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Forty years of seasonal affective disorder

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Summary

In 2024, we observe the fortieth anniversary of the publication, where, for the first time, the term Seasonal Affective Disorder (SAD) was used. Presently, SAD is regarded as a special category of mood disorder. In the American Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V), the seasonality makes a specifier, "with seasonal pattern", both for recurrent depression or Major Depressive Disorder (MDD), and for Bipolar Disorder (BD). The most spectacular phenomenon among SAD is winter depression. Its symptomatology is mostly similar to atypical depression, characterized by excessive sleepiness and carbohydrate craving. SAD can pertain up to one fifth of persons with MDD or BD and is more frequent in women.

SAD can be considered as an extreme expression of the central nervous system (CNS) changes related to circannual rhythm of lighting. The seasonal changes of the CNS function apply to the secretion of melatonin, the neurotransmitters dopamine and serotonin and the hypothalamic-pituitary-adrenal axis. In the circadian and circannual processes, a significant role is played by so-called "clock genes". SAD may be a legacy of Homo neanderthalensis.

In winter depression, the therapeutic effect is obtained by an exposition to bright light (bright light therapy – BLT) as well as to blue light or using the method of dawn simulation. The therapeutic effect of phototherapy has also been ascertained in non-seasonal depression. As a counterpoint to this mechanism, promising trials have been undertaken in manic states by light restriction using blue light blocking glasses.

Key words: seasonal affective disorder, winter depression, light therapy

Introduction

In 2024, we observe the fortieth anniversary of the publication where, for the first time, the term seasonal affective disorder (SAD) was used. The article was the work of researchers from the National Institute of Mental Health (NIMH) in the USA, with Norman Rosenthal as the first author. In the 1970s, he emigrated from South Africa to the USA to continue his medical and research career. In 1979, he started his psychiat-

ric practice in Washington, D.C., and received an NIMH research grant in Bethesda. On his path to identifying SAD, Rosenthal was likely seeking an explanation for his depressed mood he experienced during the winter months in the USA. The article describes 29 patients who developed depression during winter, with symptoms of lack of energy, excessive sleepiness and carbohydrate craving. The patients were living in a temperate climate, and in the majority of them, bipolar disorder type 2 could be diagnosed. The symptoms of depression completely remitted during spring and summer when, oftentimes, a state of excessively good mood appeared. Because Rosenthal reckoned that one of the factors contributing to winter depression was light deficiency, 11 patients were exposed to artificial light, obtaining an antidepressant effect [1]. Rosenthal's crowning achievement related to SAD was the popular book *Winter Blues*, published in 1993, where in a masterly way he described seasonal depression in the context of symptoms, treatment as well as the human relationship with the seasons of the year. For example, in one of the final chapters of the book, he describes a possible association between seasonality and artistic creativity. The book has had four updated editions, the most recent of which was in 2013 [2].

The article from 1984 published by the NIMH research team, with Rosenthal as the first author, can be regarded as the formal introduction of seasonal affective disorder into psychiatric literature. However, it should be noted that the seasonality of depression had been recognized by many physicians and researchers, beginning with Hippocrates. The "Father of Medicine," in his aphorisms written in the fifth century B.C., postulated that the changes in seasons were a frequent cause of illnesses, including melancholia [3].

Despite forty years of existence, seasonal affective disorder has not yet gained the status of a distinct diagnostic category and is still regarded as a specific variant of mood disorders. In the recent American Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), seasonality is used as a specifier, "with seasonal pattern," for both recurrent depression or major depressive disorder (MDD), and for bipolar disorder (BD). For MDD, it pertains to depression occurring regularly during the fall-winter period. However, in many patients, depression appears in the context of BD where, besides episodes of depression occurring in the fall-winter period, states of elevated mood and activity appear during the summer months [4]. In the International Classification of Diseases, ICD-10 and ICD-11, SAD is classified as a variant of recurrent depression [5, 6].

1. Winter depression

The most spectacular phenomenon of SAD is winter depression, also known as seasonal depression. In DSM-5, it is recognized as major depressive disorder with a seasonal pattern. The symptoms of depression appear during the fall-winter period, where a deficit of light occurs, and usually subside with the advent of spring. Winter depression is most characteristic of temperate climates, which experience a signifi-

cant shortage of light during winter compared to other seasons, especially summer. The symptomatology of winter depression is to a great extent similar to that of so-called atypical depression, where excessive sleepiness and increased appetite with carbohydrate craving occur. In addition to these, the classical symptoms of depression, such as low mood, anhedonia, loss of energy, psychomotor retardation, feeling of worthlessness and pessimistic thoughts, are also present. For a diagnosis of winter depression, such a yearly pattern should be observed for at least two years.

