Cortisol and Seasonal Changes in Mood and Behavior

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The degree to which season changes affect mood, energy, sleep, appetite, food preference, or desire to socialize with others has been called "seasonality." Identification of a seasonal pattern can only be made if both the patient and physician actively look for it.

Whoever wishes to pursue the science of medicine in a direct manner must first investigate the seasons of the year and what occurs in them." --Hippocrates

Since ancient times, people have been aware of seasonal changes in mood and behavior. Poets have described the sense of sadness, loss, and lethargy that can accompany the shortening days of fall and winter. Many cultures and religions have winter festivals associated with candles or fire. These festivals represent attempts to raise spirits in a season when the days are short.

Historical background

The concept of seasonal mood disorders dates back to the dawn of medicine. Seasonal depressions were described by the Greek physician Hippocrates circa 400 bc. About 2000 years ago, the Greek philosopher Posidonius wrote that "melancholy occurs in autumn, whereas mania in summer." In the second century, Greco-Roman physicians were treating depression and lethargy with sunlight directed toward the eyes. In 1894, explorer Frederick Cook linked seasonal loss of sunlight to a mood disorder. Cook described a syndrome characterized by a loss of sexual desire and energy, fatigue, and a profoundly depressed mood. The French neurologist Esquirol and the German psychiatrist Kraepelin both described seasonal changes in mood in books published in the years 1845 and 1921, respectively.

Characteristics of seasonal affective disorder

In 1984, Rosenthal and associates described the syndrome of "seasonal affective disorder" (SAD), a condition in which depression in fall and winter alternates with nondepressed periods in spring and summer. It was suggested that in order for a diagnosis of SAD to be made, the following criteria must be met: a history of a major depressive disorder; at least 2 consecutive previous years in which depression developed during fall or winter and remitted by the following spring and summer; absence of any other Axis I psychiatric disorder; and absence of any clear-cut, seasonally changing psychosocial variables that would account for the seasonal variability in mood and behavior.

Later, an opposite pattern--depression in the summer and nondepressed periods in the winter--was described. These 2 types of SAD probably represent a subset of a variety of seasonal behavioral disorders. SAD has been included in DSM-III-R and DSM-IV as having a "seasonal pattern," an adjectival modifier of any form of seasonally recurrent mood disorder.

The onset of winter SAD usually occurs between the age of 20 and 30 years, but affected people often do not seek psychiatric help for some time. Many patients with SAD report disliking winter since their teenage years, although the problem usually becomes severe only in adulthood. Sadness, anxiety, irritability, decreased activity, difficulties at work, social withdrawal, changes in appetite, decreased libido, and changes in sleep are characteristic symptoms of winter SAD. Most patients with winter SAD have atypical depressive symptoms such as increased sleep duration, increased appetite, weight gain, and carbohydrate craving. Depressive episodes are generally mild to moderate, but some patients need hospitalization.

The neurovegetative symptoms of subsyndromal SAD are similar to those of SAD, but major depression is absent. Patients with winter SAD may experience a reversal of their winter symptoms in summer, including mild hypomania; elevated mood; increased libido, social activity, and energy; and decreased sleep requirements, appetite, and weight. Most episodes of SAD occur within unipolar major depressive disorder, a substantial minority have accompanying hypomanic episodes (bipolar II disorder), and very few are associated with manic episodes. Patients with summer SAD usually report typical vegetative symptoms such as insomnia and loss of appetite and weight.

The degree to which season changes affect mood, energy, sleep, appetite, food preference, or desire to socialize with others has been called "seasonality." Seasonality can manifest in different
degrees in different individuals. It can be viewed as a dimension ranging from the absence of seasonal changes to the occurrence of extreme seasonal changes (eg, some people experience only very mild seasonal changes while others are severely affected).

Children with SAD usually present with fatigue, irritability, difficulty in getting out of bed in the morning, and problems in school. Sadness and changes in appetite have also been observed in children with SAD. Children with winter SAD tend to blame the external world (parents, teachers, etc) for treating them poorly.

Seasonality of mood and behavior is common throughout the US population. Surveys suggest that the prevalence of SAD in the United States increases with increasing latitude—ranging from 1.4% in Florida to 9.7% in New Hampshire. A survey in the Washington, DC, area found that about 4% of the population have winter SAD and over 10% more have subsyndromal features of SAD. Twenty-seven percent of respondents reported that changes in the seasons were a problem for them, 66% reported seasonal changes in energy level, 64% reported some seasonal changes in mood, and 49% reported seasonal changes in weight. Another survey, in New York City, indicated that about 6% of the population had seasonal impairment equivalent to that of patients with SAD, 18% reported milder symptoms that were bothersome, and 35% noted symptoms but did not complain.

