The Interface

Sunshine, Serotonin, and Skin: A Partial Explanation for Seasonal Patterns in Psychopathology?

by Randy A. Sansone, MD, and Lori A. Sansone, MD

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked.

ABSTRACT

A number of studies indicate that there can be seasonal variations in the expression of psychiatric phenomena, especially mood and anxiety symptoms, as well as completed suicide. Indeed, in acknowledgement of the potential for seasonal effects in depressive disorders, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* indicates the specifier, "with seasonal pattern." However, the explanations for the relationships between seasonal changes and exacerbations of psychopathology remain unclear, although the empirical literature indicates that an association between sunshine and serotonin is likely. Given that the relationship between sunshine and serotonin is probably a multimediated phenomenon, one contributory facet may be the role of sunshine on human skin. Human skin has an inherent serotonergic system that appears capable of generating serotonin. In this edition of The Interface, we discuss the relationships among psychopathology, sunshine, serotonin, and the skin.

KEY WORDS

Seasonal effects, seasonality, serotonin, sun, sunshine

"Let the sun shine,
Let the sun shine in,
Let the sun shine in…"
—Hair, 1968

INTRODUCTION

Seasonal exacerbations of psychiatric symptoms have been described for a number of psychopathologies, including mood and anxiety disorders. However, the explanations for these symptom variations remain indistinct. While serotonin is a likely mediator, the explicit process accounting for the observed fluctuations in serotonin levels is unclear. The effects of sunlight via the retina to the central nervous system (i.e., the retinoraphe tract) are a plausible explanation. However, according to recent research, the skin may also function as a means of modulating serotonin. In this edition of The Interface, we review this research and discuss the seasonal exacerbation of mood and anxiety disorders, serotonin, the sun, and the skin.

SEASONAL EFFECTS AND PSYCHOPATHOLOGY

It is well established that some forms of psychopathology appear to undergo distinct seasonal exacerbations. We define "seasonal effects on psychopathology" as an increase in pre-existing psychiatric symptoms that occurs during a particular time of the year, most commonly during the winter months but not always (e.g., reverse seasonal affective disorder). While it is not known if all psychiatric disorders have the potential to undergo seasonal effects to some degree, the extant literature confirms that seasonal effects may occur among some individuals with various psychiatric phenomena, including mood disorders (major depressive disorder, bipolar disorder),[1–6] anxiety disorders (anxiety syndromes, panic symptoms),[1,3,7] and completed suicide.[8–11]

Mood disorders. Mood disorders can be susceptible to seasonal influences, with a typical worsening in the winter months. As for empirical examples of seasonal effects on pre-existing mood disorders, Oyane et al[1] examined more than 10,000 men and women in a single county in Norway. As hypothesized, the researchers confirmed the presence of seasonal effects among participants with mood disorders, characterized by modestly higher levels of depressive symptoms during the period from November through March. Grimaldi et al[2] examined a representative Finnish community sample of nearly 6,000 individuals. In this study, 85 percent of participants reported seasonal variations in mood, characterized by more intense symptoms in the winter months compared to the summer months. These variations were not related to latitude. Finally, in a study from the Netherlands, Winhorst et al[3] examined 2,168 individuals who were part of a larger study on depression and anxiety. As anticipated, a significant proportion of participants in this sample (53.5%) reported seasonal effects with regard to mood, with lower mood most commonly reported during the winter months. These large epidemiological studies indicate that a significant proportion of individuals with pre-existing mood disorders may experience exacerbations of depressive symptoms in a seasonal manner, classically during the winter months. While these seasonal effects with regard to mood are reasonably established, findings do not seem to affect the time of the year that patients actually present for psychiatric treatment.[4]

In addition to depressive symptoms, bipolar symptoms may undergo seasonal tempering, as well. For example, Akhter et al[5] reported significant seasonal variation of established symptoms among 314 patients with bipolar I and II disorders. In this study, hypomanic or manic symptoms peaked around the time of the fall equinox whereas depressive symptoms peaked around the time of the winter solstice.

Because of the identified potential for mood disorders to exhibit seasonal effects, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) provides for depressive disorders the specifier, "with seasonal pattern."[6] Rather than merely a seasonal exacerbation alone, this specifier refers to an episodic pattern of mood highlighted by distinct seasonal expression (i.e., an extreme form of seasonality). To meet the criteria for this specifier, the individual must 1) experience the onset of a mood disorder during a particular time of the year; 2) experience full remission of the episode during a characteristic time of the year; 3) have experienced this pattern for at least two years; and 4) have experienced more seasonal episodes than nonseasonal episodes. In this context, the seasonal specifier represents a mood syndrome that goes beyond the seasonal exacerbation of pre-existing symptoms alone.

