Epidemiology, Etiology, and Natural Treatment of Seasonal Affective Disorder

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Abstract

There is much more seasonal difference in higher latitudes than in lower latitudes. In a significant portion of the population of the northern United States, the shorter days of fall and winter precipitate a syndrome that can consist of depression, fatigue, hypersomnolence, hyperphagia, carbohydrate craving, weight gain, and loss of libido. If these symptoms persist in the winter, abate as the days grow longer, and disappear in the summer, the diagnosis of seasonal affective disorder (SAD) can be made. Many hypotheses exist regarding the biochemical mechanisms behind the predisposition toward this disease, including circadian phase shifting, abnormal pineal melatonin secretion, and abnormal serotonin synthesis. Although the mechanism(s) behind this disease is not fully known, one treatment appears to address each of the theories. Light therapy is a natural, non-invasive, effective, well-researched method of treatment for SAD. Various light temperatures and times of administration of light therapy have been studied, and a combination of morning and evening exposure appears to offer the best efficacy. Other natural methods of treatment have been studied, including L-tryptophan, *Hypericum perforatum* (St. John's wort), and melatonin.
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Introduction

Areas of the world in latitudes closer to the equator have fewer seasonal changes than geographic areas further from the equator. In contrast, areas of North America in the higher latitudes have greater, and sometimes drastic, differences in yearly seasons. In the fall and as winter approaches, the days shorten and temperatures drop. This signals some species to gather food for winter, while other species go into hibernation. Most humans are not seriously affected by the shorter days and longer nights of fall and winter; however, some individuals experience sufficiently severe changes in mood, energy, and appetite to be diagnosed with seasonal affective disorder (SAD). This condition can include depression, hypersomnolence, fatigue, loss of interest in sex, increased carbohydrate consumption, and weight gain in the fall and winter months. For an individual to be diagnosed with SAD the symptoms must occur only in the fall and winter, abate as the days lengthen, and be absent in the spring and summer. In fact, some individuals with SAD go to the other extreme in the spring and summer, experiencing a manic state.

Epidemiology/Etiopathology of SAD

Epidemiological studies of individuals with SAD demonstrate an incidence of SAD in the general population of 4-10 percent,[1-5] with a higher incidence in women than men. The most commonly used SAD diagnostic research tools are the Seasonal Pattern Questionnaire (SPAQ) and the Structured Interview

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Guide for the Hamilton Depression Rating-Seasonal Affective Disorder (SIGH-SAD), which can ascertain whether the patient has SAD or a sub-syndromal SAD (S-SAD).

The sub-syndromal form of SAD consists of milder, albeit clinically significant, seasonal affective symptoms. Cumulatively, the occurrence of SAD and S-SAD together is 11-21 percent. This indicates that a significant portion of the population suffers from varying degrees of seasonal depression. Other diagnostic methods are available, including the Seasonal Health Questionnaire (SHQ). A newer tool, the SHQ was compared recently to the SPAQ in 809 patients in the United Kingdom in a study in which subjects completed both tests. The researchers concluded the SHQ was more sensitive and specific in determining whether a patient indeed suffered from SAD. The SPAQ showed a prevalence of 10.7 percent, while the SHQ noted a lower incidence of 5.6 percent.[6]

Whichever diagnostic tool is used, it cannot be refuted that a significant number of individuals are negatively affected by the change in seasons. The mildest seasonal impairment can be described as "seasonality," in which the individual functions less efficiently in the winter months. The personal impact of the fall/winter seasonal change appears to be on a continuum, with seasonality on one end, the profound symptomatology of SAD on the other, and S-SAD in the middle. Kasper studied patterns of seasonal mood change in a population in Montgomery County, Maryland, and found 27 percent of subjects who took the SPAQ described seasonal changes as a "problem," while 10 percent experienced seasonal impairments severe enough to be on the level of SAD.[1]