Many clinical studies report that winter SAD mainly affects women. However, the high proportion of women seen in research clinics may be a result of selection bias. Blazer and colleagues suggested that SAD with major depressive episodes is more frequent among men, whereas women more commonly experience minor depression with a seasonal pattern.

Identification of a seasonal pattern can only be made if both the patient and physician actively look for it. Clinicians should ask the following questions when SAD is suspected. When the seasons change, do you:

- Feel down or depressed?
- Have less energy than usual?
- Feel less productive or creative?
- Need more sleep?
- Have less control over your appetite?

If physicians fail to ask these questions, many patients with SAD may be labeled as having a nonseasonal depressive disorder.

**HPA function**

Various hypotheses related to the pathophysiology of SAD have been proposed. One of these hypotheses suggests that abnormalities of hypothalamic-pituitary-adrenal (HPA)-axis function may contribute to the pathogenesis of SAD. The HPA axis controls the secretion of corticotropin-releasing hormone (CRH), corticotropin (adrenocorticotropic hormone), and cortisol. CRH is secreted from the paraventricular nucleus of the hypothalamus as well as from extrahypothalamic sites. It acts on the anterior pituitary gland to cause the release of corticotropin into the bloodstream, where it acts on the adrenal cortex to cause the production and release of cortisol into the bloodstream. Cortisol has diverse and widespread actions throughout the body and brain. It secondarily inhibits corticotropin and CRH release via negative feedback, although it may augment CRH release in the amygdala. Feedback inhibition is mediated via low-affinity glucocorticoid receptors (GRs) and high-affinity mineralocorticoid receptors (MRs). In the brain, MRs are located primarily in the hippocampus; GRs are more widely distributed in the hypothalamus, pituitary, cortex, and elsewhere. Species from humans to the most ancient organisms share components of the HPA axis.

**Cortisol and the circadian rhythm**

Release of CRH from the hypothalamic-pituitary-adrenal (HPA)-axis is increased by stress, blood levels of cortisol, and the sleep-wake cycle. In healthy persons, levels of cortisol rise rapidly after waking, reaching a peak within 30 to 45 minutes. They then gradually diminish over the day, rising again in late afternoon. Cortisol levels fall in late evening, reaching a trough during the middle of the night. The circadian pattern of cortisol release is controlled by the suprachiasmatic nucleus (SCN) of the hypothalamus, also known as the "body clock." Nerve signals from the SCN cause the paraventricular nucleus of the hypothalamus to release pulses of CRH roughly once per hour, resulting in HPA-axis activation and cortisol release. There are also direct links between the SCN and the adrenal gland itself (bypassing the HPA axis) through sympathetic nerve fibers, causing the adrenal gland to become more sensitive to corticotropin stimulation during the morning and further adding to the circadian pattern of cortisol release throughout the day. The HPA axis and depression

Over the past 2 decades, there has been a shift from viewing excessive HPA activity in depression as
an epiphenomenon to its having specific effects on symptom formation and cognition. Studies have demonstrated that hypercortisolism is involved in the pathogenesis of depressive disorders. Researchers have suggested that HPA dysregulation is involved in the causality of depression and have proposed that antidepressants may act through normalization of pathologic HPA-axis changes. The following clinical observations have been made in patients with depression:

- The number of cortisol and corticotropin secretory pulses is increased, which is also reflected in elevated urinary cortisol production rates.
- Levels of CRH in the cerebrospinal fluid are elevated.
- The number of CRH-secreting neurons in limbic brain regions is increased.
- The number of CRH-binding sites in the frontal cortex is reduced as a secondary effect of increased CRH concentration.
- The dexamethasone suppression test (DST), CRH stimulation test, combined DST-CRH stimulation test, and other neuroendocrine function tests indicate the presence of HPA dysregulation.

The DST showed that a high proportion of patients with various affective disorders have elevated cortisol levels, thus escaping the suppressive effect of dexamethasone. After CRH became available for clinical studies, the DST was combined with CRH administration. In this test, patients are pretreated with a single dose of dexamethasone at 11 pm and receive CRH intravenously at 3 pm the following day. The resulting DST-CRH stimulation test proved to be much more sensitive in detecting HPA system alterations than the DST alone. Several studies showed that depressed patients pretreated with dexamethasone reacted with an exaggerated corticotropin and cortisol response. A number of studies found that cortisol can affect mood and behavior and disrupt memory and recall.