Anxiety disorders. Anxiety symptoms may also flux with seasonal changes, with a worsening of symptoms during the winter months. As empirical examples, these associations were confirmed in the Oyane et al[1] and Winthorst et al[3] studies. In addition, in an Australian study, Marriott et al[7] examined 133 patients with anxiety symptoms and panic attacks; as anticipated, investigators confirmed seasonal influences characterized by a worsening of both symptom types during the winter months.

Completed suicide. To further augment the theme of seasonal effects with regard to various forms of psychopathology, several studies have demonstrated seasonal patterns in relationship to completed suicide. For example, in a review of this literature, Havaki-Kontaxaki et al[8] summarized that most studies of completed suicide identify peaks in the late spring with accompanying troughs during the winter. In another literature review, Christodoulou et al[9] confirmed that the majority of studies demonstrate a seasonal spring peak for completed suicide—particularly among male individuals, among older individuals, and those who use violent methods of suicide. In a third literature review, Woo et al[10] underscored that the seasonal spring peak for completed suicide is highly replicable. Finally, as an example of a recent study, Vyssoki et al[11] examined over 16,000 suicides

in Austria and confirmed a clear seasonal pattern, with the highest frequencies between March and May. In this latter study, investigators also found that the average number of hours of sunshine per month was significantly correlated with completed suicide as well as the use of violent methods. (One wonders if the relative increase in serotonin with the advent of spring/sunshine is akin to initial exposure to an antidepressant, with the resulting change in serotonin levels potentially creating an agitated dysphoria that results in suicidal ideation/suicide in susceptible individuals.)

To summarize, there is clear empirical support for seasonal patterns with various types of psychiatric phenomena, such as mood disorders, anxiety disorders, and completed suicide. Importantly, there may be other psychiatric syndromes that undergo seasonal influences as well. As a caveat, findings are not meant to imply that all individuals with the preceding syndromes experience seasonal effects.

SEROTONIN: A LIKELY MEDIATOR

Serotonin has been implicated in the etiology and treatment of depression since the advent of the tricyclic antidepressants during the middle of the last century.[12] Since that time, various types of disruptions in the serotonin system have been implicated in a number of psychopathologies, including mood disorders and schizophrenia.[13] In keeping with this theme, the serotonin system may be one potential mediator of the seasonal exacerbations encountered in individuals with various types of psychopathology.

Serotonin synthesis and catabolism—a primer. Serotonin is a neurotransmitter that is primarily located in three areas of the body: 1) the central nervous system, 2) the mucosa of the gastrointestinal tract (the largest producer of serotonin), and 3) the blood platelets.[13] Serotonin is synthesized from the essential amino acid tryptophan, which is orally ingested and found in foods such as bananas, pineapples, plums, turkey, and milk. Tryptophan is initially hydroxylated by the enzyme tryptophan hydroxylase to form 5-hydroxytyptophan.[13] 5-hydroxytryptophan is then decarboxylated by the enzyme amino acid decarboxylase, which results in the formation of 5-hydroxytryptamine or serotonin.[13] At this juncture, serotonin is a functional neurotransmitter. In this role, serotonin is released into the synaptic cleft to potentially interact with pre-synaptic and post-synaptic receptors. After being awash in the synaptic cleft, serotonin transporters convey serotonin from the synaptic cleft back into the presynaptic cell for recycling or metabolic degradation.[13] In this way, serotonin transporters play a meaningful role in the dynamics and regulation of serotonin in the synaptic cleft.[13] In addition, serotonin in the blood is cleared through the liver or lungs.[14]

Serotonin, normal seasonal variations, and sunlight. According to the empirical literature, there appears to be a relationship between normal seasonal variations in the levels of serotonin and the amount of available sunshine. At the very basic science level, exposure to light has been reported to activate the synthesis of serotonin in yeast extracts, suggesting a direct relationship between sunshine and the production of serotonin.[15] Available data also suggest that serotonin exhibits some customary or natural seasonal variation in the central nervous systems of normal human adults. For example, seasonal variations have been reported in platelet serotonin uptake and paroxetine binding, hypothalamic concentrations, plasma levels, and concentrations of metabolites in the cerebral spinal fluid as well as with neuroendocrine challenges with serotonin antagonists.[16] In addition, light has been reported to influence the binding of serotonin at the serotonin 1_A receptor site, with lower light levels associated with lower binding levels in the cortical and subcortical limbic regions of the brain.[17] Serotonin transporters have also demonstrated binding potentials that vary in normal humans throughout the year—a finding that was statistically related to the average duration of daily sunshine.[18] In direct support of customary seasonal variations in serotonin, Lambert et al[19] sampled jugular blood from 101 healthy male volunteers, one sample each during 12 months, and determined that serotonin levels were lowest in the winter.[19]