This continuum was further delineated by Rosen et al, who built on the previous work by Kasper by studying individuals in four U.S. latitudes: Nashua, NH; New York, NY; Montgomery County, MD; and Sarasota, FL. In this study, 40 percent of all subjects (total, 1,576) who filled out the SPAQ reported they felt the worst in the winter months. When the study centers were analyzed, there was a significantly higher percentage of respondents in the northern latitudes who "felt worst in winter:" Nashua, NH – 48.7 percent; New York City – 46.9 percent, Montgomery County – 47.7 percent, and Sarasota, FL – 17.6 percent. These seasonal changes were felt to be "a problem" by subjects in a similar north-to-south pattern: 26.1, 24.2, 22.0, and 13.5 percent, respectively. When the SAD diagnostic criteria were considered in residents of New Hampshire, New York, Maryland, and Florida, the incidence was 9.7, 4.7, 6.3, and 1.4 percent, respectively. This study demonstrated a significantly greater incidence of seasonality, seasonal problems, S-SAD, and SAD in higher latitudes compared to the lower latitude of Florida.[2]

SAD incidence appears to increase in populations further north, which has been demonstrated in studies of populations in Alaska and other areas of the world close to the arctic. In a study of U.S. Army soldiers, a SAD prevalence of 13.1 percent for women and 6.5 percent for men was noted.[7] A study of Fairbanks residents who had lived there for more than three years found an overall incidence of 9.2 percent, with a 3:2 female-to-male ratio.[8]

In addition to the classic symptoms of SAD experienced in winter, cognitive function might also be affected by the seasons. This is illustrated in research performed at the University of Alaska, Anchorage, in which hospital medication errors were analyzed over a five-year period. The majority of hospital medication errors – 58 percent – occurred in the first three months of the year. The study's authors also determined medication errors were almost twice as likely in December than in September.[9] A group of researchers in Norway, however, studied cognitive processes in 100 individuals from the general population living at 69 degrees north latitude and found no worsening of cognition in the winter months.[10]

People from southern latitudes who move north may have an increased risk of SAD, as it appears some individuals develop a tolerance to seasonal changes over time. Using the SPAQ and the Beck Depression Inventory, researchers in Maine assessed the incidence of SAD and S-SAD in 76 college students. They found higher SAD rates than other studies, with SAD incidence of 13.2 percent and combined SAD and S-SAD of 19.7 percent. This overall higher incidence could be due to other factors, including environment or lifestyle issues; however, students who had moved from lower latitudes to Maine were more likely to suffer from winter depression than New England natives.[11]

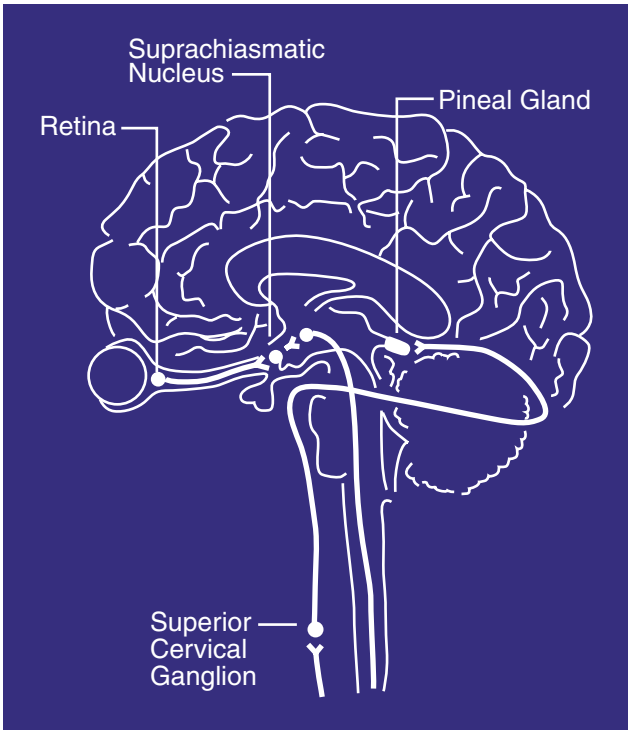
The above studies provide ample evidence for a "latitude theory" of SAD incidence; i.e., decreased exposure to sunlight in the winter in northern climates increases the risk of SAD. However, studies of populations native to Iceland discovered a possible genetic adaptation to the low light of winter in the arctic north. Magnusson and Axelsson[12] looked at 252 people who were direct descendants of Icelandic emigrants and living in an area of Manitoba, Canada (lat. 50° N). This population had a SAD and S-SAD prevalence of 1.2 and 3.3 percent, respectively. This occurrence was significantly lower ($p<0.001$) than that of the eastern U.S. populations of Nashua, NH; New York City; and Montgomery County, Maryland, studied by Rosen.[2] The prevalence in the Icelandic descendants was also significantly less than a group of non-Icelandic Canadians living in the same area ($p <0.01$), which gives more credence to a protective genetic component in the Icelanders.[4] The last test in this series of studies compared SAD incidence in a group of 587 individuals currently living in Iceland[13] to the Icelandic Canadians in Manitoba. The combined prevalence of SAD and S-SAD in the Icelanders (lat. 64-67° N) was significantly greater ($p<0.025$) than in the Canadian-Icelandic population. Therefore, there appears to be a genetic component that protects Icelanders from SAD, compared to other populations; but within Icelandic populations there is still an increased occurrence in northern latitudes.