### Seasons and cortisol

Most seasonal investigations into cortisol have found the highest levels to be present in winter. Quarterly measurements of morning and evening cortisol levels were determined in a longitudinal study of healthy male and female volunteers. There was a seasonal variation in cortisol levels with significantly higher levels found in winter and fall than in spring and summer. Walker and associates also reported that in healthy men, winter plasma cortisol levels were significantly higher than summer values. Studies that investigated the circadian profile of cortisol in healthy individuals indicated that circadian rhythm was delayed in winter. In an Antarctic study, the circadian rhythm of cortisol showed low amplitude and a phase advance in summer when compared with other seasons. The circadian rhythms of cortisol obtained without a "constant routine" (a protocol used in circadian rhythms or sleep studies to minimize exogenous effects such as changes in body position, temperature, and meals) were found to be similar in SAD patients and controls in both phase and amplitude; the rhythms did not change with successful bright light therapy. Since sleep has a suppressing effect on cortisol, those cortisol data do not reflect the unmasked endogenous circadian rhythm of cortisol. Avery and colleagues assessed cortisol rhythms during a constant routine in patients with winter SAD and in healthy controls. After sleep was standardized for 6 days, the subjects were sleep-deprived and restricted to bed rest for 27 hours while cortisol levels were assessed. The minimum level of the cortisol rhythm was phase-delayed in the SAD group compared with the control group; however, with bright light treatment, the minimum level advanced. Another study reported that SAD patients had normal cortisol and corticotropin levels but their responses to CRH were delayed and significantly reduced. With bright light therapy, the responses of cortisol and corticotropin to CRH increased significantly.

We have studied the question of whether there are circannual effects on clinical parameters, baseline cortisol and prolactin levels, and cortisol and prolactin responses to fenfluramine hydrochloride administration in subjects with nonseasonal major depression. We compared subjects experiencing major depressive episodes in fall or spring (the spring/fall group) with subjects experiencing major depressive episodes in summer or winter (the winter/summer group) and found that baseline cortisol levels were significantly higher in the spring/fall group compared with the winter/summer group. Our observation that baseline plasma cortisol levels were higher in the spring/fall group than in the winter/summer group suggests that these 2 groups may represent different biologic subtypes of...
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major depression. This hypothesis is supported by the observation by Beck-Friis and associates, who examined the per-month frequency of patients with one or more depressive episodes registered yearly from first onset of illness. The frequencies—calculated from the patients' previous records—were a percentage of the maximum number of patients and were separated for patients with normal and abnormal results on the DST. The authors demonstrated a trend for higher incidences of depression during spring and fall among the patients with normal DST results, whereas the distribution of depressive periods during the year in the abnormal DST group was more uniform. Another study of depressed patients showed a significantly biannual rhythm in the postdexamethasone cortisol values in depressed men, with peaks in June and December and troughs in March and September. The hypothesis that the spring/fall group and the winter/summer group represent different biologic subtypes of major depression is also supported by the observation that the number of binding sites to serotonin receptors during spring and fall is 12% higher than in winter and summer.

Treatment of SAD
Light therapy is recommended as a first-line treatment for SAD in expert and consensus clinical guidelines. It is possible that light therapy reduces HPA-axis abnormalities associated with SAD. It has also been shown that antidepressants may prevent and treat SAD. A recent report suggests that light treatment showed earlier response onset and lower rates of some adverse events relative to fluoxetine, but there were no other significant differences in outcome between light therapy and antidepressant medication. Another study concluded that it is possible to prevent recurrence of SAD episodes by beginning bupropion treatment early in the season while patients are still well. Antidepressants may act by normalizing the pathologic changes in HPA function in SAD patients. Also of interest, a recent report suggests that mifepristone, a steroid antagonist, may be useful for the treatment of SAD.

Increased cortisol secretion caused by major and minor stressful events may contribute to the development of SAD and other depressive disorders in vulnerable individuals. Therefore, one of the goals of prevention of such stress-related disorders is to help individuals to be more competent in managing their behavior and emotions in reaction to the negative aspects of their environment.

Dr Sher is an associate clinical professor of psychiatry at Columbia University College of Physicians and Surgeons and a research psychiatrist in the department of neuroscience at the New York State Psychiatric Institute in New York City. He reports no conflicts of interest regarding the subject matter of this article.

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