretion has been implicated, but researchers are far from settled on this theory as the main cause of SAD. Nevertheless, low-dose melatonin taken at night has been shown to be effective in improving mood in patients with SAD (Lewy AJ et al 1998a; Rohr UD et al 2002).

Additional Nutritional Support for SAD

Nutrient therapy for SAD operates along principles similar to those of pharmacological therapy: increased serotonin levels may relieve symptoms. To understand how these nutrients work, it is necessary to understand how serotonin is synthesized. In the body, tryptophan is converted to 5-hydroxytryptophan (5-HTP) by the enzyme tryptophan hydroxylase; this conversion can be inhibited by a deficiency in vitamin B6 or by insufficient magnesium (Birdsall TC 1998). In turn, 5-HTP is converted to serotonin, which is subsequently converted to melatonin, with S-adenosyl-L-methionine (SAMe) serving as the methylating agent (Macchi MM et al 2004; McKee T et al 1999). Thus any nutrients that support healthy levels of tryptophan or promote

healthy methylation would at least theoretically help improve levels of serotonin and relieve the symptoms of SAD.

Tryptophan. Light therapy is usually considered the first-line treatment for SAD, but about 40 percent of patients treated with light therapy do not respond (Ghadirian AM et al 1998). This may be due in part to a deficiency of tryptophan (Lam RW et al 1996), which is necessary for the synthesis of serotonin and is sometimes recommended as a natural antidepressant. Some data suggest that light stimulates the conversion of tryptophan to serotonin (Lam RW et a 1996). Some studies indicate that tryptophan may be used to enhance light therapy (Lam RW et al 1997), while others show that tryptophan can produce benefits equal to those of light therapy in patients with SAD and may lengthen the time to relapse (Ghadirian AM et al 1998). One study in patients with SAD who had been treated with light therapy noted that rapid depletion of tryptophan resulted in a reversal of the therapeutic effects of bright light treatment (Lam RW et al 1996).

Tryptophan depletion in an experimental setting in patients with SAD has also been associated with an increase in plasma neopterin (Stastny J et al 2003). Neopterin is a marker of immune function; high levels are associated with increased immune system activity. This suggests that low levels of tryptophan may cause elevated neopterin levels, which, in conjunction with reduced serotonin, may worsen the depression associated with SAD (Stastny J et al 2003). These findings have important implications in patients with autoimmune disorders, such as rheumatoid arthritis, multiple sclerosis, or Alzheimer's disease, in which levels of immune system cytokines (such as interleukin-6) may already be elevated (Maini RN et al 2000; McGeer PL et al 1995; Thornton AE et al 1997).

Tryptophan was a popular dietary supplement until 1989, when an epidemic outbreak of eosinophilia-myalgia syndrome (EMS) was associated with the use of tryptophan in the United States. About 95 percent of those cases were traced to a single overseas supplier, although many people who took tryptophan from this supplier did not develop EMS. In 1989 the Food and Drug Administration issued a nationwide recall for all products containing tryptophan, and it subsequently banned importation of tryptophan from overseas sources (Das YT et al 2004).

5-HTP. 5-HTP is the immediate precursor in the biosynthesis of serotonin from tryptophan. Oral 5-HTP crosses the blood-brain barrier easily and can be as effective as tryptophan in increasing levels of serotonin (Birdsall TC 1998). Administration of 200 mg to 600 mg 5-HTP has been shown to be effective in treating insomnia and improving quality of sleep (Guilleminault C et al 1973; Soulairac A et al 1977; Wyatt RJ et al 1971). 5-HTP has been found safe in treating SAD when used alone but has been shown to increase cortisol levels (Jacobsen FM et al 1987). It is important to note that concomitant use of 5-HTP and SSRIs or monoamine oxidase inhibitors can result in serotonin syndrome, a condition characterized by agitation, confusion, delirium, tachycardia, diaphoresis, and fluctuations in blood pressure (Martin TG 1996). However, no definitive cases of toxicity have emerged worldwide in the past 20 years in patients using 5-HTP as a dietary supplement by itself (Das YT et al 2004).

Vitamin B6 and SAMe. The conversion of tryptophan to 5-HTP can be inhibited by a deficiency of vitamin B6 or by insufficient magnesium (Birdsall TC 1998). Also, the conversion of 5-HTP to serotonin, and serotonin's subsequent conversion into melatonin, rely on SAMe as a methylating agent (Macchi MM et al 2004; McKee T et al 1999). Vitamin B6 is an important cofactor involved in the production of serotonin. Vitamin B6 deficiency should be considered in SAD, particularly in the elderly, who may suffer from vitamin deficiencies (Hvas AM et al 2004).

Magnesium. Studies indicate that a healthy circadian rhythm is associated with normally fluctuating magnesium levels, which peak in the evening, with fluctuations noted in the morning (Touitou Y et al 1978; Ising H et al 1995). Insufficient levels of magnesium can inhibit the conversion of tryptophan to 5-HTP, which can affect the production of serotonin and melatonin (Birdsall TC 1998). Research suggests that magnesium depletion may be associated with the dysregulation of the biological clock, resulting from either an increase or a decrease in melatonin, as is evident in SAD (Durlach J et al 2002).

St. John's wort. St. John's wort has been shown to be effective against severe depression and the depressive symptoms of SAD (Vorbach EU et al 1997; Kasper S 1997). In one study, 900 mg of hypericum, an extract of St. John's wort, was found to be as effective as light therapy in SAD (Kasper S 1997). Another study found that 900 mg hypericum in combination with bright light (3000 lux) or dim light (< 300 lux) therapy reduced depressive symptoms in patients with SAD (Martinez B et al 1994). The exact mechanism of action of St. John's wort has not been clearly established; however, researchers propose that St. John's wort affects the uptake and reuptake of monoamines like serotonin and norepinephrine (Nangia M et al 2000).

Omega-3 fatty acids. Omega-3 fatty acids have a role in the synthesis of serotonin, and there are encouraging data about their use in depressive disorders. Also, because the incidence of SAD is associated with higher latitudes, it seems logical that people who live in the Arctic would suffer from very high rates of a winter depressive disorder. Researchers, however, have found to their surprise that SAD is very rare among Icelandic peoples, who eat a lot of omega-3 fatty acids in coldwater fish. Interestingly, when fish consumption goes down, the incidence of SAD begins to increase (McGrath-Hanna NK et al 2003; Cott J et al 2001; Magnusson A et al 2000).

As mentioned previously, pro-inflammatory cytokines cause greater production of enzymes that deplete tryptophan in the blood, which can result in serotonin deficiency in the brain. These new findings about cytokine-induced degradation of tryptophan explain why nutrients like fish oil (which suppress inflammatory cytokines) alleviate depression.

Although studies haven't been conducted examining the role of omega-3 fatty acid supplementation in SAD, these essential oils have multiple health benefits, and considering the suggestive data in Arctic people who consume a lot of fish oil, it is probably prudent to add omega-3 fatty acids to a supplementation program.