The latest research on the prevalence of SAD, conducted by Swiss authors, is based on the population of the Zurich cohort study ($N = 499$), in which several comprehensive diagnostic interviews at intervals over more than 20 years were made. Repeated winter depression in the course of recurrent depression and BD was diagnosed in 3.44% of subjects, with five times more women than men. The autumn-winter seasonality was observed in 7.52% of subjects with major or minor depressive mood states. In seasonal depression, the symptoms of atypical depression (with hypersomnia and increased appetite) were most commonly observed, along with a high comorbidity with social anxiety disorder and agoraphobia, a high incidence of diurnal mood variation (with evening improvement), and a high rate of oversensitivity to light, noise or smell [7].

2. Bipolar mood disorder – seasonal

Longitudinal studies performed by Catalan authors indicated that a seasonality of the course may affect about one-fifth of BD patients. These are mostly patients with type 2 BD, in whom the onset of the illness manifested as a depressive episode [8]. A more recent investigation by these researchers showed the prevalence of bipolar SAD as 16.5% among patients with BD, as well as a relationship with BD type 2, a family history of mood disorders, lack of clear polarity of the course and lower intensity of aggressive behavior [9].

For several years, studies involving many centers in the world (75 centers in 42 countries across six continents) have been performed on the relationship between solar insolation in different locations on Earth and the prevalence and characteristics of BD. These studies are coordinated by Michael Bauer, chairman of the Department of Psychiatry at the University of Dresden and longtime president of the International Group for the Study of Lithium-Treated Patients (IGSLI). From Poland, the Department of Adult Psychiatry at the Poznań University of Medical Sciences is participating in this research. The studies have shown, among other findings, that the greater the solar insolation during the spring period in a given location, the earlier the onset of bipolar disorder [10]. In another study, a significant inverse association between the difference in solar insolation between winter and summer and a history of suicide attempts in bipolar type 1 patients was demonstrated [11]. Also, it was found that the larger the change in solar insolation throughout the year, the greater the likelihood that the polarity of the first episode will be depression [12].

3. Etiopathogenesis of seasonal affective disorder

3.1 Reflecting the seasonality of brain function

Circadian and circannual rhythmicity play a significant role in brain function, which may be relevant for the pathogenesis of SAD [13]. In the 1960s, the term "Zeitgeber" was introduced, which means an external cue for the synchronization of an organism's biological clock to the 24-hour rhythm of the sequence of light and darkness [14]. In humans, the most important central structure connected with the synchronization of external time cues is the suprachiasmatic nucleus (SCN) of the hypothalamus. Light, the strongest Zeitgeber, reaches the SCN via the retinohypothalamic tract. Neural pathways connect the SCN to the pineal gland, where melatonin is secreted. The secretion of melatonin is suppressed by light. In the processes of the biological clock, the nodular part of the pituitary gland (hypophysial pars tuberalis) is also involved, responsible for the activity of various hormones [15].

In melatonin formation, the precursor is tryptophan, leading to the synthesis of serotonin. The enzyme N-acetyltransferase transforms serotonin into N-acetylserotonin. Further, with the participation of the hydroxyindole-O-methyltransferase enzyme, melatonin (5-methoxy-N-acetyltryptamine) is created. Melatonin acts on the regulation, among others, of sleep and circadian rhythms, by the activation of two kinds of melatonin receptors, M1 and M2 [15]. Melatonin suppression influenced by light is caused by the action of melanopsin, a protein present in the cells of retinal ganglion [16].