Another genetic finding is a tendency for SAD to occur more often in relatives of those who have SAD; i.e., SAD runs in families. Madden et al studied seasonality and SAD in 3,331 twins in Australia and found genetic effects accounted for 29 percent of the variance in seasonality.[14]

Mechanisms of Seasonal Changes in SAD

Seasonal changes in daylight appear to influence the behavioral changes in SAD, but the exact mechanism by which SAD symptoms arise from these seasonal changes is not fully known. Theories abound, and many are well researched. It may be that certain mechanisms apply to specific genetic types, so a one-size-fits-all mechanism may not be found.

Figure 1. Neural Pathway of Melatonin Regulation

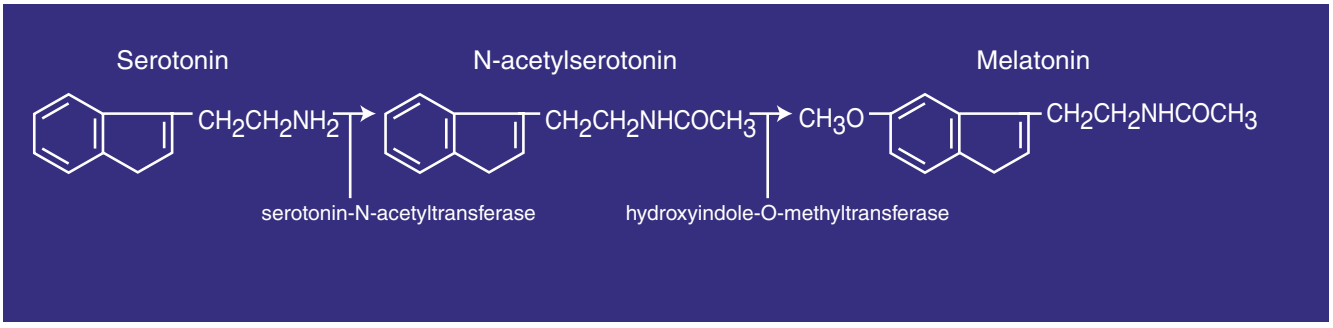


Melatonin's Possible Contribution to SAD

The literature reveals that individuals with SAD have a longer period of melatonin synthesis at night in the winter. In addition, daytime melatonin levels may be higher in SAD sufferers in the winter, compared to those without SAD. Melatonin synthesis can also be suppressed by application of light therapy in the daytime, which also relieves SAD symptoms. This information leads some researchers to believe abnormal melatonin synthesis is the culprit in SAD.

Melatonin synthesis is triggered by darkness. Daylight blood levels are typically very low, with a nocturnal peak and diminishing levels over the ensuing hours. The diurnal and circadian rhythm of this secretion is brought about by light entering the retina, which stimulates the suprachiasmatic nucleus of the hypothalamus. This in turn inhibits the pineal gland from converting serotonin to melatonin (Figure 1). After dark, this inhibitory mechanism is no longer present and the pineal gland begins synthesizing melatonin. Serotonin in this gland is acetylated, then methylated, forming melatonin (Figure 2).