While there have been some inconsistencies among these studies (e.g., a lack of seasonal variation in serotonin transporters has been reported),[20,21] they collectively suggest that normal adults tend to exhibit elevated serotonin levels in the late summer and fall, and reduced serotonin levels in the spring—likely in relationship to available sunlight. Given these normal variations, it may be that individuals who are susceptible to seasonal effects are especially sensitive to these changes in the presence of psychopathology.

Serotonin and the skin. In addition to other body sites (e.g., brain, gut, platelets), serotonin is

present in human cutaneous tissue. This conclusion is founded upon the discovery that the machinery of the serotonergic system is present in the skin. For example, tryptophan hydroxylase, the initial enzyme in the synthesis of serotonin, is found in human skin.[14] Likewise, serotonin and serotonin transporters have been detected in human keratinocytes, the predominant cell type (90%) in the epidermis. This leads to the deduction that mammalian skin can actually produce serotonin.[14] Stated in scientific prose, Slominski et al[22] posit that human skin expresses intrinsic serotonin biosynthetic pathways. Slominski et al also point out the common embryological ectodermal origin of the brain and the epidermis, which supports the presence in both of similar biological elements. These researchers even suggest that the cutaneous serotonergic system may be the evolutionary remnant of an ancestral system that operated primarily in the periphery.[14]

Skin and light—an explanation for seasonal variation? While there are other contributing explanations for the relationship between light and serotonin, such as the retinoraphe tract[23] (i.e., a tract between the retina and raphe nuclei that might account for the light-induced modulation of serotonin), the role of the skin in the generation of serotonin remains a competing possibility. In support of the role of the skin in the photostimulation of serotonin, Gambichler et al[24] conducted an intriguing study. These investigators examined the effects of light exposure in the laboratory for three weeks on 42 subjects in comparison with 11 controls. All participants wore opaque goggles, which for those exposed to light were designed to block out ultraviolet-A radiation (i.e., to eliminate the retinal mediation of serotonin effects). Individuals exposed to light evidenced higher serum serotonin levels during this experiment than controls, which the authors proffered might be explained by a "cutaneous pathway."

While the preceding data are preliminary, findings suggest that the seasonal alterations in serotonin may partially be the result of the serotonin infrastructure in the skin. In other words, it is possible that the skin, itself, is involved in the production and bio-regulation of serotonin. (This phenomenon might partially explain the human predilection for sunbathing.) This is not meant to exclude other pathways such as the retinoraphe tract.

CONCLUSION

In keeping with clinical experience and the empirical literature, a number of psychiatric symptoms/disorders have the potential to undergo seasonal exacerbations, such as mood and anxiety disorders. While the explicit reasons for these observed seasonal patterns are unclear, the role of sunshine in the production of serotonin is a likely possibility. While the photostimulation of serotonin may be mediated in a number of ways, including the retinoraphe tract (i.e., via the retina), one intriguing possibility is that sunshine may directly stimulate the production of serotonin through the skin. Research indicates that the skin has the serotonergic machinery to perform this task. This may explain the popular appeal of sunbathing, traveling during the summer months, and being outdoors in the sunshine. Clearly, the seasonal influences expressed in psychiatric symptoms are of relevance and importance to clinicians, both in primary care and psychiatric settings.

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AUTHOR AFFILIATIONS: R. Sansone is a professor in the Departments of Psychiatry and Internal Medicine at Wright State University School of Medicine in Dayton, OH, and Director of Psychiatry Education at Kettering Medical Center in Kettering, OH. L. Sansone is a civilian family medicine physician and Medical Director of the Family Health Clinic at Wright-Patterson Air Force Base Medical Center in WPAFB, OH. The views and opinions expressed in this article are those of the authors and do not reflect the official policy or position of the United States Air Force, Department of Defense, or United States Government.

ADDRESS CORRESPONDENCE TO:
Randy A. Sansone, MD, Sycamore Primary Care Center, 2115 Leiter Road, Miamisburg, OH 45342; E-mail: randy.sansone@khnetwork.org.