SAD can be considered an extreme expression of the central nervous system (CNS) changes related to the circannual rhythm of lighting. In terms of the pathogenesis of changes in the sleep-wake rhythm in SAD, the short photoperiod hypothesis and the phase-delay shift hypothesis have been proposed. These hypotheses are supported, among other things, by the association of the prevalence of SAD with the geographical latitude [17], as well as the therapeutic effect of morning light, which causes an acceleration of the diurnal rhythm phase [18]. Chinese researchers attempted to develop a SAD model in rhesus monkeys using a paradigm of the short photoperiod. These conditions triggered depressive behavior characterized by lowered activity and psychomotor reactivity, weight loss, anhedonia and increased cortisol concentrations. All these symptoms remitted with the use of antidepressant medication [19]. Some investigators suggest that there are two types of predisposition to SAD (the so-called dual-vulnerability hypothesis), pointing to distinct factors for seasonality and depression [20]. For example, it turns out that increased melatonin secretion in winter is primarily observed in persons with SAD, and to a much lesser extent in others [21]. Recently, researchers from Pittsburgh demonstrated that persons with SAD exhibit a decreased retinal reaction to light, defined as post-illumination pupil response (PIPR), in winter compared to the summer season. This was not observed in the control group. The PIPR reaction is connected with the activity of melanopsin [22].

Apart from melatonin, circannual seasonality also applies to serotonergic and dopaminergic neurotransmission, as well as the hypothalamic-pituitary-adrenal (HPA) axis.

Swedish researchers using neuroimaging methods demonstrated circadian and circannual differences in serotonin 5-HT1A receptors (with higher activity during increased solar insolation), and the serotonin transporter [23]. Meanwhile, Aumann et al. [24] studied the midbrain dopaminergic neurons in individuals who died during summer versus winter. They found that the activities of the enzyme tyrosine hydroxylase, the rate-limiting step for dopamine synthesis, as well as the dopamine transporter were significantly lower during winter than in summer. On the other hand, British researchers showed that patients with SAD had a lower increase of cortisol after awakening, i.e., the cortisol awakening response, (CAR) during winter, but not in summer [25].

The pattern of psychiatric admissions due to mood disorders also shows a tendency to seasonality. Geoffroy et al. [26] performed a meta-analysis in 2014 of 32 studies on the hospitalizations of BD patients due to various episodes. It turned out that the peak of admissions for depressive episodes occurs in the early winter period, and, to a lesser extent, in summer. As for manic episodes, the peak of admissions occurs in the spring-summer period, with a lesser peak in autumn. Hospitalizations due to mixed episodes mainly occur in early spring and late summer. An analysis performed in 2015 on the hospitalizations of patients with mood disorders admitted to the Institute of Psychiatry and Neurology in Warsaw showed a higher frequency of admissions due to various kinds of depression in the autumn and spring periods, due to mania in spring-summer and mid-winter, and for mixed episodes – in spring and winter [27]. These studies partially support the seasonality of depression in the autumn-winter period and mania in the spring-summer period.

3.2 Genetic factors

Circadian biological rhythms (circa 24 hour) are generated by the biological clock consisting of so-called "clock genes", being a part of several transcriptional loops. The most important genes in these loops are *CLOCK* (circadian locomotor output cycles kaput), *ARNTL* (aryl hydrocarbon receptor nuclear translocator-like), *NPAS2* (neuronal pas domain protein 2), *PER1,2,3* (clock protein PERIOD), and *TIM* (timeless circadian clock) [28]. For the discovery of the molecular-genetic mechanisms of circadian rhythms, American scientists Jeffrey Hall, Michael Rosbach and Michael Young were awarded the Nobel Prize in physiology and medicine in 2017 [29].

Polymorphisms in clock genes in mood disorders have been studied using the so-called "candidate gene" method. In the Poznań center, we identified the role of *ARNTL* and *TIM* gene polymorphisms in the mechanism of lithium prophylactic activity in BD [30], as well as in hyperthymic, cyclothymic and anxious temperaments measured by the TEMPS-A (Temperament Evaluation of Memphis, Pisa and San Diego Autoquestionnaire) scale. We also found that the polymorphism of the *PER3* gene is associated with depressive temperament on this scale [31]. Several studies have been devoted to investigating these genes in SAD. Johansson et al. [32] found an association between predisposition to SAD and polymorphism of the *NPAS2* gene. In a 2007 paper, an

association between SAD andpolymorphism of three transcriptional loop genes such as *ARNLT, NPAS2* and *PER2* was demonstrated [33]. French investigators showed an association between BD with a seasonal course and five SNPs (single nucleotide polymorphisms) of the *NPAS2* gene and one SNP of the *CRY2* (cryptochrome circadian regulator 2) gene [34]. Meanwhile, American authors identified two rare variants of the *PER3* gene in a family of individuals showing a high index of seasonality, depressive symptoms and a shift of the sleep phase during winter [35]. The results of studies on clock genes may also indicate a genetic relationship between circadian and circannual rhythms.