Figure 2. Conversion of Serotonin to Melatonin



The timing and duration of melatonin secretion appears to be affected by the length of day and night. In SAD patients there is a delayed nocturnal onset of melatonin secretion.[15,16] Wehr et al found the period of nocturnal melatonin secretion in women with SAD is increased in winter compared to summer. In contrast, women without SAD symptoms do not appear to demonstrate this seasonal variance in melatonin synthesis.[17] How this circadian shift in SAD patients brings about symptoms, or even if this shift is involved in the etiology of this disease, is not known. Elevated daytime blood melatonin levels have also been observed in SAD patients.[18]

In one of the earlier SAD studies, Lewy found that bright evening light suppresses melatonin synthesis.[16] Other researchers have noted similar results,[19] while others, including Lewy's group, have shown morning light therapy delays the onset of melatonin secretion,[20] but overnight plasma and salivary levels are elevated.[15] Regardless of the timing of light therapy, melatonin levels in both SAD patients and controls respond similarly. Also, no significant difference has been noted in melatonin secretion after light therapy in responders compared to non-responders; the melatonin response is the same whether SAD symptoms remit or persist. These findings may negate the hypothesis that a shift in melatonin secretion is the cause of SAD symptomatology.

The Phase-Shift Hypothesis

As noted above, the suprachiasmatic nucleus in the hypothalamus entrains the body to a 24-hour circadian rhythm. It has also been seen that the onset of melatonin secretion may be delayed in SAD patients and controls. Possibly SAD patients have some other hormonal response or other as yet unknown negative reaction to this normal phase shift. Lewy and Sack first brought forth the phase-shift hypothesis of SAD after demonstrating morning bright light phase-advanced circadian rhythms and led to an antidepressant effect.[16]

Avery et al[21] studied circadian body temperature, cortisol, and thyroid-stimulating hormone (TSH) rhythms in six SAD patients and six controls before and after morning bright light therapy. The overnight minimum body temperature was delayed in the SAD group compared to controls (5:42 am vs. 3:16 am) and was corrected after light therapy. The nighttime cortisol nadir was phase-delayed as well, and was also corrected with light treatment. TSH levels were not significantly different before or after light treatment. Others previously found similar phase delays in temperature and TSH.[22,23] It appears that in addition to melatonin, other hormones and the nocturnal body temperature are also phase-delayed in SAD.

The Serotonin Hypothesis

In addition to the melatonin and phase-shift theories, researchers have examined serotonin and catecholamine levels in SAD patients and normals. Since melatonin is the immediate downstream metabolite of serotonin, and serotonin is involved in brain function, it is plausible that low brain levels of serotonin might contribute to SAD symptoms. Also, SAD patients tend to exhibit hyperphagia and carbohydrate cravings, symptoms typical of inadequate brain serotonin. It has been suggested the increased carbohydrate craving in SAD may be a coping mechanism that stimulates the release of serotonin. Sixteen patients with SAD and 16 controls were studied before

and after two different meals: a protein-rich meal and a high-carbohydrate meal. Patients and controls were crossed over after the initial meal. The meals were isocaloric; however, SAD patients reported increased alertness and decreased fatigue following the carbohydrate meal, compared to increased fatigue in the controls.[24] This indicates SAD patients may be "self medicating" with carbohydrate-rich foods in a subconscious attempt to correct abnormal brain serotonin levels.

One method of investigating whether serotonin is involved in SAD is to deplete the body of dietary tryptophan. Animal and human studies show decreasing the availability of this serotonin precursor results in behavioral changes typical of serotonin depletion (depression, anxiety, carbohydrate craving, hypersomnia, etc.).[25,26] Researchers studied SAD patients in summer remission by exclusively feeding them a beverage containing no tryptophan. This regimen induced a transient depressive relapse,[27] as did tryptophan depletion or catecholamine depletion in SAD patients after bright light therapy.[28] However, other researchers did not see a difference in behavior in a similar experiment using tryptophan depletion.[26] Since the cohort relapsed with tryptophan depletion, Neumeister et al concluded the symptomatic relief experienced by SAD patients both with light therapy and in summer must be a result of a homeostasis of serotonergic activity. Another finding adding credence to the serotonergic theory is that ingestion of tryptophan, as well as serotonin reuptake inhibitor drugs, has been shown to improve the symptoms of SAD.[29-31]

Other cofactor substances involved in serotonin synthesis might be involved in SAD. Hoekstra et al studied the effect of light therapy on tryptophan, biopterin, and neopterin in 19 SAD patients. Biopterin is a vital cofactor in tryptophan hydrolase's conversion of tryptophan to serotonin. Neopterin is a marker of cell-mediated immunity. This study found significantly lower baseline plasma tryptophan and biopterin, and higher neopterin levels, in patients compared to controls. After light therapy, biopterin levels normalized, but dropped again in the summer. Neopterin levels did not change after therapy, and tryptophan levels did not increase significantly. The authors suggest the lower baseline and summer biopterin levels, as well as the high neopterin, might predispose patients to relapse in subsequent winters.[32]

As with other forms of depression, there may be a catecholamine dysfunction component in SAD. The evidence is not as strong as the serotonin/melatonin research, but plasma norepinephrine levels have been shown to be lower in more depressed SAD patients.[33] In addition, Neumeister's group administered a tyrosine hydroxylase inhibitor, which inhibits catecholamine synthesis, and showed a reappearance of symptoms in patients previously in remission after light therapy.[28] Similar results were demonstrated with the same methods of tryptophan and catecholamine depletion in a subsequent study.[34]

Natural Treatments of Seasonal Affective Disorder

Light Therapy

The least invasive, most natural, and most researched treatment of SAD – natural or otherwise – is light therapy. The original theory behind light therapy was that it would cause a normalization of the phase-shift delay in SAD. It was then thought to lengthen the photoperiod in winter in those with SAD. It has also been used to suppress the production of melatonin by the pineal gland. Whatever the mechanism of action of light therapy on the body, it has been shown in numerous patient populations to be an effective method of treatment of SAD. It has an overall positive treatment response of up to 70 percent, with rarely any side effects. Studies have applied bright light (3300 lux), medium light intensity, and dim light, all with positive clinical response. The timing of light therapy has also been studied extensively, and it appears that morning, midday, and evening application is effective. In addition, full spectrum with ultraviolet (UV), full spectrum without UV, cool white, red spectrum, and blue/green/yellow spectrum have been used with success. What needs to be elucidated now is the relative effectiveness of these varying therapies.

Morning bright light therapy (2500 lux cool white lightbox) for two hours (6-8 am) normalized body temperature, cortisol, and mood measured by the SIGH-SAD in a four-week study.[21]

In another study, full spectrum or cool white light was administered from 6-8 am for seven days.

SIGH-SAD scores were significantly better in the treatment group, with no significant difference between cool white and full spectrum therapy, suggesting treatment with a light spectrum similar to the sun is not necessary in SAD.[15]

In a study comparing morning and evening bright light therapy (10,000 lux x 30 min), similar positive clinical results were obtained in both groups. Using the SIGH-SAD scale, light therapy caused an antidepressant effect regardless of morning or evening administration.[35]

Because many patients have a problem sitting in front of a bright light box for 30 minutes to two hours each day, researchers in Basel, Switzerland, studied the effects of artificial bright light (2800 lux x 30 min/day) or a daily one-hour walk outdoors in natural light. The natural light group performed significantly better than the artificial light group on the SIGH-SAD after one week. The walk group also spent less time in bed, arose earlier, and reduced carbohydrate intake.[36]

Another aspect of light therapy is the use of "dawn simulation" in SAD patients. The objective of this treatment is to improve the phase delay of melatonin, the difficulty in awakening, and morning fatigue experienced by SAD patients. Avery et al used a device that slowly increased the intensity of light for 1.5 hours in the early morning for six weeks. The light intensity eventually reached 250 lux at 6 am. This therapy was compared with a placebo (low intensity red light) and bright light therapy (10,000 lux for one-half hour upon arising). Dawn simulation resulted in a greater response ($p<0.001$) and remission of SAD symptoms ($p<0.001$) than placebo or bright light treatment.[37] A second study found improved awakening and less morning drowsiness with dawn simulation in 55 SAD patients.[38]

The best comparison to date of the variety of light therapy applications is a recent meta-analysis of 40 light-therapy studies. There was no significant difference in time of day of light therapy in this analysis; patients responded similarly regardless of morning, midday, or evening administration. When comparing single-time-period (morning, midday, or evening) with a regimen using morning and evening light application, a significantly greater response was seen in the morning and evening light group. Therefore, it is not crucial when light therapy is used if it is done only once per day, although, a greater effect will be seen by a morning-evening combination.[39]

Light therapy has been used in combination with a number of other therapies, including cognitive-behavioral therapy (CBT), L-tryptophan, and *Hypericum perforatum* (St. John's wort). In a six-week study of the combination of light and CBT, patients responded similarly to treatment, whether it involved CBT, light, or both. In the subsequent winter the combination of CBT and light, or CBT alone, demonstrated a lower remission rate than light therapy alone.[40]

Since there is a subset of individuals with SAD who do not respond to light therapy, a combination of light (10,000 lux cool white x 30 min daily) and L-tryptophan (1 g three times daily) was given to 14 SAD patients who were unresponsive after two weeks of light therapy alone. Two subsequent weeks on tryptophan resulted in a significant reduction in depression scores.[41] Tryptophan is available by prescription, and it makes sense that the use of 5-hydroxytryptophan, the immediate precursor to serotonin, might garner similar results at a lower dose.