In 2018, the first GWAS (genome-wide association study) was performed in SAD. The study included 1,380 persons with SAD in the course of BD and recurrent depression which were compared with 2,937 control persons. The strongest association with SAD was found for the *ZBTB20* (zinc finger and bric-a-brac domain containing protein 20) gene [36]. This gene encodes a transcription factor that plays an important role in hippocampal activity [37].

3. Evolutionary hypothesis

In 2012, American psychologist Julia Sherman proposed an evolutionary concept of BD, called EOBD-R (Evolutionary origin of bipolar disorder – revised). The hypothesis postulates that "bipolar" behavior developed during the middle Pleistocene as a seasonal adaptation to winter in the temperate zone [38]. This applied to human species living in this climate zone at the time, i.e., the Neanderthal man. Such an adaptation can be supported by, among other things, the pyknic body type of Neanderthals, which conserved warmth and was adapted to cold. The transmission of this predisposition to modern humans was a result of crossbreeding between *Homo neanderthalensis* and *Homo sapiens.* In 2020, a paper by Spanish researchers appeared showing that the Neanderthal man had the ability to hibernate during the winter. Among the archeological finds in the Spanish Atapuerca caves, skeletons originating from about 500 thousand years ago had the features of lesions in bones and kidneys as a consequence of hibernation [39]. Therefore, it can be suggested that the climatic adaptation of the Neanderthal man may contribute to the pathogenesis of BD, particularly winter depression. The presence of this illness in modern humans may be a consequence of the introgression of Neanderthal genes associated with biological rhythms and depression into the *Homo sapiens* genome [40]. It is worth mentioning that already in late 1980s, American researchers Peter Whybrow (psychiatrist) and Robert Bahr referred to winter depression as the "hibernation response" [41]. Thus, the concept of Julia Sherman primarily applies to seasonal winter depression in both unipolar and bipolar mood disorders occurring in temperate climates. In African populations, which had never had a chance to encounter *Homo neanderthalensis*, the prevalence of BD, and especially SAD, is significantly lower than in populations living in a temperate climate [42].

4. Treatment of seasonal affective disorder

A specific feature of winter depression is the therapeutic effect obtained by the exposition to light, which was already ascertained in the original 1984 paper [1]. Among the precursors of the therapeutic application of light is the Italian physician Vincenzo Chiarugi, who, due to his revolutionary modern attitude towards psychiatric patients, can be called "an Italian Pinel". In his work of 1794, he recommended increasing exposure to sunlight in patients with depression and avoiding the exposition to light and noise in agitated patients by placing them in dark rooms [43].

The paper by Rosenthal et al. [1] drew upon the earlier study of the NIMH group showing that exposition to light influences circadian rhythm by inhibiting melatonin secretion [44] as well as the very first trials of using light in the treatment of winter depression [45, 46]. Since the mid-1980s, bright light therapy (BLT) of winter depression has become increasingly widespread. The efficacy of such therapy in seasonal depression was documented in meta-analyses from 2005 [47] and 2020 [48], showing it to be equipotent to antidepressant drugs. French researchers compared BLT and antidepressant drugs and found similar efficacy, while the combination of both methods proved to be significantly more effective [49].

The BLT has two modifications. The first of them involves using blue light with a wavelength of 450-480 nm. The inspiration for developing this method came from the discovery that melanopsin, which is responsible for the change of circadian rhythm, is most sensitive to this light [50]. However, in practice, it was found that blue light is not necessary for effective phototherapy, and using blue light alone is not more efficacious than BLT [51]. The second therapeutic technique is so-called dawn simulation. It consists in gradually increasing the light intensity during the last 30 minutes of sleep and maintaining it for 15 minutes after awakening with an alarm clock. Comparative studies have found similar efficacy between dawn stimulation and BLT in moderate depression, but a better efficacy of BLT in more severe depression [52].