Light therapy has also been shown to be effective in other forms of depression, including antepartum depression[42] and major depression in institutionalized elderly patients.[43] Bright light therapy decreased winter binge frequency in women with bulimia nervosa in a double-blind, placebo-controlled study of 34 patients,[44] and jet lag has also been effectively treated.[45]

Tryptophan Treatment of SAD

Tryptophan was shown above to be of benefit in non-responders to light therapy. In another study, four weeks of treatment with tryptophan alone (2 g twice daily, increased to 2 g three times daily if initially no response) was compared to light therapy (10,000 lux x 30 min daily in the morning). At the end of seven weeks, responses were similar in both groups, with no significant difference between them. However, when light therapy was discontinued, patients quickly relapsed, whereas patients on tryptophan had a slower relapse rate.[46] McGrath found similar results in 13 SAD patients treated with light or tryptophan.[29]

Hypericum perforatum (St. John's wort) in SAD

St. John's wort (SJW) has been used successfully in numerous studies in the treatment of mild-to-moderate and major depression.[47] In the initial study, an extract (900 mg/day) was combined with light therapy (either 300 or 3000 lux x 2 hours daily) in 20 SAD patients. There was a significant antidepressant response in both groups, with improvements in fatigue, depression, anxiety, lethargy, appetite, libido, and sleep, indicating SJW is an effective antidepressant in SAD.[48] St. John's wort by itself was subsequently investigated in a four-week study using 900 mg of a standardized extract daily. SJW use was associated with significant improvement in the SIGH-SAD; there was no significant improvement when bright light therapy was added to the treatment. When SJW was compared to fluoxetine, a specific serotonin reuptake inhibitor, the results were similar.[49]

Wheatley studied SJW (300 mg standardized extract three times daily) in 168 SAD patients and compared the results to SJW plus light therapy. A significant ($p<0.001$) reduction in the Hamilton scale was seen in the SJW group and in the SJW plus light therapy group, with no significant difference between groups.[50]

Melatonin in SAD Treatment

Since melatonin rhythms appear to be phase-delayed in SAD, researchers anticipated they could phase-advance normal melatonin secretion by giving exogenous low-dose melatonin. In a pilot study in 1998, five patients were given melatonin (0.125 mg) in the afternoon for three weeks; five were given placebo. Melatonin significantly improved the SIGH-SAD score in the melatonin group compared to placebo.[51] In a recent study, 58 subjects with S-SAD or weather-associated mood changes were given 2 mg of a controlled-release melatonin preparation or placebo once each evening for three weeks. In the S-SAD group a significant improvement was noted in quality of sleep and vitality; however, melatonin was ineffective in the weather-associated mood group. This is the first study to show higher-dose melatonin is well tolerated and possibly effective, at least in improving sleep in patients with SAD.[52]

Conclusions

A significant percentage of the U.S. population, especially in northern latitudes, is affected negatively by the shorter days of fall and winter. Some are mildly affected, while others are seriously debilitated by these seasonal changes, resulting in depression, hypersomnia, hyperphagia, weight gain, and loss of libido. Numerous hypotheses exist regarding the potential neuroendocrine and biochemical malfunctions occurring in SAD patients. Whatever the biochemical cause(s) of SAD, natural, well-researched remedies are available to the SAD patient. In fact, this is one of very few disease states in which the treatment of choice is a natural and non-invasive one – light therapy. It is easily administered, effective, and without side effects. In those individuals who do not totally respond to light therapy, or in those who find light therapy cumbersome, St. John's wort has been shown to be an effective adjunct or single treatment. It should be noted that SJW can interact adversely with a number of prescription drugs, so the metabolism of a concurrent prescription drug should be researched before starting SJW. Although it remains to be researched, 5-hydroxytryptophan may provide relief. Melatonin treatment is also in its infancy and should be used with caution.

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