Recently, an expert review of light therapy in winter depression was published. The first author of the article is Swiss researcher Anna Wirz-Justice, probably the most eminent connoisseur of this issue presently. The article states that the primary indication for phototherapy is SAD. However, in recent years, the efficacy of this therapy has been demonstrated in both non-seasonal depression and many other psychiatric disorders. In phototherapy, the light acts through the visual system, rather than through the skin, because the lamps do not emit light in the ultraviolet or infrared ranges. Recently, the lamps used in phototherapy generate a light intensity of 10,000 lux, and the distance of the patient from the lamps is strictly defined by the manufacturer. The 30-minute light therapy procedure, lasting for at least a week, should be conducted in the early morning hours (e.g., 7:30 AM). The therapy can be started slightly later (e.g., 8:45 AM) in persons with high indexes of the eveningness chronotype. The phototherapy can be combined with antidepressant drugs (synergistic effect), except for photosensitizing

medications such as hypericin (an extract from St. John's wort). The side effects of phototherapy, such as headache, vertigo, nausea and eye fatigue, are not frequent and usually disappear after a few days [53].

Can winter depression in patients with SAD be prevented? In recent years, analytic papers such as Cochrane Reviews have been published on this issue. They indicate the difficulties in assessment, mostly due to the methodological heterogeneity of the studies. However, in one of them, the possibility of preventive action by using BLT was demonstrated [54]. Among antidepressant drugs, the most data show the possibility of preventing winter depression through the use of bupropion [55]. No convincing evidence has been obtained for preventing winter depression with agomelatine, melatonin [56], vitamin D supplementation [57] or psychotherapy [58]. So far, no studies have been performed on the possibility of preventing SAD relapses through the use of long-term administration of mood-stabilizing drugs, although it seems that such research would be highly justified.

The excellent effect of phototherapy in seasonal depression has contributed to research on such treatment in other types of depression. Recent meta-analyses have provided evidence for the therapeutic effect of light therapy in non-seasonal depression [50], and the augmentation of antidepressant drugs with phototherapy [59]. Attempts have also been made to apply light therapy in other illnesses, usually as an adjunct to ongoing treatment. For instance, in Poland, promising results were obtained from using phototherapy in patients with depression in the course of the restrictive form of anorexia nervosa [60].

If light is therapeutic for depression, perhaps darkness could be therapeutic for a mental state opposite to depression, such as mania? Similar to the recommendations of Vincenzo Chiarugi mentioned earlier, a Polish physician, Ludwik Perzyna, in his book *Lekarz dla włościan* (A Physician for Peasants) published in 1793, referring to the manic state as "madness" writes: "The room in which 'the madman' is to be kept should be somewhat dark and cold" [61, 202]. Contemporary trials of the applications of "darkness" involve the use of glasses that block blue light (blue-blocking glasses – BBG). Danish researchers, using BBG in patients during a manic episode as an adjunct to pharmacological treatment, demonstrated a significantly better therapeutic effect compared to placebo [62], as well as notable sleep improvement [63]. Recently, a summary of the BBG application in BD was published, highlighting the most important practical and research issues [64].

Summing-up

Seasonal affective disorder, especially so-called winter depression, is now widely recognized both in the psychiatric domain and in common knowledge. Forty years of its presence have significantly contributed to the progress of both chronobiology and chronotherapy. The names of both these fields come from the Greek word *chronos*, meaning "time".

Chronobiology is a branch of biology that investigates biological rhythms i.e., cyclical phenomena occurring under the influence of internal (physiological) and external factors, such as the sequence of light and darkness and seasons of the year. A contemporary evidence for honoring these phenomena is the awarding of the 2017 Nobel Prize in Physiology or Medicine to three American scientists for their molecular-genetic research on circadian rhythm [29]. The SAD may represent a manifestation of changes in the central nervous system linked to circannual lighting rhythm. Research on SAD has contributed to a better understanding of, among other things, the seasonal functioning of melatonin and the relevance of clock genes. These findings may also allude to the 2022 Nobel Prize, awarded to Swedish scientist Svante Pääbo for his research on the Neanderthal man and the Neanderthal heritage in *Homo sapiens*. It is very likely that SAD constitutes such a legacy.

Chronotherapy in psychiatry is defined as a controlled exposure to environmental factors that influence biological rhythms, resulting in a therapeutic effect in psychiatric disorders. Thanks to SAD, phototherapy has now become a flagship form of chronotherapy. It is positioned alongside such methods of depression treatment as sleep deprivation and sleep phase advance. A psychotherapeutic equivalent of chronotherapy is social rhythm therapy, used in BD. After proving its effectiveness in SAD, phototherapy has been successfully used in non-seasonal depression and other psychiatric disorders It has also provided the basis for the treatment of manic states with "darkness" through the use of blue-light blocking glasses.

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